Merging of the Senses

Interactions between Auditory and Proprioceptive modalities

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Declaration

I, hereby, declare that this dissertation is my own personal effort. Any assistance or collaborative work has been duly acknowledged in the dissertation. Moreover, I would like to confirm that this dissertation has not been used as an examination paper elsewhere. I also declare that this present work is original, and, to the best of my knowledge, does not breach any copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Shashank Ghai

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Abstract

This doctoral work reports the influence of self-generated auditory feedback i.e. movement sofication on motor control, learning and imagery. In its structure, this research work incorporates a detailed literature review, meta-analyses followed by three experimental studies and two futurized perspective articles.

Initially, a total of seven systematic reviews and dose-response meta-analyses were performed to evaluate the influence of music-based auditory stimulation therapies i.e. rhythmic auditory cueing, patterned sensory enhancement and movement-sonification on gait rehabilitation, postural stability, movement kinematics in healthy population groups and in individuals affected from neurological disorders such as, Cerebral palsy, Parkinson's disease, Multiple Sclerosis, and Stroke. The systematic review and meta-analyses adhered to the PRISMA guidelines. In total, 200 studies including 6,164 participants were included in the review studies. The findings from all of these studies were used to understand the efficacy of auditory-motor training interventions and their underlying neurophysiological mechanisms. The findings from these reviews comprehensively demonstrated efficient, cost-effective benefits of music-based auditory stimulation therapies in recovering motor, cognitive and sensory functioning in both healthy and neurologically affected population groups. Moreover, the studies also reported effective auditory-motor training dosages that could be applicable to attain maximum benefits during an intervention. The findings from these review studies were also utilized to derive research questions and hypotheses for the experimental studies performed in this doctoral research work.

In the following three experimental studies, our group demonstrated the intricate relationship between auditory-proprioceptive modalities and demonstrated the beneficial influence of self-generated real-time auditory feedback (movement sonification) to facilitate active knee-joint proprioceptive perceptions. Firstly, our group demonstrated the beneficial effects of direct application of sonification on knee re-positioning accuracy. Moreover, in the same experiment we also demonstrated the intricate auditory-proprioceptive interaction during a subliminal step-wise transposition of the auditory feedback's pitch (±2.6 Hz). Here, subliminal transposition during the performance of a knee re-positioning task led to goal-directed modulation of proprioceptive perceptions in the opposite direction of transposition. Further, in the second experiment, our group demonstrated that an intensive bilateral training with self-produced auditory feedback led to robust enhancements in knee proprioceptive accuracy after 25-30 minutes of training. The enhancements in proprioceptive perceptions were both retainable (without auditory feedback after 15 minutes and 24 hours) and transferrable (on untrained target angles). This experiment for the first time demonstrated the beneficial influence of auditory on intermodal learning. In the third experiment, our group elucidated the influence of self-generated auditory feedback on motor imagery. Here, we demonstrated that performing auditory-guided mental imagery after an auditory-motor training led to enhanced knee-proprioceptive perception as compared to conventional mental imagery i.e. imagining movements without any auditory feedback. Again, the enhancements observed in knee-joint proprioception were both retainable and transferred to untrained angles in the absence of auditory feedback. The findings from these experiments are novel and have immense practicality for application in both musculoskeletal and neurological rehabilitation protocols.

Finally, two future perspective articles were included in this dissertation that propose possible applications of different auditory feedback based training regimens in patients undergoing neurotoxic oncologic therapies and patients under minimal conscious states. The prospective influences of auditory feedback proposed in these perspective articles are derived from the findings of both the review and research studies performed in this doctoral research work.

In conclusion, this doctoral work demonstrates the intricate relationship between the auditory and proprioceptive modalities that could be utilized to develop efficient training and rehabilitative interventions. This research work for the first time developed a state of the art knowledge from the existing literature for the influence of auditory-motor training interventions. This novel work also demonstrates how self-generated auditory stimulations could be effectively used to facilitate proprioceptive perceptions i.e. an integral component of motor control and performance.

Key words: Sonification, motor control, motor learning, rehabilitation, joint position sense

Abstract

Diese Doktorarbeit berichtet über den Einfluss von selbst generiertem auditorischem Feedback, d.h. Bewegungssonifikation, auf die motorische Steuerung, das Lernen und die Bildsprache. In seiner Struktur beinhaltet diese Forschungsarbeit eine detaillierte Literaturübersicht, Metaanalysen, gefolgt von drei experimentellen Studien und zwei futurisierten perspektivischen Artikeln.

Zunächst wurden insgesamt sieben systematische Übersichtsarbeiten und Dosis-Wirkungs-Meta-Analysen durchgeführt, um den Einfluss musikbasierter auditorischer Stimulationstherapien zu bewerten, d.h. rhythmisches Cueing, musterhafte sensorische Verbesserung und Bewegungssondierung auf die Gangrehabilitation, Haltungsstabilität, Bewegungskinematik in gesunden Bevölkerungsgruppen und bei Personen, die von neurologischen Störungen wie Cerebralparese, Parkinson, Multiple Sklerose und Schlaganfall betroffen sind. Die systematische Überprüfung und Meta-Analysen orientierten sich an den PRISMA-Richtlinien. Insgesamt wurden 200 Studien mit 6.164 Teilnehmern in die Übersichtsstudien einbezogen. Die Ergebnisse all dieser Studien wurden genutzt, um die Wirksamkeit von Interventionen des auditorisch-motorischen Trainings und die zugrunde liegenden neurophysiologischen Mechanismen zu verstehen. Die Ergebnisse dieser Übersichtsarbeiten zeigten umfassend den effizienten, kostengünstigen Nutzen musikbasierter auditorischer Stimulationstherapien bei der Wiederherstellung der motorischen, kognitiven und sensorischen Funktionsfähigkeit sowohl bei gesunden als auch bei neurologisch betroffenen Bevölkerungsgruppen. Darüber hinaus berichteten die Studien auch über effektive auditorisch-motorische Trainingsdosen, die anwendbar sein könnten, um den maximalen Nutzen während einer Intervention zu erzielen. Die Ergebnisse dieser Übersichtsstudien wurden auch genutzt, um Forschungsfragen und Hypothesen für die in dieser Doktorarbeit durchgeführten experimentellen Studien abzuleiten.

In den folgenden drei experimentellen Studien zeigte unsere Gruppe den komplizierten Zusammenhang zwischen auditorisch-propriozeptiven Modalitäten und den positiven Einfluss von selbst generiertem Echtzeit-Audit (Bewegungssonifikation), um aktive kniegelenkbezogene propriozeptive Wahrnehmungen zu ermöglichen. Erstens zeigte unsere Gruppe die positiven Auswirkungen der direkten Anwendung der Sonifikation auf die Genauigkeit der Neupositionierung des Knies. Darüber hinaus haben wir im selben Experiment auch die komplizierte auditorisch-propriozeptive Interaktion während einer

unterschwelligen schrittweisen Transposition der Tonhöhe des auditorischen Feedbacks (±2,6 Hz) gezeigt. Hier führte die unterschwellige Transposition während der Durchführung einer Knie-Repositionierungsaufgabe zu einer zielgerichteten Modulation propriozeptiver Wahrnehmungen in die entgegengesetzte Richtung der Transposition. Weiterhin zeigte unsere Gruppe im zweiten Experiment, dass ein intensives bilaterales Training mit selbstproduziertem auditorischem Feedback nach 25-30 Minuten Training zu einer robusten Verbesserung der propriozeptiven Genauigkeit des Knies führte. Die Verbesserungen der propriozeptiven Wahrnehmungen waren sowohl beibehalten (ohne auditorisches Feedback nach 15 Minuten und 24 Stunden) als auch übertragbar (bei untrainierten Zielwinkeln). Dieses Experiment zeigte zum ersten Mal den positiven Einfluss des Gehörs auf das intermodale Lernen. Im dritten Experiment hat unsere Gruppe den Einfluss von selbst generiertem akustischem Feedback auf die motorische Bildgebung aufgeklärt. Hier haben wir gezeigt, dass die Durchführung von auditorisch geführten mentalen Bildern nach einem auditorisch-motorischen Training zu einer verbesserten kniepropriozeptiven Wahrnehmung im Vergleich zu herkömmlichen mentalen Bildern führte, d.h. die Vorstellung von Bewegungen ohne auditorisches Feedback. Auch hier waren die bei der Kniegelenkpropriozeption beobachteten Verbesserungen sowohl haltbar als auch in Abwesenheit von auditorischem Feedback auf untrainierte Winkel übertragbar. Die Ergebnisse dieser Experimente sind neuartig und haben eine immense Zweckmäßigkeit für die Anwendung in den Protokollen der Rehabilitation des Bewegungsapparates und der Neurologie.

Schließlich wurden zwei zukünftige perspektivische Artikel in diese Dissertation aufgenommen, die mögliche Anwendungen verschiedener auditorischer Feedback-basierter Trainingsprogramme bei Patienten mit neurotoxischen onkologischen Therapien und Patienten mit minimalem Bewusstsein vorschlagen. Die prospektiven Einflüsse des auditorischen Feedbacks, die in diesen perspektivischen Artikeln vorgeschlagen werden, ergeben sich aus den Ergebnissen der Review- und Forschungsarbeiten, die in dieser Doktorarbeit durchgeführt wurden.

Abschließend zeigt diese Doktorarbeit den komplizierten Zusammenhang zwischen den auditiven und propriozeptiven Modalitäten, die zur Entwicklung effizienter Trainings- und Rehabilitationsmaßnahmen genutzt werden könnten. Diese Forschungsarbeit entwickelte erstmals einen Stand der Technik aus der vorhandenen Literatur zum Einfluss von auditorisch-motorischen Trainingsmaßnahmen. Diese neuartige Arbeit zeigt auch, wie selbst

erzeugte auditorische Stimulationen effektiv genutzt werden können, um propriozeptive Wahrnehmungen zu erleichtern, d.h. ein integraler Bestandteil der motorischen Steuerung und Leistung.

Schlüsselwörter: Sonifikation, motorische Steuerung, motorisches Lernen, Rehabilitation, Gelenkslageerkennung

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4. Ghai, S. (2018). Effects of real-time (sonification) and rhythmic Auditory Stimuli on Recovering Arm Function Post Stroke: A Systematic Review and Meta-Analysis. *Frontiers in Neurology, 9*(488).
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5. Effenberg, A. O., Ghai, S., Hwang, T., & Schmitz, G. (2017) Auditory modulation of multisensory representations. Proceedings of the 13th International Symposium on Computer Music Multidisciplinary Research (CMMR), Matosinhos, Portugal.
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Preface

Background

The sense of body ownership feels to be intrinsic, stable and absolute. The development of this combined sense depends upon the joint processing of sensory and motor signals that accompany an activity (Tsakiris, Longo, et al., 2010). Moreover, the perception of owning one's own body is adaptive and relates to correctly identifying oneself in an environment (Damasio, 1999; Tamar R Makin et al., 2008; Northoff et al., 2006). Research has suggested that multisensory integration of different sensory afferents might necessarily contribute towards attribution of the different body parts (Botvinick & Cohen, 1998; Tsakiris, Carpenter, et al., 2010), and also in the development of self-consciousness (Maravita et al., 2003). This joint multisensory integration of our senses helps in promoting the localized schematics for the perception of our body scheme, and the surrounding peripersonal space (Holmes & Spence, 2004).

According to Haggard and Wolpert (2005), our brain constitutes multiple representations of our body. The signals from proprioceptive receptors such as mechanoreceptors, muscle spindles, Golgi tendon organs, tactile receptors, interoceptors etc constantly project afferent signals to map the body segments, structure and surface in the primary somatosensory cortex. This information is then used to process and construct a higher order cognitive representation of the "body scheme". Here, the body scheme can be defined as a central representation of the spatial orientation of the body parts i.e. length, shape, configuration and hierarchical arrangement of limbs. This representation is not always incorporated in the conscious awareness and plays a major role in both the spatial and temporal organization of any performed bodily activity. Together, this central sensorimotor representation of the body schematics provides an adaptable, updated, supramodal, coherent representation of the body and its related activities (for a detailed explanation see (Haggard & Wolpert, 2005)).

Recent empirical evidence has supported this notion from a range of studies. For instance, findings from single neuron recordings in primates (Iriki et al., 2001; Umiltà et al., 2008), neuroimaging studies in humans (Chaminade et al., 2005; Meredith, 2002), behavioural studies in healthy population groups (Maravita et al., 2002), and lesion specific injuries in humans i.e. post traumatic neurological injuries (Berti & Frassinetti, 2000; Maravita & Iriki, 2004) have conclusively supported this notion of joint integration of multiple sensory information to develop the body scheme in the brain (for detailed neural substrate meta-analysis see Di Vita et al. (2016)). Moreover, research has pointed out the presence of a causal relationship between the sensory modalities for the development of an ultimate perceptuomotor representation (Driver & Spence, 1998). This causal relationship between the sensory modalities can be best explained in the classic medical case of peripheral deafferentation i.e. lack of proprioceptive afferent in patient I.W (Gallagher & Cole, 1995). The patient I.W was completely deafferented below the neck for tactile and proprioceptive perceptions due to a virulent disease. The patient had no additional motor paralysis symptoms. The authors Gallagher and Cole (1995) revealed that although the patient retained a high level of motor control post training. This increment in performance, however, was strongly dependent upon the concomitant visual feedback, and conscious attention from the patient. I.W needed to explicitly monitor his body segments visually to identify their specific locations and often failed to properly execute motor tasks under higher information processing constraints induced for instance, in a dual-task setting (Gallagher, 1995; Gallagher & Cole, 1995). Therefore, the authors suggested that the importance of other sensory modalities such as, proprioceptive and tactile afferents for the development of body scheme and for computing and anticipating its actions (Gentilucci et al., 1994; Sarlegna & Sainburg, 2009; Touzalin-Chretien et al., 2010). Furthermore, affirmations can also be drawn from blind population groups where learning and performing a motor action is generally automatic, even in the absence of vision, and under a dual-task setting (Limanowski & Blankenburg, 2016; Sarlegna & Sainburg, 2009).

Based on the current state of literature, proprioceptive afferent information is considered to be a predominant modality required in formulating the sensorimotor representations of the body schematics. Having said that, the role of other congruent perceptual information i.e. vision, audition etc is also substantial (Cappagli et al., 2017; Harris et al., 2015; Liu & Medina, 2017). For instance, it has been presumed that coherent sensorimotor interaction of sensory input, such as, visual, auditory afferents with proprioceptive inputs together are also imperative in developing body schematics (Samad et al., 2015). Further, research concerning "body schema" during the past decades has asserted the predominant role of inert perceptuomotor representation for the computation and development of “neural models” for envisaging (Head & Holmes, 1911; Sekiyama, 2006).

Additionally, in terms of aiding motor performance, the current state of evidence suggests a substantial role of this coherent, multisensory integration process for evaluating the peripersonal space (Cléry et al., 2015; di Pellegrino & Làdavas, 2015; Tamar R. Makin et al., 2007). Here, this the term peripersonal space can be referred to as the relative position of body segments in association with the nearby objects and environment i.e. (di Pellegrino & Làdavas, 2015; Schicke, 2007). The neural substrates of the peripersonal space are preserved in the interconnected parietal and frontal regions of the brain (Cléry et al., 2015; di Pellegrino & Làdavas, 2015; Schicke, 2007). Moreover, the primary role of the peripersonal space can be pivotal in the sensory guidance of the motor behaviour, allowing a person to mediate interactions with surrounding objects and other people (Cléry et al., 2015; di Pellegrino & Làdavas, 2015). Primarily the literature suggests the exclusive role of this computation of peripersonal space schematics as a primordial defence mechanism for survival (Roncone et al., 2016). However, recent literature suggests that this computational framework could also account for a fine-tuned motor execution of voluntary actions in the environment (Brozzoli et al., 2010; Tamar R. Makin et al., 2007; Murray & Wallace, 2011; Schicke, 2007).

Together, the importance of this internally integrated sensorimotor representation of the body scheme, movements, the peripersonal space during motor control can be affirmed from literature suggesting its predominant role during the development of neural planning models (Avanzino et al., 2016; Dreher & Grafman, 2002; Emken & Reinkensmeyer, 2005; Flanagan & Wing, 1997; Fujiwara et al., 2016; Imamizu et al., 2003; Thoroughman & Shadmehr, 1999; Daniel M Wolpert et al., 1995; D. M. Wolpert & Miall, 1996). According to Daniel M Wolpert et al. (2011), the process of internal representation involves establishment of associations between motor and sensory variables i.e. internal models, which can represent features of movement, and/or environment. Here, the central nervous system computes the development of neural models for motor commands on the basis of information from past movement experiences. Initially, the internal perceptuomotor representation of the body, movements and the environment are used to compute sets of motor commands that will execute a task. In this process, two main types of neural models govern the aspects of motor functioning (Daniel M Wolpert et al., 2011). Firstly, the feed-forward models generate sensory consequences expected from a movement i.e. the model converts motor commands and estimates outcomes in terms of sensory afference information. After this, the computations from this model in terms of its accuracy can determine whether the motor task will accomplish its goal or will have to be adjusted for attaining the desired goal. Secondly, the inverse or feedback model after the movement is concluded allows the predictive sensory model to be updated by actual feedback information (van Beers et al., 2002; Daniel M Wolpert et al., 2011; Daniel M Wolpert et al., 1995; D. M. Wolpert & Miall, 1996). Research from computational models, neuroimaging, behavioural and neuropsychological studies have conclusively supported the existence of such neural models for developing efficient motor commands (Boisgontier & Nougier, 2013; Dean et al., 2009; Flanagan & Wing, 1997; Miall & King, 2008), and ultimately facilitating motor performance.

Deficits in body scheme representation

Studies have suggested that the deficits in internal sensorimotor representation of the body scheme can account for a wide array of deficits during the execution of voluntary motor activities (Avanzino et al., 2016; Blanke et al., 2004; Boisgontier & Nougier, 2013; Haswell et al., 2009; Thaler, 2002). The discrepancies in the sensorimotor integration of information can lead to some wide range pathologies in sensory inputs, spatial organization of body segments, segmentation, and bodily coherence (Boisgontier & Nougier, 2013; Corbett & Shah, 1996; Haggard & Wolpert, 2005). As mentioned before, the updating of the body schematics is dependent the upon constant integration of sensory afferents and motor commands. Here, a disruption in the integration of these two sources of information for instance due to deficits in sensory afferent information or incongruence between sensory and motor information could affect the development, resolution of the sensorimotor representations. Thereby, affecting the development of efficient motor planning, anticipation, and impacting motor control and coordination processes of the body.

Thaler (2002) for instance proposed that a decline in the available state of sensory information might affect the state of a system and its response. Here, affirmations can be drawn from literature suggesting a neurological deficit associated decline in functioning of sensory systems (Bolognini et al., 2016; Ghai & Ghai, 2018; Ghai et al., 2017; S. Ghai et al., 2018; Ghai, et al., 2018). Neurological patients with sensorimotor deficits have also been reported to have disrupted sensorimotor representations concerning the body schematics which further affects motor planning and execution. For instance, among the aged population groups (Boisgontier & Nougier, 2013), patients affected from stroke (Bolognini et al., 2016; Murphy et al., 2017), traumatic neurological injuries (Puopolo et al., 2013), Parkinson's disease (Avanzino et al., 2013; Sharpe et al., 1983), multiple sclerosis (Fling et al., 2014), have been documented with profound deficits in sensory and motor domains.

Predominantly, a mismatch incongruency of sensorimotor information or a decrease in the quality of perceptual information can promote sensorimotor deficits concerning the spatio-temporal components of the body schematics which further affects motor planning and execution (Boisgontier & Nougier, 2013; Skoura et al., 2005). Moreover, the sensorimotor discrepancies are supposedly thought to adversely impact the repertoire of the neural models, thereby affecting the efficient development of the motor commands which might limit the system's ability to perform fine-tuned adjustments during voluntary activities. Furthermore, these sensorimotor deficits can account for a wide range of motor symptoms ranging from pain (Brun et al., 2017), fatigue (Chumacero et al.; Kuppuswamy et al., 2015), stiffness, inefficient movement patterns (Meyer et al., 2014) and more (for a detailed review see (Levit-Binnun et al., 2013)).

Interventions

Several interventions have been incorporated as rehabilitation strategies to facilitate the development of these sensorimotor representations. For instance, external sensory stimulations (Kalisch et al., 2008; Thaut, 2005), biofeedback (Bisson et al., 2007; Hasegawa et al., 2017; Sterman et al., 1974), mental imagery (Toppi et al., 2014), physiotherapy (Chen & Shaw, 2014), augmented reality (Adamovich et al., 2009; Yen et al., 2011), electrical stimulations (Jack et al., 2009; Vuckovic et al., 2015), physical therapy (McCaskey et al., 2018), and more (Makino et al., 2016). Nevertheless, recently a lot of emphases has been laid on mediating the sensory deficits together with motor rehabilitation by applying external sensory stimulation as a neuroprosthetic (Ghai et al., 2017; Ghai, et al., 2018; Hatem et al., 2016; Lam et al., 2008; Scholz et al., 2016a; Urra et al., 2015). The external sensory information has been reported to facilitate the saliency of the deficit internal sensory pathways and facilitate the spatiotemporal components of the sensorimotor representations of the motor tasks in the brain (Huang et al., 2006; Schmitz et al., 2013). This then might allow in an enhanced representation of the body schematics, the peripersonal space and support the development of predictive neural models. Thereby, assisting in the development of stable internal feedback and feedforward loop of motor planning (Effenberg, 2005; Effenberg et al., 2016; Effenberg & Schmitz, 2018; Effenberg et al., 2015; Ghai et al., 2017; Ghai, et al., 2018; Ghai, et al., 2018; Schmitz et al., 2013).

Recent research in the field of sensory neuroprosthetics have analyzed the effects of different sensory stimuli in auditory, visual and tactile domain on motor performance (Hatem et al., 2016; Lam et al., 2008; Urra et al., 2015). However, the literature predominantly supports the beneficial role of auditory stimuli (Ghai et al., 2017; Spaulding et al., 2013; Thaut & Abiru, 2010). The main reasons which underlie the beneficial effects are thought to be multifaceted. Firstly, rich neuroanatomical interconnectivity has been reported between auditory and motor cortex (Ermolaeva & Borgest, 1980; Felix et al., 2011; Thaut et al., 2014). Here, an inference can be drawn from literature evaluating auditory startle reflex on animal models (Mirjany et al., 2011; Nodal & López, 2003). Studies using Double-labelling experiments have revealed that cochlear root neurons in the auditory nerve can project bilaterally to sensorimotor paths, including synapsing on reticulospinal neurons (de la Mothe et al., 2006; Ermolaeva & Borgest, 1980; Nodal & López, 2003). Likewise, patterns of thalamocortical and corticocortical inputs unique to auditory cortex have also been reported (for a detailed review see (Read et al., 2002)). In humans, neuroimaging data confirms the presence of cortico-subcortical network involving putamen, supplementary motor area, premotor cortex and the auditory cortex especially for perceiving and processing rhythmic auditory stimuli (Chen et al., 2006; Giovannelli et al., 2012; Grahn & Rowe, 2009; Tecchio et al., 2000). Secondly, the human auditory system can consistently perceive auditory cues 20-50ms faster as compared to its visual and tactile counterparts (Nombela et al., 2013; Spidalieri et al., 1983; Thaut et al., 1999). Thirdly, the auditory system has a strong bias to identify temporal patterns of periodicity and structure as compared to other sensory-perceptual systems (Grahn, 2012; Repp & Su, 2013; Thaut et al., 1999). For instance, auditory rhythmic perception has been reported to exist well beyond the limits of temporal resolution of visual modalities i.e. when periodicities are presented at a rate of approximately 300-900 ms (Grahn, 2012; Noorden & Moelants, 1999).

Furthermore, the external auditory stimulations which when presented in a coherent multimodal context can enhance the activation in areas associated with biological motion perception i.e. the action observation system and in sub-cortical structures involving striatal-thalamic frontal motor loop (Brock et al., 2012; Scheef et al., 2009). This then might improve perceptual analysis of a movement i.e. movement and body schematics, ultimately resulting in efficient motor planning and execution (Schmitz et al., 2013). Although, several studies have provided substantial evidence concerning the beneficial effects of external auditory stimulations, such as patterned sensory enhancement, rhythmic auditory cueing, movement sonification etc. None of the studies, till date and to the best of my knowledge have elucidated the contextual relationship concerning the merging of afferent sensory inputs i.e. especially between auditory and proprioceptive modality (both of which are substantially involved in the development of body schematics). Therefore, I believe that analysing the contextual relationship between the auditory and proprioceptive sensory modalities is strongly warranted. Addressing these contextual relationships between the auditory and proprioceptive modalities will not only assist in the development of effective rehabilitation protocols but also would extend our understanding of how these sensory modalities converge to develop the effective body scheme. Moreover, certain studies have also supported the notion of the application of external sensory stimulations as a rehabilitation intervention because of their viability and cost-effectiveness (Wright et al., 2016; Young et al., 2016).

This present thesis attempts to elucidate these questions, in three distinct parts i.e. literature review, experimental studies, and future perspectives and directions. The main aim of the initial literature review for this thesis was to undermine how external auditory stimulations might influence proprioception. However, to the best of my knowledge, no study could be identified that analysed how the auditory stimulations could influence proprioception. Therefore, the initial literature review attempted to focus on the influence of external auditory stimulations on the motor outcomes in terms of gait performance, arm's reach, postural stability, and kinematic changes. These effects were studies in a range of systematic reviews and meta-analyses on population groups which were healthy, affected from neurological disorders such as, Parkinson's disease, Stroke, Multiple Sclerosis, and Cerebral Palsy. The outcomes from the literature reviews allowed in development of three distinct experimental studies where the influence of external auditory stimulations on proprioception was studied. Finally, a futurized implementation of such external auditory stimulation has been suggested in the field of rehabilitation medicine. The following section briefly outlines the structure and the main outcomes of the present thesis.

Thesis structure

In the first chapter, a systematic review and meta-analyses analysed the influence of rhythmic auditory stimulations on spatiotemporal parameters of gait in healthy population across different age groups. Here, a systematic review of 34 studies (PEDro score 4.7 i.e. "fair quality") involving 854 participants i.e. 499 young and 355 elderly participants revealed a beneficial effect of rhythmic auditory stimulations on the spatiotemporal parameters of gait such as gait velocity, stride length, and cadence. A meta-analysis of the included studies revealed a positive *large* effect of rhythmic auditory cueing on gait velocity i.e. Hedge's g: 0.85, and cadence g: 1.1. A *medium* positive effect size on stride length g: 0.61 and a *small* positive effect on the coefficient of variability on stride time g: 0.41. Additionally, this meta-analysis also revealed the beneficial effects of rhythmic auditory stimulations to counteract higher information processing constraints induced during a dual-task scenario. For instance, a *large* positive effect size for gait velocity was observed for young participants performing a dual-task with instructions to walk fast g: 0.81, and for elderly g: 0.58. This review for the first time evaluated the influence of rhythmic auditory cueing in population groups across aging. Moreover, this review provides an important insight on how rhythmic auditory stimulations could be incorporated in training interventions for healthy population groups to promote auditory motor entrainment and to reduce higher cognitive constrains that promote fall related injuries.

In the second chapter, A systematic review and meta-analyses were carried out to analyse the influence of rhythmic auditory stimulations on spatiotemporal parameters of gait in patients affected by Parkinson's disease. Here, a systematic review of 50 studies (PEDro score 5.4 i.e. "fair quality") involving 1892 participants revealed a beneficial effect of rhythmic auditory stimulations on spatiotemporal parameters of gait such as gait velocity, stride length, and cadence. A meta-analysis of the included studies revealed a small effect of rhythmic auditory cueing on gait velocity i.e. Hedge's g: 0.23, and a *medium* positive effect on stride length g: 0.42, double limb support phase g: 0.5. Moreover, a negligible *small* reduction in cadence g: -0.05, and a *large* reduction in turn time g: 2.2 were reported. This review for the first tie demonstrated that training with rhythmic auditory stimulations promoted a stabilizing ait for patients with Parkinson's disease i.e. cadence which usually increases during a shuffling gait in patients with Parkinson's disease was reduced. The article predominantly reviewed and reported the neurophysiological mechanisms underlying "kinesia paradoxica" which utilize the preserved structures of the brain to bypass the deficit internal timing circuitry involving the basal ganglia, and thalamus. Furthermore, the article also for the first time reported the specific training dosages that can be incorporated with the application of rhythmic auditory stimulations i.e. a minimal training of 20-45 minutes per session for three to five days a week. Moreover, this review provides important insights into how auditory stimulations could be incorporated in training interventions for patients with Parkinson's disease to promote auditory-motor interactions for reducing higher cognitive constraints that promote fall-related injuries.

In the third chapter, a systematic review and meta-analyses were carried out to analyse the influence of rhythmic auditory stimulations on spatiotemporal parameters of gait in patients affected from stroke. Here, a systematic review of 37 studies (PEDro score 5.7 i.e. "fair quality") involving 938 participants revealed a beneficial effect of rhythmic auditory stimulations on spatiotemporal parameters of gait such as gait velocity, stride length, and cadence. A meta-analysis of the included studies revealed a *medium* effect of rhythmic auditory cueing on gait velocity i.e. Hedge's g: 0.73, stride length g: 0.58, and cadence: 0.75. Moreover, enhancements in dynamic postural stability were demonstrated by a large effect size reduction in timed up and go test g: -0.76. This review overcame the limitations of the previously published systematic reviews and meta-analysis and demonstrated that training with rhythmic auditory stimulations promoted a stabilizing gait for patients with stroke. Furthermore, the article also for the first time reported the specific training dosages that can be incorporated with the application of rhythmic auditory stimulations i.e. a minimal training of 20-45 minutes per session for three to five days a week. This review provides important implications for developing essential training interventions by modifying auditory signal characteristics for enhancing the saliency of sensory information. Further, this might ultimately support the development of perceptuomotor representations and enhance motor performance and learning.

In the fourth chapter, a systematic review and meta-analyses were carried out to analyse the influence of rhythmic auditory stimulations, real-time auditory feedback on arm recovery following stroke. Here, a systematic review of 23 studies (PEDro score 5.7 i.e. "fair quality") involving 585 participants revealed a beneficial effect of rhythmic auditory stimulations on arm recovery parameters such as Fugl-Meyer assessment, elbow range of motion, Wolf motor function test, and stroke impact scale. A meta-analysis of the included studies revealed a *large* effect of the auditory stimulation strategies on Fugl-Meyer assessment g: 0.79, stroke impact scale g: 0.95, a *medium* positive effect on elbow range of motion g: 0.37. A negative *medium* effect was observed in wolf motor function time test g: -0.55. In a novel aspect, the review for the first time synthesized the data for the influence of real-time auditory feedback or sonification on arm recovery. Here, the beneficial effects of real-time auditory feedback were demonstrated on Fugl-Meyer scores as compared to rhythmic auditory stimulations i.e. g: 1.3 as compared to 0.6 observed with rhythmic auditory cueing, respectively. Furthermore, the article also for the first time reported a specific auditory-motor training dosage that can be incorporated with the application of rhythmic auditory stimulations i.e. a minimal training of 30 minutes to 1 hour per session for three to five days a week. This review provides important implications for developing essential training interventions by modifying auditory signal characteristics for enhancing the saliency of sensory information. Moreover, the article also provides important implications of incorporating bilateral training interventions with rhythmic auditory cueing. This article in depth focusses on the shared and distinct neurophysiological mechanisms between the rhythmic auditory stimulations and real-time kinematic auditory feedback i.e. sonification strategies.

In the fifth chapter, a systematic review and meta-analyses were carried out to analyse the influence of rhythmic auditory stimulations on gait performance in people with cerebral palsy.

Here, a systematic review of nine studies (PEDro score 5.7 i.e "fair quality") involving 227 participants i.e. 108 children and 119 adults revealed a beneficial effect of rhythmic auditory stimulations on spatiotemporal, kinematic parameters of gait in people with cerebral palsy. A meta-analysis of the included studies revealed a *large* effect of rhythmic auditory cueing on gait velocity Hedge's g: 1.1. A *medium* positive effect was observed on stride length g: 0.50, and cadence g: 0.30. Moreover, enhancements in dynamic gait stability were demonstrated by a joint kinematic analysis of lower limb demonstrated in gait dynamic index. Here, a *large* effect size in positive domain in g: 0.90 indicated beneficial effects of rhythmic auditory cueing on kinematic parameters of gait. This review for the first time demonstrated that training with rhythmic auditory stimulations promoted a stabilizing gait for people with cerebral palsy. Furthermore, the article also for the first time reported the applicability of tainting intervention with auditory cueing as a home based, cost-effective rehabilitation intervention.

In the sixth chapter, a systematic review and meta-analyses were carried out to analyse the influence of rhythmic auditory stimulations on gait performance in patients with multiple sclerosis. Here, a systematic review of five studies (PEDro score 5.2 i.e. "fair quality") involving 188 participants revealed a beneficial effect of rhythmic auditory stimulations on spatiotemporal parameters of gait in people with cerebral palsy. A meta-analysis of the included studies revealed a *large* positive effect of rhythmic auditor stimulations on cadence Hedge's g: 1.0, a *medium* positive effect on gait velocity Hedge's g: 0.67 and stride length g: 0.7. Moreover, enhancement in dynamic gait, postural stability was demonstrated by a small effect size reduction in the Timed 25 feet walking test g: -0.17. This review revealed novel outcomes from neuroimaging studies suggesting the incidences of white matter plasticity with musical training. Moreover, this review suggests the implications of home-based interventions with rhythmic auditory cueing and mental imagery to promote enhancements in spatiotemporal gait parameters.

In the seventh chapter, a systematic review and a meta-analysis evaluated the influence of information processing constraints induced by dual-tasks on postural stability in population groups across aging, and neurological disorders such as stroke, and multiple sclerosis. Furthermore, the secondary analysis involved elucidating the influence of training with a cognitive-motor dual-task i.e. dual-task training. The reason why this analysis was performed was to study how information processing cognitive constraints might play a key role in influencing the autonomic functioning i.e. proprioception needed to maintain postural stability. Here, a systematic review of 42 studies (PEDro score 4.7 i.e. "fair quality") involving 1480 participants revealed a beneficial effect of dual-task training for enhancing postural stability. Moreover, an inverse relationship between the complexity of dual-task and postural stability was also reported in the review. Firstly, the meta-analysis report revealed that performing a dual-task training resulted in enhanced postural stability with a *large* effect size i.e. a positive effect in Berg Balance Scale Score Hedge's g: 1.63. Here, as a novel finding, the analysis revealed that a variable priority ensured during a training intervention allows enhanced performance in postural stability as compared to a fixed priority regimen. Moreover, these outcomes bore practical applications that helped in the development of efficient audio-motor training protocols in the experiments performed in this thesis. For instance, evaluation of variable priority parameter allowed us to develop our instructions in the following experimental designs as to not explicitly ask the participant to focus specifically on either the proprioceptive task or the auditory feedback. The meta-analysis also revealed an age-related decline in cognitive performance. Finally, as a novel aspect, this review for the first time demonstrated the neurophysiological mechanisms suggesting an increased complexity with the verbal component of a dual-task. Outcomes from this systematic review and meta-analysis can allow future studies to develop effective rehabilitation protocols to facilitate cognitive performance and reduce falls.

These chapters concluded the literature review section of the thesis. Hereon, interpretations from the literature review assisted in the development of research hypothesis for the thesis to elucidate the contextual relationship between auditory and proprioceptive modalities. Here, the studies were designed to critically analyse the influence of external auditory stimulations i.e real-time kinematic auditory feedback (sonification) on proprioceptive perceptions, intermodal learning and its joint influence during internal motor simulation of movements.

The predominant role of real-time auditory feedback has been emphasized in rehabilitation by several studies (Aman et al., 2014; Gay et al., 2010; Laskowski et al., 2000; Lephart et al., 1997; Ribeiro & Oliveira, 2007; Rosenkranz et al., 2009). Therefore, in this present thesis, I believe that exploring the possible influences of concurrent auditory feedback on proprioception might provide multifaceted benefits. First and foremost, the outcomes might provide a better understanding of intervention designs in rehabilitation, and sports settings with auditory feedback. Moreover, the evaluation of audio-proprioceptive coupling during an arbitrary action (knee-joint proprioception) might allow a better understanding of the transmodal activity of auditory and motor domains beyond music and language (Altenmüller et al., 2009). Finally, a better comprehensive understanding might be developed to support the psychophysical (Butler et al., 2012), neurophysiological (Ishikawa et al., 2015), studies analyzing the multisensory and cross-modal integration between auditory and proprioceptive domains. Till this date, only a handful of researchers have attempted to answer the possible effects of real-time auditory feedback on proprioception (Danna & Velay, 2017; Dyer et al., 2017; Ghez et al., 2000; Scholz et al., 2016b). However, their interpretations of proprioceptive-auditory substitution are mostly speculative. For instance, none of the performed studies excluded vision during the performance of the motor task. As a result, possible influences from the visual modality during multisensory or cross-modal integration processes can be expected (Lonn et al., 2000; Plooy et al., 1998; Verschueren et al., 1998). Research indicates the importance of isolating inputs from specific sensorimotor structures to provide a better understanding of direct influence over proprioception (Gay et al., 2010). Therefore, in the following studies, our group analysed the contextual relationship between the auditory and proprioceptive modality.

In the eighth chapter, fifty healthy participants were randomly allocated to control (n=15), and experimental group I (15), and experimental group II (20). This experiment was performed in two steps. Firstly, the control group and experimental group I performed an active knee-repositioning task using their dominant leg, with/without additional real-time auditory feedback where the frequency was mapped in a convergent manner to two different target angles (40° and 75°). Statistical analysis revealed significant enhancement in knee re-positioning accuracy for the constant and absolute error with real-time auditory feedback, within and across the groups. Besides this convergent condition, we established a second divergent condition. Here, a step-wise transposition of frequency was performed to explore whether a systematic tuning between auditory-proprioceptive repositioning exists. No significant effects were identified in this divergent auditory feedback condition.

After the first experiment, the experimental group II (n=20) was further included to better understand the relationship between subliminal pitch transposition and proprioceptive perceptions. Here, we investigated the influence of a larger magnitude and directional change of step-wise transposition of the frequency. In a first step, results confirm the findings of experiment I i.e. auditory feedback enhanced knee proprioceptive repositioning “transiently”. Moreover, significant effects on knee auditory-proprioception repositioning were evident when divergent auditory feedback was applied. During the step-wise transposition, participants showed systematic modulation of knee movements in the opposite direction of transposition. The results from this study provide evidence of the intricate relationship between the auditory and proprioceptive modality. The experiment concludes that providing real-time auditory feedback can enhance knee repositioning accuracy in a transient manner.

In the ninth chapter, thirty healthy participants were randomly allocated to control (n=15), and experimental groups (15). Participants performed an active knee-repositioning task, bilaterally, with/without additional real-time auditory feedback. Here, the frequency of the auditory feedback was mapped to four target angles (20°, 40°, 60° and 80°). Retention measurements were performed on the same four angles, without auditory feedback, after 15 minutes, 24 hours of the final proprioceptive test. Thereafter, a "generalized" knee proprioceptive test was performed to assess motor skill transfer on three untrained angles (15°, 35°, 55°). Statistical analysis revealed significant enhancement in knee proprioception with real-time auditory feedback. This enhancement in proprioception was also evident in tests performed between the auditory-motor training blocks i.e. 5th and 6th blocks (without auditory feedback) in the experimental group. Enhancement in proprioception also remained stable during delayed retention measurements (post 15-minute, 24-hour). Similarly, enhancement in the "generalized" proprioceptive accuracy on untrained angles was evident in the experimental group as compared to the control group. This study extends the results of the previous experiment and demonstrates beneficial effects of real-time auditory feedback to facilitate intermodal learning by enhancing knee proprioception in a retainable and a generalized manner.

In the tenth chapter, forty-two healthy participants were randomly allocated into three training groups. This study aimed to primarily extend the findings of the previous study i.e. chapter ten. All the groups initially trained bilaterally at the knee joints with real-time auditory feedback for four target angles (20°, 40°, 60° and 80°). Thereafter, training was performed with/without mental practice, and with/without auditory guided mental practice. During mental imagery condition, the participants were verbally instructed to imagine the knee position at the trained four angles whenever instructed. Retention measurements were performed after the training blocks i.e. after 15 minutes and 24 hours of the final test. A generalized proprioceptive test assessed the unspecific transfer of proprioception on four different angles (10°, 30°, 50° and 70°). Statistical analysis revealed significant enhancement in proprioceptive accuracy for the auditory guided mental practice group as compared to the group performing mental practice without auditory guidance, and the group performing no mental practice. All the groups demonstrated an enhancement in proprioception during a generalized unspecific proprioceptive test. Further, a strong correlation was reported for enhanced levels of attention for auditory guided mental practice group as compared to unguided mental practice group. This study, for the first time demonstrates beneficial effects of auditorily guided mental imagery on knee proprioception and a suggests strong correlation with attention. This trial was registered in the German Clinical Trial Registry DRKS00014244.

In conclusion, these experimental studies demonstrate the potential of the such a spatial-temporally congruent auditory feedback for enhancing motor perception and mediating intermodal learning. In the second and the third experimental studies, I was also able to substantiate the findings of the meta-analyses which suggested a shorter auditory-motor training duration i.e. 20-45 minutes, which could effectively establish robust motor learning parameters. Moreover, the third experiment demonstrates novel findings of the joint application of auditory-motor training with an internal motor simulation of movements to possibly extend the benefits of physical training. Nevertheless, each chapter outlines detailed steps that could be implemented in future studies to address the limitations in the current and the future state of literature.

In the eleventh chapter, a novel rehabilitation intervention as a futuristic perspective was published. Here, a rehabilitation strategy has been mentioned while jointly incorporating multimodal feedback augmenting strategies for instance, real-time auditory feedback and virtual reality. This perspective proposes how a sensory stimulus could be associated with emotion such as, fear to facilitate rehabilitation in patients with higher cortical dysfunctions. In this chapter possible scenarios are discussed during which memory consolidation might be instigated habitually (implicitly) and might also promote internal simulation of movements independent of the cortical structures. This perspective suggests delivery of subliminal, aversive and kinematic audio-visual stimuli via neuroprosthetics in patients with neocortical dysfunctions. Moreover, possible scenarios are suggested by which these stimuli might bypass damaged neocortical structures and possibly assisting in motor relearning. Anticipated neurophysiological mechanisms and methodological scenarios have been discussed in this perspective. This approach introduces novel perspectives into neuropsychology as to how subcortical pathways might be used to induce motor re-learning.

In the twelfth chapter, a perspective is presented to portray the influence of external auditory stimulations on rehabilitation in patients with cancer. Typically, patients undergoing chemotherapy, radiotherapy and immunotherapy are subjected to neurotoxicity in the central and peripheral nervous system. These neurotoxic changes promote joint adverse effects in motor, sensory and cognitive domains, further predisposing the patients towards fall related morbidity and mortality. Based on the findings of our literature review and experimental studies this chapter as a perspective discusses the possible underlying mechanisms by which external auditory stimulations might influence motor performance in patients subjected to neurotoxic changes due to cancer treatment.

Taken together, the current thesis demonstrates the strong influence of auditory system over the motor domain modality. In the group of systematic reviews and meta-analyses the synthesized published literature conclusively suggests the effects of auditory stimulations on motor control. Furthermore, the experimental evidence from chapter nine, ten and eleven provide evidence of the contextual, intricate relationship between the auditory and proprioceptive modalities. Here, the evidence suggests that high level of spatiotemporal congruency between the sensory modalities i.e. auditory and proprioceptive modality can provide a concomitant increase in the sensory perception of proprioception and its intermodal learning. Finally, in the range of experiments, we demonstrated the strong influence of kinematic real-time auditory feedback on motor perception, intermodal learning and its joint effects with internal motion simulation. The clinical implications of the auditory modality in modern rehabilitation settings i.e. musculoskeletal and neurological conditions have been discussed in detail in the current thesis.

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Literature Review

Chapter 1: Effect of rhythmic auditory cueing on aging gait: A systematic review and meta-analysis

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Review

Effect of Rhythmic Auditory Cueing on Aging Gait: A Systematic Review and Meta-Analysis

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ABSTRACT: Rhythmic auditory cueing has been widely used in gait rehabilitation over the past decade. The entrainment effect has been suggested to introduce neurophysiological changes, alleviate auditory-motor coupling and reduce cognitive-motor interferences. However, a consensus as to its influence over aging gait is still warranted. A systematic review and meta-analysis was carried out to analyze the effects of rhythmic auditory cueing on spatiotemporal gait parameters among healthy young and elderly participants. This systematic identification of published literature was performed according to PRISMA guidelines, from inception until May 2017, on online databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST. Studies were critically appraised using PEDro scale. Of 2789 records, 34 studies, involving 854 (499 young/ 355 elderly) participants met our inclusion criteria. The meta-analysis revealed enhancements in spatiotemporal parameters of gait i.e. gait velocity (Hedge's g: 0.85), stride length (0.61), and cadence (1.1), amongst both age groups. This review, for the first time, evaluates the effects of auditory entrainment on aging gait and discusses its implications under higher and lower information processing constraints. Clinical implications are discussed with respect to applications of auditory entrainment in rehabilitation settings.

Key words: cueing, stability, rehabilitation, cognitive-motor interference, balance, entrainment, dual task

Higher prevalence to fall with aging is a matter of concern for medical practitioners [1-3]. According to WHO, every year approximately 37 million people are seriously injured, and further 424,000 people perish from falls globally [4]. Degenerative changes in cardiovascular [5], sensorimotor (somatosensory, vestibular), and neuromuscular (cortical, extra-pyramidal, cerebellum) domains are suggested to be the main reasons often leading to falls [6-8]. Moreover, medications, depression, and anxiety are additional precipitators [9-11]. Falls impact quality of life [12, 13], and inflict heavy costs at both individual, economic levels [14, 15].

Studies suggest that highest incidences for falls occur during locomotion [16-18]. In fact, aging has been associated with modifications in spatiotemporal [19], electromyographic [20], and kinematic [21], gait parameters, which in-turn are important predictors for fall. For instance, clinical characteristics for reductions in gait velocity, stride length, cadence, single limb support phase, and enhancements in stride time, double limb support phase, gait variability [22, 23], have been well documented (see also Jahn, et al. [6]). The kinematic analysis also suggests a reduction in angular impulse, torque at ankle, knee, and hip joint with aging gait [24]. Together, these factors aggravate static and dynamic instability and increase predisposition to fall. Likewise, degenerative changes observed in psychological domain in elderly might also contribute in modifying stability [25,

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26], and cognitive processing [27, 28]. Reelick, et al. [23], for instance, suggested a reduction in self-confidence with aging, and history of falls often leading to a peculiar "fear of falling" [29, 30]. Furthermore, this "fear" has been reported to additionally modify the stability during static, and dynamic postures [9, 31, 32]. Giladi, et al. [32], referred such modified gait pattern as a "cautious or fearful gait" [23]. Although these modifications are aimed to enhance stability during locomotion, they, in turn, develop a stiff, slow and unsteady gait pattern [33]. Moreover, this "fear of falling" or "cautious gait" might promote "internal" attentional focus [34], explicit motor control [25], and can eventually alleviate cognitive-motor interferences [35] (see also Young and Mark Williams [33]). Masters and Maxwell [27] suggested that such an attempt to consciously monitor or control an autonomic movement, such as posture, or gait might adversely affect its performance. Also, such higher information processing constraints have demonstrated detrimental effects on proprioceptive perceptions [36-38], which are integral for autonomic stability [36]. In addition, literature suggests that younger population groups, on the contrary, have a more resilient and stable psycho-physiological stature [35, 39]. However, falls are not uncommon [10]. Possibly, environmental [10], and lifestyle factors might play a considerable role [40]. Schabrun, van den Hoorn, Moorcroft, Greenland and Hodges [41] reported texting and reading while walking (common among youngsters) to adversely impact gait stability [42], by increasing cognitive-motor interferences [43]. Consequently, such higher attentional constraints predisposing to falls might possess serious life-threatening consequences under "high-stress" environments [8, 44], for both younger and elderly age groups.

Several strategies have been suggested in literature to curb these psycho-physiological deficits, such as pharmacotherapy (Methylphenidate) [5], virtual-reality [45], biofeedback [46], physical/occupational therapy [47], physical exercise [48], dance [49], treadmill [50], external sensory cueing [51, 52], martial arts [53, 54], dual-task training [5, 36], and more [55]. Amongst these, external sensory entrainment in rehabilitation is an emerging yet under-evaluated area of interest [56]. For instance, external auditory cueing can enhance motor performance in patients with sensorimotor deficits [57], even better vis-a-vis tactile and visual entrainment [56-59]. Possibly, due to lower rhythm perceptional thresholds for auditory cortex [56, 60, 61], rich neural connectivity [52, 62, 63], and better temporal precision [52, 62, 63]. Moreover, published literature suggests beneficial effects auditory entrainment during gait amongst patients affected from traumatic neurological injuries [64], multiple sclerosis [65], stroke [66], parkinsonism [57], and even healthy young and elderly participants [67, 68]. The auditory entrainment might supplement sensory deficits present in fall prone individuals [69], and aid in performance by mediating multifactorial neurophysiological changes [52, 70], enhancing auditory imagery [71-74], reducing variability in musculoskeletal activation [75], and possibly cognitive-motor interference [67, 76].

Additionally, rhythmic auditory entrainment is cheap [77], viable [78], easy to follow and has shown enhancements even during unsupervised home-based training programs [79, 80]. This intervention can be a useful rehabilitation tool in middle and lower income countries, where poor healthcare services [81], might precipitate to majority of the fall related deaths [4]. Thereby, strongly warranting the need for such economical, and efficient rehabilitation techniques.

High-quality systematic reviews and meta-analyses have been carried out to evaluate the beneficial effects of rhythmic auditory cueing on gait in patients affected from neurological conditions, such as stroke, and parkinsonism [57, 58, 66]. However, to the best of our knowledge, no review to date has analyzed the effects of rhythmic auditory cueing on aging gait. Therefore, we attempted to develop a state of the art knowledge for the use of rhythmic auditory cueing in gait rehabilitation across healthy population groups. The main aim of this review is to understand the effects of auditory entrainment on spatiotemporal, variability parameters for gait among young, and elderly age groups. The review also discusses possible applications of auditory entrainment in rehabilitation and activities for daily living.

METHODS

This review was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA statement [82].

Data sources and search strategy

Academic databases such as Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE and PROQUEST were searched from inception until July 2017. A sample search strategy has been provided in (Supplementary Table 1).

Data extraction

Upon selection for review, the following data were extracted from each article; author, date of publication, selection criteria, sample size, sample description (gender, age, health status), disease duration, intervention, characteristics of auditory feedback, dual-task, outcome measures, results, and conclusions. The data were then summarized and tabulated (Table 1).

The inclusion criteria for the studies was (i) Performed studies were either randomized controlled trials, cluster randomized controlled trials or controlled clinical trials; (ii) Studies reporting reliable and valid spatiotemporal gait parameters (iii) Studies reporting dynamic aspects of gait stability (iv) Studies qualified PEDro methodological quality scale (≥4 score); (v) Experiments conducted on human participants; (vi) Published in a peer-reviewed academic journal; (vii) Articles published in English and German languages.

Quality & risk of bias assessment

The quality of the studies was assessed using the PEDro methodological quality scale [83]. The scale consists of 11 items addressing external validity, internal validity, and interpretability and can detect potential bias with fair to good reliability [84], and validity [83]. A blinded rating of the methodological quality of the studies was carried out by the primary reviewer. Ambiguous issues were discussed with second (IG), third (AOE) reviewer and consensus was reached. Included studies were rated, and interpreted according to scoring of 9-10, 6-8 and 4-5 considered of “excellent”, “good” and “fair” quality [85], respectively. Inadequate randomization, non-blinding of assessors, no intention to treat analysis and no measurement of compliance were considered as major threats to biasing [86].

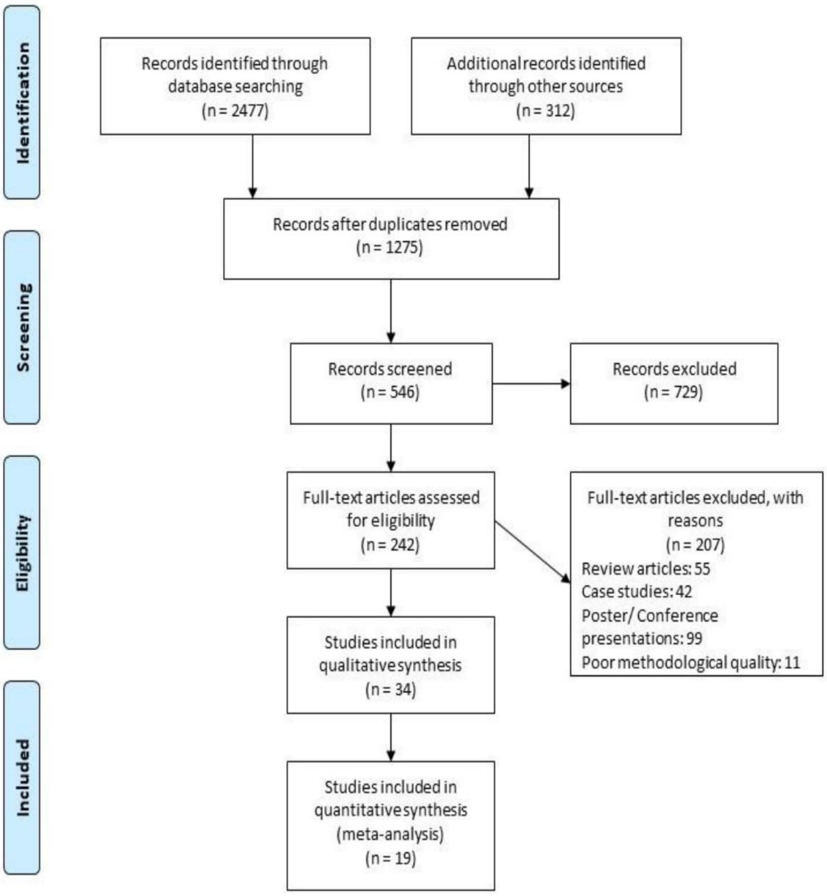

Figure 1. PRISMA flow chart for the inclusion of studies.

Data Analysis

This systematic review included a meta-analysis approach [87]. The presence and lack of heterogeneity asserted the use of either random or fixed effect meta-analysis [88], respectively. A narrative synthesis of the findings structured around the intervention, population characteristics; methodological quality (Table 1) and the type of outcome are provided. Likewise, summaries of intervention effects for each study are also provided in a tabular form (Table 1). A meta-analysis was conducted between pooled studies using CMA (Comprehensive meta-analysis V 2.0, USA). Heterogeneity between the studies was assessed using I^2 statistics. The data in this review was systematically distributed and for each available variable pooled, dichotomous data was analyzed and forest plots with 95% confidence intervals are plotted. The weighted effect sizes are reported as Hedge's g [89]. Thresholds for interpretation of effect sizes were as follows; a standard mean effect size of 0 means no change, negative effect size means a negative change, mean effect size of 0.2 considered a *small* effect, 0.5 a *medium* effect and 0.8 a *large* effect [90]. Interpretation of heterogeneity via I^2 statistics was as; 0-0%, 25%, 75% as negligible, moderate and substantial heterogeneity, respectively. Meta-analysis reports including heterogeneity among studies were evaluated to determine the reason of heterogeneity, and the included studies were then pooled separately and analyzed again. The alpha level was set at 95%.

RESULTS

Characteristics of included studies

Our initial search yielded a total of 2789 studies, which on implementing our inclusion/exclusion criteria, were reduced to thirty-four (Fig. 1). Data from the included studies have been summarized in (Table 1). Of the thirty-four included studies, one was randomized controlled trial, and thirty-three were controlled clinical trials.

Table 1. Studies analyzing the effects of rhythmic auditory cueing on gait.

Author	**Sample description, age: (M ± S.D years)**	**PEDro score**	**Assessment tools**	**Research design**	**Auditory feedback elements**	**Conclusion**
Dotov, et al. [100]	7F, 12M (60)	6	Coefficient of variation of inter-stride interval, cadence, gait velocity, stride length, DFA of short-long term series of inter-response-interval correlations, circular statistics for synchronization of footfall & beat	Pre-test, gait performance with/without RAC (no variability, biological variability, non-biological variability; randomized), post-test	RAC with no variability, biological variability & non-biological variability at +10% of preferred cadence Magnitude of biological & non-biological variability: 2% of inter-beat-interval Metronome sequence: triangle timbre Musical excerpts Amplitude modulated noise: Modulated on musical excerpt with drum ensemble, discarding tonal information	Significant enhancement in coefficient of variation for inter-stride interval after RAC in all conditions. Significant effect of RAC that was amplitude modulated for biological variability as compared to IC on short-long term correlation for term series of inter-response-interval correlations. Enhanced synchronization, cadence but reduced short-long term correlation for term series of inter-response-interval correlations during metronome based IC as compared to feedback with amplitude modulated for biological variability.
Maculewicz, et al. [141]	5F, 15M (24.4±3.2)	4	Mean square error for the asynchrony between target & performed measure & trend of tempo change obtained from slope of line fitted to measured tempo, questionnaire	Gait performance with/without real-time auditory feedback (adaptive), RAC (constant) &/or haptic feedback, with instructions to perform gait at preferred cadence or the tempo of the sound	Real-time auditory feedback (adaptive), RAC (constant) by sine, wood & gravel sounds	Significantly enhanced step wise interaction with real time auditory feedback with (sinusoid >wood>gravel). Significant reduction in asynchrony with audio-haptic feedback & real-time auditory feedback as compared to no feedback. Significant enhancement in comfort for perceiving haptic & audio-haptic feedback as compared to haptic only or no feedback in self-reported questionnaire.
Schreiber, et al. [97]	5F, 12M (37.4±15.7)	4	Cadence, gait speed, rhythmicity, stance time, double support time, gait symmetry, step length, stride length,	Gait performance with/without RAC cueing at preferred, reduced cadence (instructions & cueing randomized)	RAC at preferred & reduced cadence	Significantly reduced gait speed with RAC at preferred cadence as compared to preferred speed gait without cueing. No effect of RAC on cadence, rhythmicity, stance time, double support time, gait symmetry for RAC at preferred

			step width, EMG activity of (tibialis anterior, soleus, gastrocnemius medialis, vastus medialis, rectus femoris, semitendinosus, gluteus medius & gluteus maximus), kinematics for pelvis, hips, knees & ankle joint (sagittal, frontal, transverse plane)			or reduced cadence as compared to no cueing. Significantly reduced step width with RAC at reduced cadence as compared to reduced speed gait without cueing. Significantly enhanced step length with RAC at reduced cadence as compared to reduced speed gait without cueing. Significant differences for ankle dorsiflexion, hip flexion & hip abduction of the gait cycle with RAC at reduced cadence as compared to reduced speed gait without cueing.
Hamacher, et al. [104]	Young: 8F, 12M (24.9±4.1) Old: 11F, 9M (67.4±5.3)	5	Stride length, minimum foot clearance, stride time, stride to stride analysis (mean & coefficient of variation)	Gait performance with/without dual-task (arithmetic subtraction in 3's task) &/ RAC (randomized)	RAC at preferred cadence	Significant enhancement in stride length, stride time with RAC (with/without dual-task) in both younger & older adults. Significantly enhanced coefficient of variation of stride time in older participants under dual-task condition & with RAC Enhancement in coefficient of variation of stride to stride in older participants under dual-task condition & with RAC
Terrier [96]	22F, 14M (33±10)	4	DFA of coefficient of variability for stride time, stride length, stride speed, stride length, stride speed & stride time	Gait performance on treadmill with/without visual (stepping stones), RAC	RAC at preferred cadence	Significant reduction in stride time & stride speed with RAC as compared to no cueing. No effect on coefficient of variation for stride length, stride time & stride speed (mean & coefficient of variation) with RAC
Roerdink, et al. [162]	5F, 7M (28±6)	5	Stride-to-stride DFA for persistence of stride time, stride length, stride speed & anterior-posterior center of pressure sway	Treadmill gait performed with/without RAC with isochronous metronome & non-isochronous metronome containing inter-beat interval sequences with distinct scaling exponents (randomized)	RAC with (IC) containing equidistant inter-beat interval & 4 (non-isochronous) metronome containing inter-beat interval sequences with distinct scaling exponents Frequency: 600Hz RAC with mean inter-beat intervals being equal to mean stride time of preferred cadence.	Significant effect of IC cueing for changing the stride-to-stride fluctuations of stride length & stride time to anti-persistent & vice versa for the non-IC. Significant effect of isochronous & non-isochronous metronome cueing for changing the stride-to-stride fluctuations of stride speed to anti-persistent for both the cueing.
Wright, Spurgeon and Elliott [163]	8F, 2M (20-33)	5	Mean asynchrony, step time variability & mean percentage step correction	Gait performance with/without RAC &/or visual cueing	RAC, 500 ms (cue duration 30 ms), 800Hz	Significant enhancement in & mean percentage step correction with audio & audio-visual cueing as compared to only visual cueing Significant reduction in mean synchrony of step with RAC with audio-visual cueing as compared to only audio or visual cueing. Significant reduction in step time variability with audio & audio-visual cueing as compared to only visual cueing
Young, et al. [138]	6F, 4M (63.9±4) II: same as I III: same as I	5	I: Mean step length, % change stride length, mean step duration, % change in variability of stride length, duration II: same as I III: same as I	I: Gait performance with/without verbal instruction, verbal instruction-metronome cueing, stepping sound, stepping sound-verbal instructions, for small and wide stride length (randomized) II: Gait performance with/without stepping sound, verbal instruction-stepping sound feedback, synthesized gravel sound, synthesized gravel sound-verbal instructions, for	I: RAC (Ct: 550-649ms, Exp: 600-700ms), foot step feedback on gravel (500, 600, 700ms) II: RAC (Ct: 550-649ms, Exp: 600-700ms), foot step feedback on gravel (500, 600, 700ms), synthesized gravel step sound corresponding to plantar force (developed by using ground reaction forces vector to modulate both intensity envelop, and central frequency of bandpass filter	Significant enhancement in stride length for healthy Ct in all cueing conditions. No effect of auditory cueing or instructions on mean step duration. Significant reduction in stride length variability with synthesized feedback as compared to footstep feedback-verbal instruction, synthesized feedback-verbal instructions. Significant reduction in stride length variability with stepping, synthesized feedback, stepping-verbal instructions. Significant enhancements in stride length with rhythmic auditory cueing (synthesized) and motor imagery together. No effect on stride duration parameters.

				small and wide stride length (randomized) III: Gait performance with/without motor imagery, motor imagery-stepping sound feedback, synthesized gravel sound, synthesized gravel sound-motor imagery, for small and wide stride length (randomized)	applied to stochastic noise impulse signal) III: same as II	
Leow, et al. [105]	24F, 19M (18-20)	5	Stride velocity, step length, step time, stride width, double support, & coefficient of variability for stride length	Gait performance with/without rhythmic music, RAC (low/high groove) at 0% & +22.5% of preferred cadence	RAC (low/high groove music) at 0% & +22.5% of preferred cadence (50ms 1kHz sine tones)	Significant enhancement in stride velocity with rhythmic music cueing (high groove) & metronome at +22.5% of preferred cadence as compared to no cueing. Significant reduction in double support with metronome cueing at 0% & +25% of preferred cadence as compared to no cueing. Significant reduction in step length with high groove music at +25% of preferred cadence. Significant reduction in step time in low (0% also), high groove music cueing & RAC at +25% of preferred cadence cueing as compared to no cueing. Significant enhancement in coefficient of variability for stride length with low & high groove RAC at 0% & +25% of preferred cadence.
Sejdić, et al. [164]	8F, 7M (23.9±4.7)	5	Gait speed, mean stride interval, stride interval variability, stride interval dynamics, dynamic stability of gait in anterior-posterior, vertical & medio-lateral dimension (short: between 0th & 1st stride & long: between 4th & 10th stride, term Lyapunov exponent)	Gait performance with rhythmic auditory, visual & haptic cueing (randomly spate or together) at preferred cadence during 2 sessions	RAC at preferred cadence	Significantly reduced stride interval variability with RAC (alone & combined with visual & haptic cueing) as compared to no cueing condition. Significantly reduced stride interval dynamics (long term Lyapunov exponent) with RAC (alone & combined with visual & haptic cueing) as compared to no cueing condition. Significant enhancement in dynamic stability of gait with RAC (alone & combined with visual & haptic cueing) as compared to no cueing condition.
Terrier and Dériaz [165]	10F, 10M (36±11)	4	DFA on time series of stride time, stride length & stride speed Short & long-term local dynamic stability in anterior-posterior & medial-lateral direction	Gait performance on treadmill at slow (0.7 times preferred cadence), fast (1.3 times preferred cadence) & at preferred cadence with/ without RAC (randomly)	RAC at slow (0.7 times slower than preferred cadence), fast (1.3 times faster than preferred cadence) cadence	Significant enhancement in long term local dynamic stability with RAC Significant reduction of stride time & stride length variability at slow speed with RAC No effect on short term local dynamic stability with RAC
Roerdink, et al. [166]	10F, 10M (63.2±3.6)	5	Cadence, mean relative timing between footfalls & auditory stimuli, variability of mean relative timing (by circular statistics)	Participants performed gait at preferred cadence followed by 7 random trials with adjusted RAC i.e. 77.5%, 85%, 92.5%, 100%, 107.5%, 115% or 122.5%	Auditory input from drum RAC at 77.5%, 85%, 92.5%, 100%, 107.5%, 115% or 122.5% of preferred cadence Different pitch to pace for RAC i.e. for step left: 440Hz, right: 1000Hz	Significant effect of RAC on cadence, mean relative timing & variability of mean relative timing between footfalls & auditory inputs. Significantly fewer steps required to reach synchronization
Lohnes and Earhart [67]	Young: 7F, 4M (24±0.8) Old: 7F, 4M (70.8±10.4)	5	Gait velocity, cadence & stride length	Patients performed gait with/without RAC at -10%, +10% of preferred cadence or with additional cueing strategy "think about larger strides" with/without -10% & +10% of auditory inputs tone,	RAC at ±10% of preferred cadence.	Significant effect on gait velocity stride length, cadence for both groups with ±10% of RAC under both single and dual-task conditions. Larger effects noted in young participants as compared to older counterparts. Verbal instructions had no influence on cadence among both groups under both single and dual-task conditions.

				with/without dual-task "word generation task"		
Trombetti, et al. [167]	Exp: 64F, 2M (75±8) Ct: 65F, 3M (76±6)	8	Gait velocity, stride length, cadence, double, single support phase, stride time/length variability, TUG test, trunk angular displacement, Tinetti tests & assessment of falls	Exp: Pre-test, gait & exercise training with auditory input performed for 1-hour session/ week for 12 months, 6-month test, post-test, with/without dual-task (counting backward aloud task) Ct: started 6-month delayed intervention, with/without dual-task (counting backward aloud task)	RAC as piano music	Single task: Significant enhancement in gait velocity, stride length & stride time variability for the Exp as compared to Ct. Dual-task: Significant enhancement in stride length, decrease in stride length variability in Exp as compared to Ct Significant enhancement in 1 legged stance, Tinetti tests, TUG & decreased mediolateral angular velocity. Significantly reduced incidences of falls in Exp as compared to Ct.
Wittwer, et al. [136]	12F, 7M (79±7.8)	4	Swing time, stride time, velocity, stride length, double support %, stride width, stride length & time variability	Participants performed gait with/without auditory feedback "randomly" i.e. music or RAC	Music or metronome or RAC at participants preferred cadence	Significant enhancement in velocity, stride length with music as compared to no sound. Significant reduction in stride time, double limb support & enhancement in cadence with both music & RAC input, as compared to no auditory input. No effect on mean step width, mean temporal or spatial gat variability.
Yu, et al. [93]	13F (21.8±0.4)	5	Stride length, cadence & gait speed	Gait performance with/without RAC at 0% & ±10% of preferred cadence	RAC at 0% & ±10% of preferred cadence	Significant enhancement in stride length, cadence & gait speed with +10% RAC as compared to all conditions. Significant reduction in cadence & gait speed with -10% of RAC as compared to 0% & no cueing.
Almeida, et al. [92]	Exp I: 9 (42.7±6.6) Exp II: 10 (42.4±4.5) Ct: 9 (41.7±5)	4	Gait speed, heart rate, maximal oxygen consumption, rating of perceived exertion	Gait performance with/without (Ct) RAC at 90 bpm (Exp II) & 140 bpm (Exp I) for 30 minutes with re-tests at every 5-minute interval	RAC at 90 & 140 bpm	Significant enhancement in gait performance in Exp I as compared to Exp II & Ct. No effect on heart rate & maximal oxygen consumption in Exp or Ct.
Hunt, McGrath and Stergiou [168]	4F, 6M (28.1±5.3)	4	Stride time, sample entropy of stride time interval for individualized fractal RAC, DFA for auditory signals scaling exponent & stride time scaling exponent	Gait performance with/without individualized fractal RAC for white, pink & brown noise (randomized)	Individualized fractal RAC (embedding white, pink & brown noise variables into inter-beat interval of music) Inter-beat interval: stretched or compressed based on dynamics of pink, white or brown noise time series Amplitude: standard deviation of inter-beat intervals matched standard deviation of step time Tempo: at preferred cadence	Significant effect of RAC on sample entropy of stride interval time series (brown>pink>white>no sound) Significant enhancement of fractal scaling exponent with auditory feedback of stride interval time series (brown>pink>white>no sound)
Marmelat, et al. [169]	7F (28±6)	5	DFA of inter slide interval variability, inter-beat interval variability & asynchrony with metronome between two successive right heel strikes	Gait performed on treadmill with /without RAC with either IC or fractal feedback	RAC with either IC or fractal feedback Inter-beat intervals contained fractal Gaussian noise with corresponding scaling exponent (600 Hz)	Significant effects of pacing rhythmic metronome feedback on global exponents of inter-beat & slide intervals (persistent correlations) No effect on inter slide interval, asynchrony with RAC Participants anticipated the metronome & adapted with pacing stimuli No significant correlations between inter-beat intervals & inter-slide intervals (increased correlation with increased variability)
	5F, 7M (28±6)	5	DFA of inter slide interval variability, inter-beat interval variability & asynchrony with metronome between two successive right heel strikes	Gait performed on treadmill with /without RAC with either IC or fractal feedback	RAC with non-IC (different scaling exponents)	Significant effects of pacing rhythmic metronome feedback on global exponents of inter-slide intervals (anti-persistent correlations) No significant correlations between inter-beat intervals & interslide intervals (increased correlation with increased variability)

Franěk, et al. [68]	30F, 42M (20.2±1.2)	4	Gait speed, synchronization (inter step times)	Gait performed with/without rhythmic music feedback at 114, 124, 133 bpm	RAC at 114, 124, 133 bpm	Significant enhancement in gait speed with faster tempo music feedback as compared to slower tempo RAC & no feedback. No effect on synchronization with rhythmic music feedback.
	60F, 61M (20.6±1.5)	4	Gait speed, synchronization (inter step times)	Gait performed with/without] RAC (music motivational/non-motivational)	RAC (music motivational: 131-200 bpm, non-motivational: 52-96 bpm)	Significant enhancement in gait speed with motivational rhythmic music feedback as compared to non-motivational RAC & no feedback.
Leman, et al. [142]	11F, 7M (22-51)	4	Gait speed, gait tempo, synchronization of steps to tempo	Gait performance with 52 rhythmic music excerpts (activating & relaxing)	RAC (relaxing or activating effects) at 130 beats per minute, short fade in of 50 ms & fade out of 100 ms applied to each musical excerpt RAC superimposed at position 1, 12, 23, 34, 45, & 58	Significant effect of activating (increased gait speed), relaxing (reduced gait speed) in gait speed with RAC with same tempo. Significant enhancement in synchronization of steps with RAC
Peper, et al. [170]	Young: 4F, 8M (22-28) Old: 5F, 7M (55-69)	5	Mean reaction time, gait speed, step length, step width	Gait performed with/without RAC & visual feedback (stepping stones), dual-task (probe reaction task generating vibrating stimuli)	RAC Left (440Hz), right (1000Hz) Temporal shift of ±1/6th of interval between consecutive ipsilateral beeps, causing ±60° phase delay/advance	Significantly enhanced step length & step width RAC No effect on gait speed in young & older adults with RAC Significantly enhanced reaction times with RAC as compared to no cueing. Significantly reduced reaction time with RAC as compared to visual cueing.
Bank, Roerdink and Peper [171]	10F, 10 M (63.2±3.6)	5	Mean normalized step time, step length, relative phase shift between gait & cues	Gait performance with RAC ±22.5% (introduced in steps of ±7.5% randomly) of preferred cadence &/or stepping stone visual feedback	RAC at ±22.5% of preferred cadence Temporal shift of ±1/6th of interval between consecutive ipsilateral beeps, causing ±60° phase delay/advance	Significant effect of phase delay on increasing/decreasing step length, step time with auditory & visual feedback. However visual cueing > RAC Significantly enhanced phase shift from auditory to visual cueing condition. Significant reduction in coordination of RAC with gait as compared to visual cueing
Wellner, et al. [91]	17 (28±8)	4	Obstacle hit %, average obstacle clearance & individually chosen gait speed	Gait performance on robot assisted device with/without Rhythmic auditory feedback (distance to obstacle &/or foot clearance feedback)	Rhythmic real-time feedback for distance to obstacle & foot clearance Obstacle distance: Rhythm (repeating sound with shorter pause interval as distance decreases), continuous/discrete pitch (continuous sound with higher pitch as distance increases/decreases), dynamics (increase in volume as distance decreases) Absolute foot clearance: harmony (dissonant/consonant chords below/above obstacle), pitch with 2 & 3 levels, noise (Gaussian noise below, no sound above obstacle)	Significantly enhanced self-chosen gait speed with auditory feedback as compared to only visual feedback. Significant enhancement in gait speed with rhythmic feedback for distance to obstacle &/or foot clearance as compared to no feedback
Arias and Cudeiro [102]	6F, 5M (65.7±7.6)	5	Cadence, gait velocity, step amplitude, coefficient of variation for step amplitude & stride time	Patients performed gait with/without rhythmic cueing from auditory, visual & audio-visual condition, with frequency ranging from 70-110% increment/decrement at ±10% of preferred cadence	RAC with wave frequency of 4625 Hz delivered at frequency ranging from 70-110% increment/decrement at ±10% of preferred cadence	Significant enhancement in cadence, step amplitude in Ct with RAC No effects on gait velocity, coefficient of variability for stride time & stride amplitude.
Baker, et al. [172]	7F, 5M (71.5±2.5)	7	Gait speed, coefficient of velocity for (step	Pre-test, functional gait performance with/without RAC -10% of preferred	RAC at -10% of preferred cadence	Significant effect of RAC back and verbal instructions on enhancing stride length, gait velocity.

			time, double limb support time)	cadence, attentional cue instructions "try to take big steps", together "take a big step with the beat", & with/without a dual-task (a tray with 2 cups of water on top), post-test		Significantly reduced cadence with RAC and verbal instructions. Reduced gait speed, cadence with -10% RAC No effect on stride length.
Hausdorff, et al. [117]	14F, 12M (64.6±6.8)	5	Stride time, gait speed, stride length, swing time, stride time variability & swing time variability	Pre-test, gait performance with/without RAC at preferred cadence, +10%, Post-test 2 & 15 min short term retention test	RAC at 0% & +10% of preferred cadence	Significant enhancement in gait speed with +10% RAC Significant reduction in stride time with +10% RAC No effect on stride length, swing time, stride time variability, swing time variability with RAC
Willems, et al. [103]	9 (68.1±7.3)	5	Steps (number, time, height, width, length), step length, step width, step duration, coefficient of variation of step duration	Gait performance while turning with/without RAC	RAC at preferred cadence	Enhancement in step length. No effects on steps (number, time, height, width), step length, step width, step duration, coefficient of variation of step duration with RAC
Baram and Miller [99]	6F, 5M (25.4±1.9)	4	Gait speed, stride length, 10 meters walking test	Pre-test, followed by rhythmic auditory feedback & 10 min follow-up short term residual performance test	Rhythmic auditory feedback generated with gait step in real-time	No effects on stride length and gait velocity with rhythmic feedback generated in real-time
Willems, et al. [173]	10 (67.2±9.1)	4	Step frequency, gait speed, stride length & double support (%) phase	Pre-test, gait performance at 0%, -20%, -10%, +10%, +20% of RAC (randomized), post-test	RAC at 0%, -20%, -10%, +10%, +20% preferred cadence	Significant effect of RAC on cadence, gait speed, with 0%, -10%, +10%, +20% pacing of RAC No significant effects on double limb support, stride length
Baker, et al. [101]	7F, 4M (71.5±2.5)	6	Gait speed, step amplitude & step frequency	Pre-test, functional gait performance with/without RAC -10% of preferred cadence, attentional cue instructions "try to take big steps", together "take a big step with the beat", & with/without a dual-task (a tray with 2 cups of water on top), post-test	RAC at -10% of preferred cadence	Significant effect of RAC & attentional cue "big steps with beat" on step frequency in gait speed (single-task only), step amplitude, step frequency in Ct in both single & dual-task conditions Non-significant effects on gait speed, step amplitude & step frequency with RAC only. Effects not evitable once the RAC was removed, in post-test
Rochester, et al. [94]	4F, 6M (63.5±7)	6	Step length, step frequency, walking speed, time duration & cadence	Complex functional walking & sitting task under single & dual-motor task (carrying a tray) condition with/without RAC	RAC generated per preferred speed of patients.	No effects of RAC on gait speed, step length & cadence under single/dual-task conditions. However, reduction in cadence under dual-task conditions with RAC
Thaut, et al. [174]	10F, 6M (25-40)	4	Stride symmetry, stride duration & EMG amplitude variability (Gastrocnemius)	Gait performance tested with/without RAC 3 times for 5 weeks	RAC at 4/4-time signature (1st & 3rd beat accentuated by tambourine beat, 70dB) at preferred cadence, at slower, faster than preferred cadence	Significant enhancement in stride rhythmicity between right & left limb with RAC Significantly delayed & shortened onset of gastrocnemius EMG activity with RAC Significant reduction in EMG variability of gastrocnemius muscle with RAC Significantly enhanced integrated amplitude ratios for gastrocnemius EMG activity
McIntosh, et al. [175]	6F, 4M (72±5)	4	Gait velocity, stride length, cadence & cadence-auditory stimulus synchronization	Gait performance by participants with pre-test, with & without RAC at +10% of preferred cadence, post-test	RAC at 0%, +10% of preferred cadence	Significant enhancement in gait velocity and cadence with RAC Enhancement in stride length. No effect on gait symmetry

F: Female, M: Male, Exp: Experimental group, Ct: Control group, RAC: Rhythmic auditory cueing, DFA: Detrended Fluctual Analysis, PD: Parkinson's disease, EMG: Electromyography, IC: Isosynchronous cueing, , bpm: beats per minute.

Participants

A total of 854 participants were analyzed in the incorporated studies. Studies were then categorized into sub-groups for evaluating young and elderly participants. Three studies compared the effects of rhythmic auditory cueing amongst young and elderly participants. Eighteen studies evaluated elderly participants (68±5.6 years). A total of 355 participants were evaluated (235 females/ 100 males). Two studies did not specify the gender of the participants. All the studies evaluated a mixed gender sample size. Nineteen studies evaluated young participants (26.8±6 years). A total of 499 participants were evaluated (215 females/ 248 males). Two studies did not specify the gender of the included participants [91, 92]. Only one study evaluated a non-mixed gender sample i.e. only females [93]. Descriptive statistics relating to the age (mean ± standard deviation) of the participants were tabulated across the studies (Table 1).

Risk of bias

The review included studies scoring ≥4 on PEDro to reduce the incidence of biasing. Moreover, the limitation of research protocols to be included in the review was limited to gold standard randomized controlled trials, cluster randomized controlled trials and controlled clinical trials. The individual scores attained by the studies using the PEDro scale have been reported (Table 1, Supplementary table 2). The average PEDro score for the fifty included studies was computed to be 4.7 out of 10, indicating fair-quality of the overall studies. One study scored 8, four scored 6, fourteen studies scored 5, and sixteen studies scored 4. Publication bias was analyzed by plotting a Hedge's g against standard error (Fig. 2). Asymmetries concerning mean in the funnel plot might suggest bias (either positive or negative), in which case results are published. Risk of bias across the studies has been demonstrated in Fig. 3.

Meta-Analysis

Outcomes

The results suggest evidence for a positive impact of rhythmic auditory cueing on spatiotemporal gait parameters amongst both young and elderly participants. In the included thirty-four studies, thirty studies reported significant enhancements, two studies reported enhancements (p>0.05) [94, 95], and two studies reported significant reduction in gait parameters with rhythmic auditory cueing [96, 97].

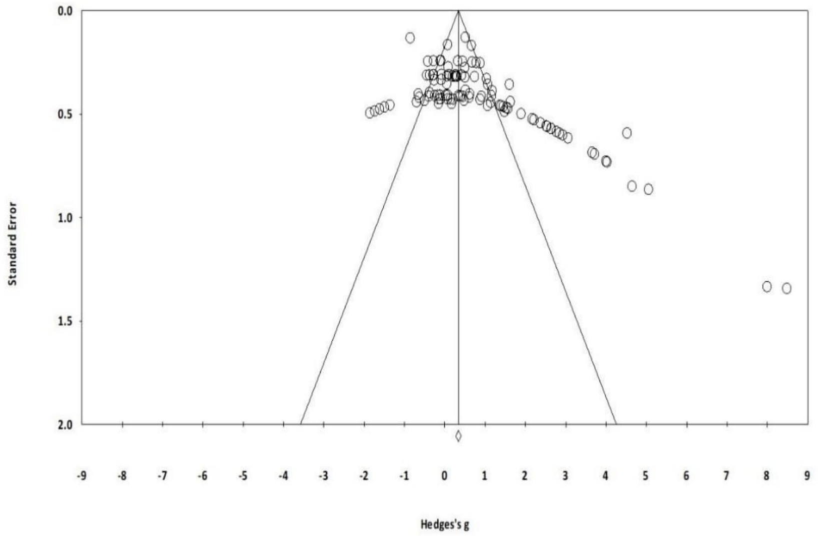

Figure 2. Funnel plot for Hedge's g & standardized effect for each effect in the meta-analysis. Each of the effect is represented in the plot as a circle. Funnel boundaries represent area where 95% of the effects are expected to abstain if there were no publication bias. The vertical line represents mean standardized effect of zero. Absence of publication bias is represented when the effects should be equally dispersed on either side of the line.

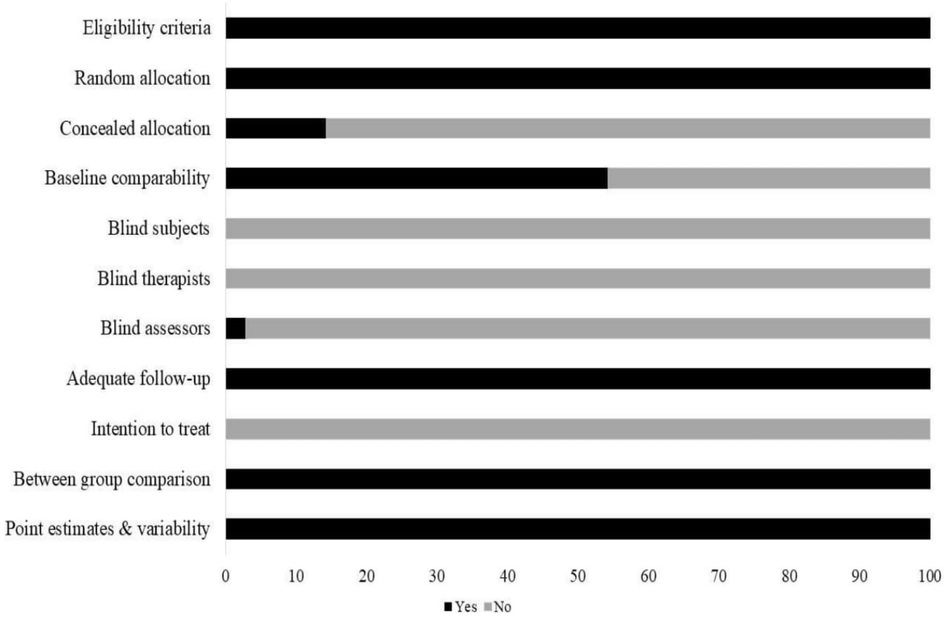

Figure 3. Risk of bias across studies.

Meta-analysis report

The evaluation of research studies via meta-analysis requires strict inclusion criteria to efficiently limit the heterogeneity [98]. However, among the pooled group of studies post strict inclusion criteria, some amount of unexplained heterogeneity was still observed. Sub-group analysis was then performed for identical studies to evaluate the cause of heterogeneity. The evaluated parameters were the spatio-temporal gait parameters such as, cadence, stride length, gait velocity, coefficient of variability for stride time and stride length. The effects of fast/slow tempo on gait parameters in the included studies was determined by keeping the patient's preferred cadence as reference. Analyses were also conducted to evaluate the effects of dual-task conditions, presence of instructions, and different tempo at which rhythmic auditory cueing was provided on gait parameters. We included a generalized group analysis first combined for all the pooled studies. A separate analysis in addition to clinical controlled trials was performed for high quality randomized controlled trails, for allowing a better interpretation of the direction and magnitude of effects. The main reason for not including the statistical approach within the studies was due to major differences in between assessment methods and lack of descriptive statistics within the manuscript. However, data was not received even after contacting the respective corresponding authors.

Gait velocity

The meta-analysis on healthy patients revealed (Fig. 4) a *large* effect size in positive domain with moderate heterogeneity (Hedge's g: 0.85, 95% CI: 0.55 to 1.16, I^2: 57.9%, p<0.01). Further, sub-group analysis was performed by dividing the groups in only young/elderly participants.

Young: The analysis for young participants performing gait with rhythmic auditory cueing revealed (Supplementary Fig. 1) beneficial effects with *large* effect and substantial heterogeneity (g: 0.92, 95% C.I: 0.42 to 1.41, I^2: 93.2%, p<0.01). Further, sub-group analysis with non-modulated rhythmic auditory cueing (Supplementary Fig. 2), under a single task condition, revealed a *large* effect size with substantial heterogeneity (Hedge's g: 1.24, 95% CI: 0.4 to 2, I^2: 90.5%, p<0.01). The heterogeneity here could be attributed to different interventions utilized by studies. Wellner, et al. [91] for instance, utilized robot assisted gait, and Almeida, et al. [92] analyzed treadmill gait. Moreover, different measures of rhythmic auditory cueing were utilized by

[99], as the study reported generation of rhythmic patterns by converting the foot strike patterns to rhythmic pattern in real-time.

Further, analysis with fast paced stimuli revealed (Supplementary Fig. 3) *large* effect size with substantial heterogeneity (g: 1.17, 95% C.I: 0.38 to 1.96, I^2: 91.4%, p<0.01). Likewise, slow paced stimuli revealed (Supplementary Fig. 4) reduction in gait velocity parameters with *medium* effect size and substantial heterogeneity (g: -0.3, 95% C.I: 90.4%, I^2: 90.4%, p<0.01). Here as well, the heterogeneity could be attributed to the type of entrainment used, for instance, low groove, non-motivating cueing and slow cueing were paired together and vice versa for the fast-paced stimuli. These stimuli differ in terms of emotional and expressiveness components, which might be considerably different from each other [68].

Dual task performance with auditory cueing in young participants with/without instructions to walk fast revealed (Supplementary Fig. 5) *large* effect size with substantial heterogeneity (g: 0.81, 95% C.I: 0.3-1.3, I^2: 95.8%, p<0.01). Further, performance under pure dual-task conditions without any instructions revealed a *medium* positive effect size with substantial heterogeneity (g: 0.38, 95% C.I: -0.16 to 0.94, I^2: 95%, p<0.01). Here, heterogeneity could be attributed to differential complexities of dual tasks incorporated within the studies, which in published literature have shown to portray different effects on motor performance [8].

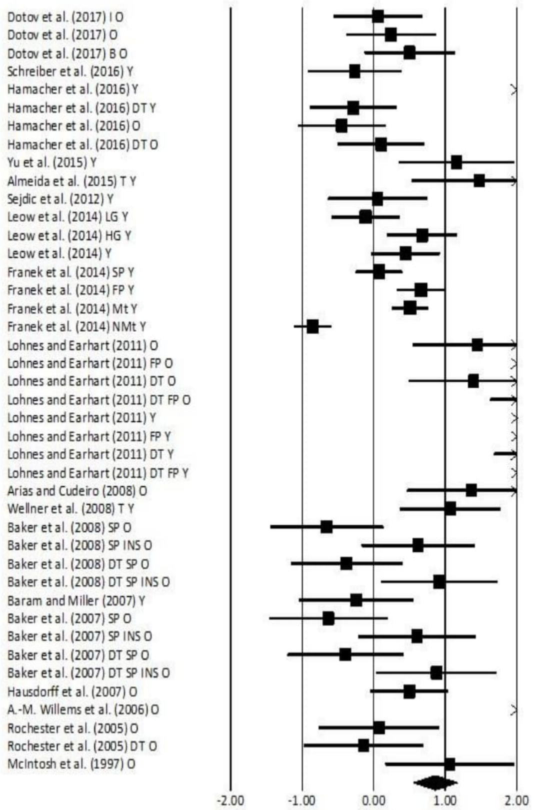

Figure 4. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young and elderly participants. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback).

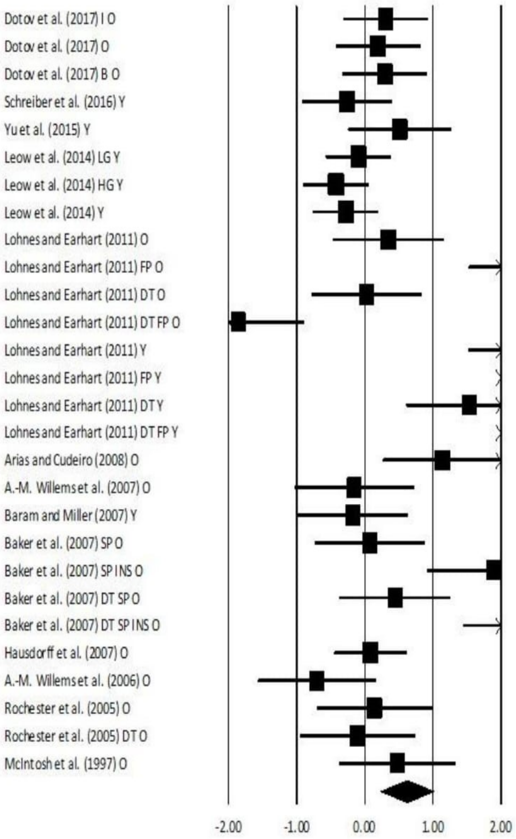

Figure 5. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among healthy young and elderly participants. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback).

Old: The analysis for old participants performing gait with rhythmic auditory cueing revealed (Supplementary Fig. 6) beneficial effects with *medium* effect and substantial heterogeneity (g: 0.68, 95% C.I: 0.28 to 1, I^2: 81%, p<0.01). Further, sub-group analysis with non-modulated rhythmic auditory cueing revealed (Supplementary Fig. 7), under a single task condition, revealed a *medium* effect size with substantial heterogeneity (Hedge's g: 0.73, 95% CI: 0.2 to 1.2, I^2: 80.2%, p<0.01). Here, Dotov, Bayard, de Cock, Geny, Driss, Garrigue, Bardy and Dalla Bella [100] evaluated the effectiveness of feedbacks which were isosynchronous, and with/without biological variability. Possibly, the heterogeneity in the sub-group analysis could be attributed to the differential cueing utilized. Further, only one study analyzed the effects of fast paced stimuli amongst elderly and further couldn't be included in sub-group analysis [67]. Slow paced stimuli, with/without verbal instructions revealed (Supplementary Fig. 8) enhancements in gait velocity parameters with *small* effect size and negligible heterogeneity (g: 0.25, 95% C.I: -0.49 to 1, I^2: 0%, p>0.05). Additional, sub-group analysis revealed a considerable effect of verbal instructions over gait velocity i.e. analysis for performance without verbal instructions revealed a negative *medium* effect size with negligible heterogeneity (g: -0.4, 95% C.I: -0.98 to 0.18, I^2: 0%, p>0.05), and including verbal instructions revealed a positive *large* effect size with negligible heterogeneity (g: 0.92, 95% C.I: 0.32 to 1.5, I^2: 0%, p>0.05). Dual task performance with auditory cueing in elderly participants with/without instructions to walk fast revealed (Supplementary Fig. 9) a *medium* positive effect size with substantial heterogeneity (g: 0.58, 95% C.I: -0.05 to 1.2, I^2: 79.2%, p>0.05). Performing under non-modulated rhythmic auditory cueing without any instructions with dual task revealed (Supplementary Fig. 10) a *medium* positive effect size (g: 0.43, 95% C.I: -0.44 to 1.3, I^2: 13.4%, p>0.05) with negligible heterogeneity.

Stride length

The meta-analysis on healthy patients revealed (Fig. 5) a *medium* effect size in positive domain with substantial heterogeneity (Hedge's g: 0.61, 95% CI: 0.23 to 1, I^2: 58.8%, p<0.05). Further, sub-group analysis was performed by dividing the groups in only young/elderly participants.

Young: The analysis for young participants performing gait with rhythmic auditory cueing revealed (Supplementary Fig. 11) beneficial effects with *large* effect and substantial heterogeneity (g: 1.2, 95% C.I: 0.38 to 2.85, I^2: 92%, p<0.01). Further, sub-group analysis with non-modulated rhythmic auditory cueing revealed (Supplementary Fig. 12), under a single task condition, revealed a *large* effect size with substantial heterogeneity (Hedge's g: 0.81, 95% CI: -0.5 to 1.7, I^2: 88%, p<0.01). Further, analysis with fast paced stimuli revealed *small* effect size with substantial heterogeneity (g: -0.01, 95% C.I: -0.4 to 0.4, I^2: 92.5%, p<0.01). The heterogeneity as stated before could be attributed to differential rhythmic stimuli utilized by studies. Moreover, none of the studies analyzing a slow-paced stimulus evaluated stride length. Dual task performance was analyzed in only one included study. Therefore, no further analysis could be carried out to evaluate the effects of higher information processing constraints on stride length.

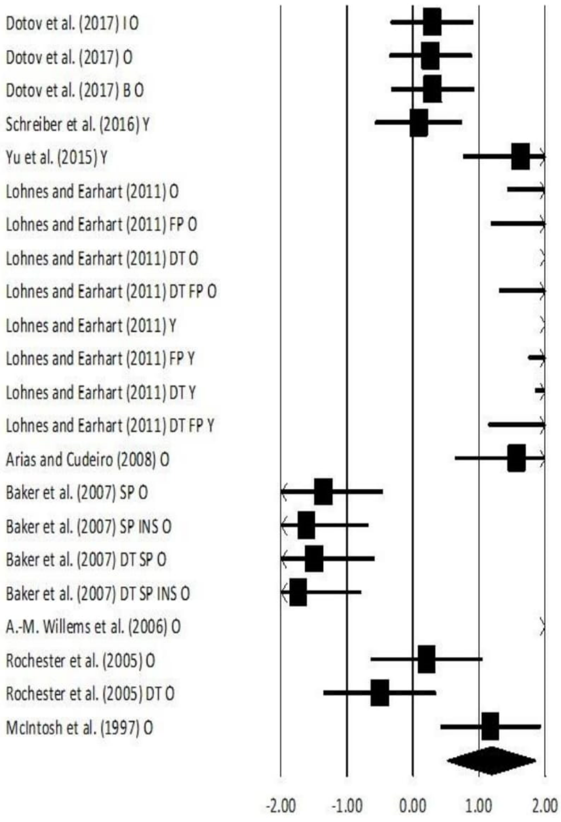

Figure 6. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence among healthy young and elderly participants. A negative effect size indicated reduction in step frequency; a positive effect size indicated enhancement in step frequency. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)

Old: The analysis for old participants performing gait with rhythmic auditory cueing revealed (Supplementary Fig. 13) beneficial effects with *medium* effect and substantial heterogeneity (g: 0.39, 95% C.I: -0.01 to 0.78, I^2: 77%, p<0.01). Further, sub-group analysis with non-modulated rhythmic auditory cueing revealed (Supplementary Fig. 14), under a single task condition, revealed a *small* effect size with negligible heterogeneity (Hedge's g: 0.22, 95% CI: -0.03 to 0.46, I^2: 10.5%, p>0.05). Further, one study each analyzed the effects of fast, slow paced stimuli amongst elderly and further couldn't be included in sub-group analysis [67, 101]. Dual task performance with auditory cueing in elderly participants was analyzed amongst two studies [67, 94], a *small* effect size with negligible heterogeneity (g: -0.03, 95% C.I: -0.64 to 0.56, I^2: 0%, p>0.05).

Cadence

The meta-analysis on healthy patients revealed (Fig. 6) a *large* effect size in positive domain with moderate heterogeneity (Hedge's g: 1.2, 95% CI: 0.51 to 1.8, I^2: 41.9%, p<0.01). Further, sub-group analysis was performed by dividing the groups in only young/elderly participants.

Young: Further, sub-group analysis with non-modulated rhythmic auditory cueing revealed (Supplementary Fig. 15), under a single task condition, revealed a *large* effect size with substantial heterogeneity (Hedge's g: 1.76, 95% CI: -0.29 to 3.8, I^2: 93.2%, p<0.01). Only one study performed [67], rhythmic auditory cueing with fast pace and no study analyzed the effects with slow paced stimulus. Therefore, no additional analysis was carried out. Dual task performance was analyzed in only one included study. Therefore, no further analysis could be carried out to evaluate the effects of higher information processing constraints on cadence.

Old: The analysis for old participants performing gait with rhythmic auditory cueing revealed (Supplementary Fig. 16) beneficial effects with *medium* effect and substantial heterogeneity (g: 0.78, 95% C.I: 0.01 to 1.54, I^2: 91.5%, p<0.01). Sub-group analysis with non-modulated rhythmic auditory (Supplementary Fig. 17), under a single task condition, revealed a *large* effect size with substantial heterogeneity (Hedge's g: 1.02, 95% CI: 0.19 to 1.84, I^2: 88.6%, p<0.01). Further, one study each analyzed the effects of fast, slow paced stimuli amongst elderly and further couldn't be included in sub-group analysis [67, 101]. Dual task performance with auditory cueing in elderly participants was analyzed amongst two studies [67, 94], a *medium* effect size with substantial heterogeneity (g: 0.68, 95% C.I: -0.03 to -1.41, I^2: 96%, p<0.01).

Coefficient of variability stride time

Analysis of coefficient of variability for stride time revealed (Supplementary Fig. 18) a *small* effect in positive domain with substantial heterogeneity (g: 0.21, 95% C.I: -0.42 to 0.85, I^2: 67.7%, p<0.05). Further, in a sub-group analysis for only old participants revealed a *medium* effect size in positive domain with substantial heterogeneity (g: 0.4, 95% C.I: -0.33 to 1.13, I^2: 63%, p<0.05) [102-104].

Coefficient of variability stride length

Analysis of coefficient of variability for stride length revealed (Supplementary Fig. 19) a *medium* effect in positive domain with moderate heterogeneity (g: 0.76, 95% C.I: 0.43 to 1.1, I^2: 48.7%, p>0.05) [102, 104, 105]. Further, in a sub-group analysis for only young participants with non-modulated rhythmic auditory cueing revealed a *medium* effect size in positive domain with negligible heterogeneity (g: 0.47, 95% C.I: -0.09 to 0.85, I^2: 4.7%, p>0.05) [104, 105]. Likewise, for only old participants a *large* effect size in positive domain with negligible heterogeneity (g: 1.01, 95% C.I: -0.17 to 2.2, I^2: 0%, p>0.05) was observed [102, 104].

Discussion

The primary objective of this present systematic review and meta-analysis was to synthesize the current state of knowledge for effects that rhythmic auditory cueing might lay over aging gait. Out of thirty-four included studies, 88% studies reported beneficial effects of rhythmic auditory cueing on primary spatiotemporal gait parameters.

Typically, spatiotemporal parameters of gait worsen with age [19, 106]. Callisaya, Beare, Phan, Blizzard, Thrift, Chen and Srikanth [107], studied age associated decline in brain structure with gait performance, and linked a reduction in gait velocity, stride length, cadence with white matter atrophy, lesions, hippocampal atrophy, and gray matter atrophy with cerebral infarcts, respectively [107, 108]. Moreover, research suggests that degenerative changes in the fronto-striatal circuits might add increasing bi-directional stress on automated control for posture, gait and cognitive processing [109-111]. Possibly, explaining the loss of gait rhythmicity in elderly (see also, Nombela, et al. [56]). Likewise, increased energy expenditure [108], weak musculoskeletal structure associated variability in muscle contraction, and force production add towards the woes [112]. The current meta-analysis reported enhancements in gait velocity (g: 0.68), stride length (0.39) and cadence (0.78), post application of rhythmic auditory cueing in elderly population groups. Likewise, beneficial effects of rhythmic auditory cueing were also observed in gait amongst younger population groups.

Several mechanisms have been suggested to ascertain the beneficial effects of rhythmic auditory cueing. Rizzo, Raghavan, McCrery, Oh-Park and Verghese [113] for instance, speculated that auditory entrainment while performing gait might act as an efficient distractor. In addition, the auditory entrainment might also have aided in reducing the errors while executing the gait [114, 115]. Possibly, by acting as an external guidance for “heel-contact” and “push-off” timings. Moreover, application of auditory entrainment is believed to allow enhancement in gait performance by bypassing or facilitating the degenerated basal ganglia-motor loop via alternative pathways [116-118]. Cunnington, Iansek, Bradshaw and Phillips [119] suggested that the external stimulation by entrainment might surpass deficient pallidal-cortical projections, and can directly serve an input supplementary motor area, thereby reducing the onset of motor deficit and aiding in performance. Moreover, the external cueing has shown to allow modulation of neuromagnetic β oscillations in auditory cortex, cerebellum, inferior frontal gyrus, somatosensory area and sensorimotor cortex [120], and reduce hemispheric asymmetry [121]. Neuroimaging studies reveal enhance activation in inferior colliculi [122], cerebellum, brainstem [117, 123], sensorimotor cortex [124, 125], further instigating cortico-cerebellar network re-organization [126]. Another crucial factor that considerably influences the aging gait is “change in tempo”. Neurophysiological analysis suggests, increased neuronal activation in fronto-occipital networks [127], and excitability of the spinal motor neurons by reticulospinal pathways, with fast-paced entrainment. A paced-stimuli is thought to reduce the response time, limit the stagnating effects of constant entrainment over fractal scaling of stride times from healthy 1/f structure [128-130], and optimizing the velocity and acceleration profiles of joint motions by scaling movement time [59].

The present-meta-analysis also observed enhancements in the spatiotemporal parameters while performing dual-tasks, for both age groups. According to literature, dual-task performance predisposes to gait instability and falls by increasing cognitive motor interferences, across age groups [8, 131-133]. Interpretations from our results suggest that rhythmic auditory cueing counteracts cognitive constraints imposed by cognitively demanding dual-tasks such as carrying a tray and that this cueing might be useful in counteracting fall while carrying out activities of daily living [8]. Lohnes and Earhart [67], suggested that co-performance of dual-tasks with rhythmic auditory cueing might allow enhancements (or even stability) in performance, by possibly freeing up cognitive resources for dual-task performance. The authors also mentioned the influence of task complexity across age groups. Possibly, the freed up cognitive resources might not be sufficient especially in elderly to perform complex dual-tasks, such as coin transfer [134], and sentence reciting tasks [135]. This might possibly explain the reduced dual tasks costs on gait performance in young participants. In addition, the enhanced performance could also be attributed as to how the participants might perceive the auditory entrainment based on their cognitive capabilities. Wittwer, Webster and Hill [136], and Thaut, Miltner, Lange, Hurt and Hoemberg [137], suggested a strong relationship in between the cognitive capabilities and the ability to interpret and discern the structure of a beat. Thereby, suggesting a better rhythmic perception and interpretation by younger population groups as compared to their older counterparts.

Moreover, the progressive degradation of neuromuscular structures with aging has further been suggested to alleviate the threshold for action relevant acoustic input [138]. To counteract this deficiency use of ecologically valid acoustic feedback has been suggested [138]. The ecologically valid action related sounds might enhance saliency of sensory information concerning spatiotemporal information, thereby aiding in movement execution [100, 138-141]. This was also demonstrated by Dotov, et al. [100], here the authors demonstrated beneficial effects in parkinsonian and healthy gait parameters with biologically variable rhythmic auditory cueing as compared to isosynchronous cueing. Moreover, recent research has also revealed the possibilities of including emotional [113], motivational [68], and expressiveness [142], component in auditory entrainment to portray differential effects on gait parameters. Unfortunately, lack of pertinent, repeatable literature concerning the specific type of modified auditory feedback makes it difficult to interpret, as to which type of feedback might be most optimal, and for which age groups. We suggest future studies to replicate data concerning the use of ecological auditory entrainment across different age groups, to allow a reliable interpretation, which could then be included in gait rehabilitation protocols. Moreover, we also suggest future researchers to analyze the “entrainment effects” while multitasking in high-stress situations pertinent to modern day scenarios (for example, walking and texting, listening to music while crossing a traffic light).

This current meta-analysis also reported an increase in coefficient of stride-time and length variability in elderly participants with rhythmic auditory cueing. Based, on the published literature initial increase in variability during learning paradigm is efficient for improving gait performance [143]. Here, interpretations could possibly be drawn from “dynamic system theory” [144]. The theory suggests that a biological system might allow variability to identify and self-organize the most stable and viable outcome [144, 145]. Thereby, interpretations could be made for regulating gait amongst young and elderly population groups to regulate gait when passing through fall-prone environments [41]. The present meta-analysis did not evaluate the the influence of gait training with rhythmic auditory cueing on ageing gait. Whereas, training regimes with auditory entrainment have demonstrated reduced variability in parkinsonism [101, 146], and stroke [126]. We suggest future research to address this gap in the literature and evaluate the effects of long term training with rhythmic auditory cueing on aging gait.

Finally, we believe that the benefits of auditory entrainment might surpass that of co-treatment techniques (for instance, biofeedback, virtual reality, physiotherapy etc.) because of its economical nature, and high viability [77, 78]. The rhythmic entrainment factor could be utilized with music in rehabilitation, day to day lives. This could allow benefits in both psycho-physiological domains [147-151]. For instance, improving stress, mediating arousal, emotions, internal motivation, memory, attention, executive functions [152], power [153], and endurance [154]. Moreover, it is important to consider that the retention of enhancements in gait parameters relies not only on the training received in the clinic but also depends largely on how much the patient follows the treatment protocol at home. Lim, et al. [13] for instance, reported enhancement in parkinsonian gait activity to 35 minutes per day (qualifying the 30 minutes criteria by WHO [155]). We believe that delivering this type of home-based intervention could possibly be beneficial for people lacking proper exposure to medical interventions in developing countries [156]. For instance, a booming number of smartphone devices in developing countries [157], can be used as a delivery tool while using a simple metronome app such as, Walkmate [129], or Listenmee [158], which with proper medical guidance might allow curbing the motor deficits associated with aging [159]. We also suggest the use of rhythmic auditory cueing as an adjunct to other rehabilitation strategies, for instance, dance, tai-chi, aerobics, as it might enhance the rehabilitation progress by focusing on both psycho-physiological components.

To the best of our knowledge, this present review for the first time analyzed the effects of auditory entrainment on aging gait. The present findings are in agreement with systematic reviews and meta-analysis carried out to analyze auditory entrainment effect on stroke [66], cerebral palsy [160], and parkinsonism [57, 161]. In conclusion, this review strongly suggests the incorporation of rhythmic auditory cueing for enhancing gait performance with aging gait. The results from the meta-analysis also direct towards the possible use of auditory entrainment to reduce the incidence of falls in high-stress situations.

Competing Financial Interests

No financial interests are declared.

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Supplemental data

Supplemental data are available online.

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Chapter 2: Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis

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Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis

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The use of rhythmic auditory cueing to enhance gait performance in parkinsonian patients' is an emerging area of interest. Different theories and underlying neurophysiological mechanisms have been suggested for ascertaining the enhancement in motor performance. However, a consensus as to its effects based on characteristics of effective stimuli, and training dosage is still not reached. A systematic review and meta-analysis was carried out to analyze the effects of different auditory feedbacks on gait and postural performance in patients affected by Parkinson's disease. Systematic identification of published literature was performed adhering to PRISMA guidelines, from inception until May 2017, on online databases; Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE and PROQUEST. Of 4204 records, 50 studies, involving 1892 participants met our inclusion criteria. The analysis revealed an overall positive effect on gait velocity, stride length, and a negative effect on cadence with application of auditory cueing. Neurophysiological mechanisms, training dosage, effects of higher information processing constraints, and use of cueing as an adjunct with medications are thoroughly discussed. This present review bridges the gaps in literature by suggesting application of rhythmic auditory cueing in conventional rehabilitation approaches to enhance motor performance and quality of life in the parkinsonian community.

Susceptibility to fall grows rapidly amongst elderly and patients with neurological deficits[1–3]. The impairments in neuromuscular functioning promotes instability[4,5], weakness[6], reduces physical activity[7], further leading to musculoskeletal deformities and a higher predisposition to fall[8]. Injuries related to such instabilities inflict heavy costs at both individual and economic levels[9], increase dependency, social isolation and affects the quality of life[10,11]. Neurological disorders such as parkinsonism presents itself with impairments in motor functions exhibiting characteristics such as, akinesia, chorea, hypokinesia, bradykinesia, motor blocks, rigidity, and problems with generation of cyclic movements, further leading to "freezing" instances[12,13]. Jankovic and Tolosa[14] suggests the degeneration of dopaminergic cells in substantia nigra in basal ganglia, which might result in its impaired excitatory output and affect its functioning (autonomic control of movement planning, scaling and initiation)[15]. Likewise, ageing together with parkinsonism results in rigorous denervation and re-innervation due to progressive reduction in functional motor units in spinal cord and myelinated ventral root fibers[16]. Together, these neurological dysfunctions impair the ability to execute and maintain autonomic motor tasks such as, posture and gait[17].

Research also suggests a "fear" related stability modification in gait, postural performance for such fall prone population groups[18], possibly leading to a range of spatiotemporal and kinematic modifications[19]. For instance, reduction in gait velocity, stride length, increase in double limb support[8,18,20], and stride-to-stride fluctuation[21] have been extensively reported. This compensatory effort to develop gait patterns that are resistant to external perturbations leads to poor static and dynamic stability[8,22]. Practically, these changes might impair an individual's ability to pass safely through high stress situations constrained by space or time, such as escalators, traffic signals[4,23], leading to an increased predisposition to fall. Studies have suggested that this modification in gait patterns is due to an alleviation in "internal" conscious attention towards autonomic control, which adversely impacts proprioception and autonomic functioning possibly because of movement specific re-investment[1,24,25,26]. The theory suggests that directing attention internally to control autonomic movements such as gait, can have an adverse impact on its performance[1]. The theory further adds that aging[23], neurological ailment and injuries[1,3] are common conditions that promote movement specific reinvestment. Such fall-prone population groups

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have a differential cortical activation pattern, which could possibly be linked with changes in task prioritization and conscious attention while carrying out cognitive or motor tasks[27]. Moreover, electromyographic analysis has revealed enhanced variability in motor unit recruitments that adversely impacts the execution of automated and voluntary motor tasks[28]. Likewise, limitations in execution of functional activities of daily living tasks have also been extensively reported[29–32].

Common treatment strategies to curb motor dysfunctions in parkinsonism include training with virtual-reality[33], biofeedback[34], physical/occupational therapy[35], physical exercise[36], dance[37], treadmill[38], external sensory feedback[39], and dual-task training[4]. Likewise, pharmacological intervention with psychoactive drug such as levodopa, dopamine agonists, monoamine oxidase type B inhibitors[40], have been reported to be effective short-term for managing motor symptoms, such as bradykinesia, tremors[41]. However their effectiveness in managing gait and postural dysfunctions in long-term is largely debated[42,43].

Spaulding *et al.*[43] argued that the lack of adequate sensory information in patients with parkinsonism plays a destructive role in autonomic motor functioning. Therefore, motor performance in parkinsonian patients might benefit from additional sensory information. Several studies have analyzed the effects of augmented external auditory, visual and tactile feedback on performance[44–47]. Nevertheless, studies have suggested the predominant role of auditory information as compared to its counterparts[39,43]. Predominantly auditory cortex has been reported to perceive stimuli with shorter reaction times (20–50 ms) as compared to its visual or tactile counterparts[45,48–50]. Further, the auditory cortex possesses rich connectivity to motor centers from spinal cord extending towards brainstem, cortical and subcortical structures[51–53]. Thereby, allowing strong cross-sensory impacts of auditory signal characteristics, such as frequency[54], timbre[55], on motor execution. Consequently, several types of external auditory feedback techniques have been analyzed in the literature, such as rhythmic auditory cueing[53], patterned sensory enhancement[46,56], and real-time auditory feedback[57]. However, rhythmic auditory cueing is most widely studied, with respect to motor performance post parkinsonism[45], stroke[58], cerebral palsy[59,60], and more[20,61–63]. Rhythmic auditory cueing is defined as a medium of repetitive isosynchronous beats applied with an aim to synchronize motor execution with a rhythm[53,58]. The underlying mechanisms for attaining benefits in the motor domain are suggested to be multifactorial[45,64]. The auditory cueing has been suggested to modulate neuromagnetic β oscillations[65], enhance biological motion perception[57,66], promote motor imagery[67,68], reducing shape variability in musculoskeletal activation patterns[69], mediate cortical reorganization, neural-plasticity[70], supressing movement specific re-investment[71], and more[72,73].

We identified high quality systematic reviews analysing the effects of external auditory cueing on Parkinsonism[42,43,74]. However, the meta-analysis due to extremely strict inclusion criteria allowed the inclusion of only randomized controlled trials for statistical analysis, and not for a joint qualitative analysis[42,43]. Moreover, findings from the meta-analysis of Spaulding *et al.*[43] were interpreted without the presence of any heterogeneity test in between the studies. Similarly, limitations concerning statistical analysis were observed for Rocha *et al.*[42]. Lim *et al.*[74] and Nombela *et al.*[45] performed excellent quality narrative reviews, but the lack of statistical analysis doesn't allow to draw firm conclusions. Moreover, none of the review studies analysed the effects of different types of tempo, different signal characteristics, training dosage, and dual-task performance with rhythmic auditory cueing. Therefore, we attempted to develop a state of knowledge for the benefit of parkinsonian patients and medical practitioners, where both qualitative and quantitative data from good quality studies can be interpreted. Moreover, to the best of our knowledge, up to now, no review has elucidated the effects of dual tasks, fast/slow paced stimuli, and the precise training dosage of rhythmic auditory cueing on spatiotemporal gait parameters in Parkinson's disease. This present review for the first time, conducted a systematic review in combination with a meta-analysis to determine the effects of rhythmic auditory cueing among parkinsonian patients.

Methods

This review was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA statement[75].

Data sources and search strategy. Academic databases Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE and PROQUEST were searched from inception until July 2017. A sample search strategy has been provided in (Table 1).

Data extraction. Upon selection for review, the following data were extracted from each article; author, date of publication, sample size, sample description (gender, age, health status), disease duration, intervention, characteristics of auditory cueing, dual-task, outcome measures, results, and conclusions. The data were then summarized and tabulated (Supplementary Table 1).

The inclusion criteria for the studies was (i) Randomized controlled trials, cluster randomized controlled trials or controlled clinical trials; (ii) Studies reporting reliable and valid spatiotemporal gait parameters (iii) Studies including static/dynamic aspects of gait/postural stability (iv) Studies scoring ≥ 4 in PEDro methodological quality scale; (v) Experiments conducted on human participants; (vi) Published in a peer-reviewed academic journal; (vii) Articles published in English, German and Korean languages.

Quality and risk of bias assessment. The quality of the studies was assessed using the PEDro methodological quality scale[76]. The scale consists of 11 items addressing external validity, internal validity, and interpretability and can detect potential bias with fair to good reliability[80], and validity[76]. A blinded rating of the methodological quality of the studies was carried out by the primary reviewer (SG). Ambiguous issues were discussed with second and third reviewers (IG, GS, AOE) and consensus was reached. Included studies were rated according to scoring of 9–10, 6–8 and 4–5, and were interpreted as "excellent", "good" and "fair" quality studies[78],

DATABSE	EMBASE
DATE	10/07/2017
STRATEGY	#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7
#1	('rhythmic auditory feedback' OR 'rhythmic auditory cueing' OR 'rhythmic acoustic feedback' OR 'rhythmic auditory entrainment' OR 'metronome feedback' OR 'metronome' OR 'rhythmic metronome feedback' OR 'acoustic stimulus' OR 'acoustic feedback' OR 'acoustic cueing' OR 'external stimuli' OR 'external feedback' OR 'external cueing' OR 'music therapy' OR 'Neurological music therapy' OR 'tempo' OR 'beat' OR 'rhythm' OR 'RAC' OR 'NMT')/de OR (rhythmic auditory feedback OR rhythmic auditory cueing OR rhythmic acoustic feedback OR rhythmic auditory entrainment OR metronome feedback OR metronome OR rhythmic metronome feedback OR acoustic stimulus OR acoustic feedback OR acoustic cueing OR external stimuli OR external feedback OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT)ti,ab
#2	('Parkinson's disease' OR 'Parkinsonism' OR 'Parkinson disease' OR 'Parkinson' OR 'Parkinson's' OR 'PD')/de OR (Parkinson's disease OR Parkinsonism OR Parkinson disease OR Parkinson OR Parkinson's OR PD); ti,ab
#3	('cognitive task' OR 'concurrent task' OR 'dual task' OR 'dual task' OR 'dual task paradigm' OR 'dual task paradigm' OR 'cognitive task training' OR 'dual task training' OR 'dual task training')/de OR (cognitive task OR concurrent task OR dual task OR dual task OR dual task paradigm OR dual task paradigm OR cognitive task training OR dual task training OR dual task training'):ti,ab
#4	('rehabilitation' OR 'treatment' OR 'rehab' OR 'management' OR 'therapy' OR 'physiotherapy' OR 'physical therapy' OR 'prevention' OR 'risk prevention')/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
#5	('walking' OR 'gait' OR 'locomotion' OR 'range of motion' OR 'ROM' OR 'ambulation' OR 'mobility' OR 'treadmill gait' OR 'balance' OR 'stability' OR 'stride' OR 'gait training' OR 'gait rehabilitation')/de OR (walking OR gait OR locomotion OR range of motion OR ROM OR ambulation OR mobility OR treadmill gait OR balance OR stability OR stride OR gait training OR gait rehabilitation);ti,ab
#6	('age groups' OR 'adolescent' OR 'young' OR 'elderly' OR 'old' AND ('gender' OR 'male' OR 'female') AND ('athlete' OR 'elite athlete' OR 'recreational athlete' OR 'novice athlete' OR 'trained athlete' OR 'sedentary'))/de OR (age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female) AND (athlete OR elite athlete OR recreational athlete OR novice athlete OR trained athlete OR sedentary));ti;ab
#7	clinical trial/exp OR ('intervention study' OR 'cohort analysis' OR 'longitudinal study' OR 'cluster analysis' OR 'crossover trial' OR 'cluster analysis' OR 'randomized trial' OR 'major clinical study')/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab

Table 1. Sample search strategy on EMBASE database.

respectively. Inadequate randomization, non-blinding of assessors, no intention to treat analysis and no measurement of compliance were considered as major threats for biasing[79].

Data Analysis. This systematic review also included a meta-analysis approach to develop a better understanding of the incorporated interventions[80]. The presence and lack of heterogeneity asserted the use of either random or fixed effect meta-analysis[81]. A narrative synthesis of the findings structured around the intervention, population characteristics; methodological quality (Supplementary Table 1) and the type of outcome are provided. Likewise, summaries of intervention effects for each study were provided in a tabular format (Supplementary Table 1). A meta-analysis was conducted between pooled homogenous studies using CMA (Comprehensive meta-analysis V 2.0, USA). Heterogeneity between the studies was assessed using I^2 statistics. The data in this review were systematically distributed and for each available variable pooled, dichotomous data were analyzed and forest plots with 95% confidence intervals are reported. The effect sizes were adjusted and reported as Hedge's g[82]. Thresholds for interpretation of effect sizes were as follows; a standard mean effect size of 0 means no change, negative effect size means a negative change, mean effect size of 0.2 considered a *small* effect, 0.5 a *medium* effect and 0.8 a *large* effect[83]. Interpretation of heterogeneity via I^2 statistics was as; 0%, 25%, 75% as negligible, moderate and substantial heterogeneity, respectively. Meta-analysis reports indicating heterogeneity among studies were evaluated to determine the reason of heterogeneity, and the included studies were then pooled separately and analyzed again. The alpha level of 0.05 was adopted.

Results

Characteristics of included studies. Our initial search yielded a total of 4794 studies, which on implementing our inclusion/exclusion criteria, were reduced to fifty (Fig. 1). Data from the included studies have been summarized in (Supplementary Table 1). Of the fifty included studies, seven were randomized controlled trials, and forty-four were controlled clinical trials.

Participants. A total of 1892 participants were analyzed in the incorporated studies. In the included studies, forty-eight studies incorporated mix gender patients. Two studies incorporated only male participants[84,85]. Two studies didn't specify the gender of the included participants[86,87]. The included studies provided data on 1892 participants (n = 745 females/1089 males). Descriptive statistics relating to the age (mean ± standard deviation) of the participants were tabulated across the studies. In addition, the age of participants was mentioned in range by six studies[88–93], and only a mean value was provided by two studies[31,94]. Disease duration of parkinsonian patients have been mentioned (see Supplementary Table 1).

Risk of bias. To reduce the risks of bias, studies scoring ≥ 4 on PEDro were included in the review. Moreover, the limitation of research protocols to be included in the review was limited to gold standard randomized controlled trials, cluster randomized controlled trials and controlled clinical trials. The individual scores attained by the

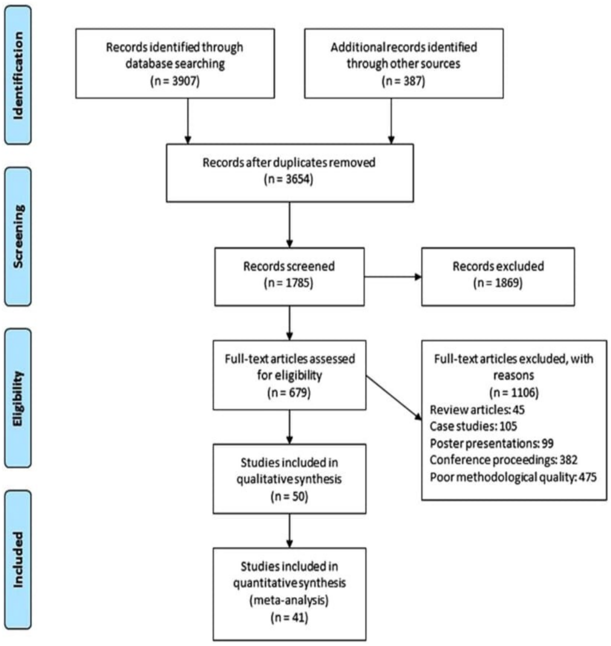

Figure 1. PRISMA flow chart for the inclusion of studies.

studies using the PEDro scale have been reported (Supplementary Tables 1 and 2). The average PEDro score for the fifty included studies was computed to be 5.4 out of 10, indicating fair-quality of the overall studies. Seven studies scored 8, three scored 7, twelve studies scored 6, thirteen studies scored 5, and seventeen studies scored 4. Publication bias was analyzed by plotting a Hedge's g against standard error (Fig. 2). Asymmetries concerning mean in the funnel plot might suggest bias (either positive or negative). Risk of bias across the studies has been demonstrated in (Fig. 3).

Meta-Analysis. *Outcomes.* The results suggest clear evidence for a positive impact of rhythmic auditory cueing on spatiotemporal gait parameters amongst parkinsonian patients. An enhancement in gait parameters were also observed when rhythmic auditory cueing was introduced with biological variability[94,95], and music[56,93,96–98]. In the included fifty studies, one study reported enhancements ($p > 0.05$)[96], two studies reported negligible effects[100,101], one study reported significant reduction of rhythmic auditory cueing on spatiotemporal gait parameters[102]. Forty-six studies reported significant enhancements in primary spatiotemporal gait parameters while receiving rhythmic auditory cueing.

Meta-analysis report. The evaluation of research studies via meta-analysis requires strict inclusion criteria to efficiently limit the heterogeneity[103]. However, among the pooled group of studies post strict inclusion criteria, some amount of unexplained heterogeneity was still observed. Thereafter, sub-group analyses were performed among homogenous studies to exclude and evaluate the cause of heterogeneity. The evaluated parameters were the spatio-temporal gait parameters such as, cadence, stride length, gait velocity, double limb support duration, and turn time. Analyses were also conducted to evaluate the effects of dual-task conditions, the effects of different training durations, presence/lack of medication, early/late phase of treatment, presence of treadmill, and different tempi at which rhythmic auditory cueing was provided on gait parameters. We included a generalized group analysis combined for all the pooled studies. A separate analysis in addition to clinical controlled trials was performed for high quality randomized controlled trails, for allowing a better interpretation of the direction and magnitude of effects. The main reason for not including the statistical approach within the studies was due to major differences in between assessment methods, patient characteristics, auditory stimuli and lack of descriptive statistics within the manuscript. However, attempts were made to retrieve data from respective corresponding co-authors.

Gait velocity. Gait velocity was analyzed among thirty-five studies. Additional sub-group data were extracted from thirteen included studies[71,86,87,89,94,99,104–108]. In the additional analyses, two studies analyzed early and late treatment groups[89,99]. Two studies analyzed normal and treadmill gait performance[82,103]. Six studies compared cueing between fast and slow tempo[86,93,104,105,109,110]. Five studies analyzed the effects with only fast paced[111–115], and two with only slow paced tempo[116,117]. Seven studies analyzed cueing at slow tempo[86,93,104,105,109,116,117]. The fast/slow tempo in the included studies was determined by keeping the patient's preferred cadence as reference. Three studies analyzed patients in "on" and "off" stages of medications[71,107,110], signifying the presence and

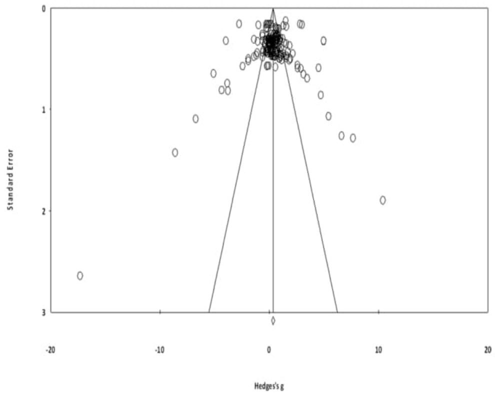

Figure 2. Funnel plot for Hedge's g and standardized effect for each value in the meta-analysis. Each of the effect is represented in the plot as a circle. Funnel boundaries represent area where 95% of the effects are expected to lie if there were no publication biases. The vertical line represents the mean standardized effect of zero. Absence of publication bias is represented by symmetrically distributed effects around the line.

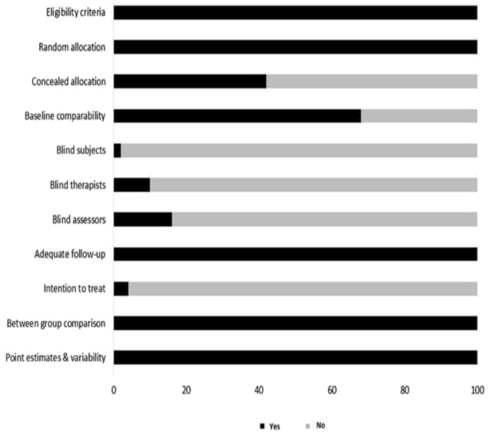

Figure 3. Risk of bias across studies.

absence of medications, respectively. A positive effect here refers to enhancement in gait velocity, and a negative effect refers to reduction in gait velocity.

The analysis of studies revealed (Fig. 4) a *small* effect size in the positive domain (g: 0.23, 95% C.I: 0.1 to 0.3). Substantial heterogeneity was observed in between the studies (I^2: 87.4%, $p > 0.01$). Further, sub-group analyses were conducted among homogenous studies to explore heterogeneity. An analysis between "on" and "off" medications patients (Supplementary Figures 1 and 2), revealed a positive *small* effect size for "off" group with negligible heterogeneity (g: 0.43, 95% C.I: 0.11 to 0.75, I^2: 18.8%, $p = 0.29$), and positive *medium* effect size for "on" group with negligible heterogeneity (g: 0.55, 95% C.I: 0.23 to 0.87, I^2: 0.0%, $p = 0.44$). A sub-group analysis for treadmill training groups (Supplementary Figure 3) revealed a positive *large* effect size with negligible heterogeneity (g: 1.0, 95% C.I: 0.33 to 1.67, I^2: 24.6%, $p = 0.24$). A sub group analysis between "fast" and "slow" externally paced auditory cueing (Supplementary Figure 4), revealed a positive *medium* effect for the "fast" group with negligible heterogeneity (g: 0.7, 95% C.I: 0.50 to 0.89, I^2: 0.0%, $p = 0.44$), and a negative *small* effect for the "slow" group (Supplementary Figure 5) with negligible heterogeneity (g: −0.24, 95% C.I: 10.51 to 0.19, I^2: 23.53%, $p = 0.24$). Further, twenty-one studies analyzing the effects of a simple rhythmic auditory cueing were analyzed (Supplementary Figure 6). The sub-analysis revealed a positive *small* effect size (g: 0.05, 95% C.I: −0.07 to 0.17, I^2: 86.4%, $p < 0.01$) with substantial heterogeneity. The analysis revealed two main types of sub-groups analyzing the effects of rhythmic auditory cueing with and without training. The analysis of ten studies analysing the direct effects of rhythmic auditory cueing i.e. without training (Supplementary Figure 7) revealed a negative *small* effect size (g: −0.34, 95% C.I: −0.5 to −0.18, I^2: 85.9%, $p < 0.01$) with substantial heterogeneity. The studies were then categorized according to the disease duration of parkinsonian patients in the studies i.e. >9 years or <9 years. Six studies evaluated the effects of rhythmic auditory cueing on gait performance, with patients having mean

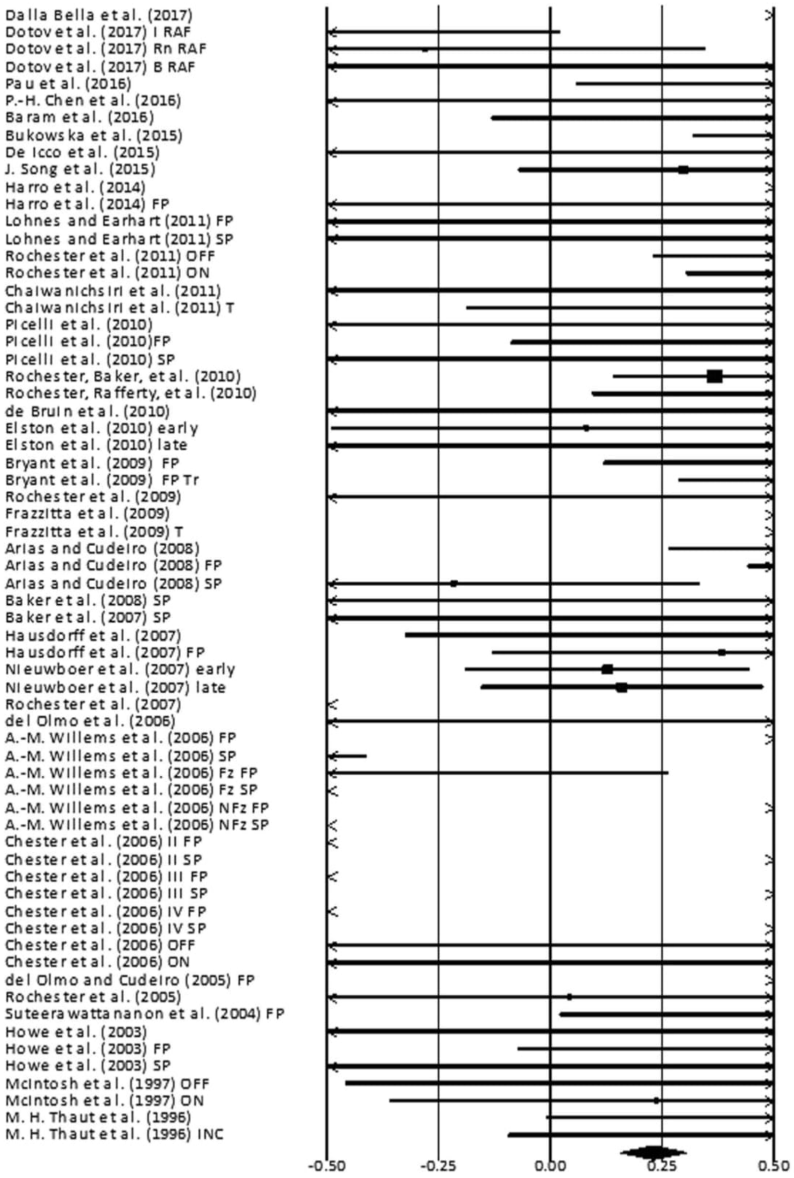

Figure 4. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among parkinsonian patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. (FP: Fast paced, SP: Slow paced, Fz: Freezers, NFz: Non-Freezers, ON: with medications, OFF: without medications, INC: Inclined training, T: Treadmill training, FP T: Fast paced training, I: Isosynchrounous cueing, Rn: Random, BL Biological variability, RAC: Rhythmic auditory cueing).

disease duration <9 years. The analysis revealed a positive *small* effect size (g: 0.16, 95% C.I: −0.12 to 0.44, I^2: 0%, $p = 0.56$) with negligible heterogeneity. The studies analysing severe parkinsonian patients i.e. >9 years of disease duration revealed a negative *small* effect size (g: −0.37, 95% C.I: −0.62 to −0.13, I^2: 91%, $p < 0.01$) with substantial heterogeneity. Upon further evaluation of heterogeneity in the sub-group we observed that the experimental procedures differed considerably between each other. For instance, Chen *et al.*[118] analysed gait performance during gait turning, Arias and Cudeiro[104] utilized a varied range of frequency that differed from other studies, and Rochester *et al.*[119] utilized a complex functional task that required the patients to perform a sitting to stand and carrying a tray. Therefore, a further sub-analysis was not carried out.

A sub-group analysis for thirteen studies analysing the effects of training with rhythmic auditory cueing (Supplementary Figure 8), revealed a positive *medium* effect size (g: 0.63, 95% C.I: 0.49 to 0.76, I^2: 74.1%, $p < 0.01$) with substantial heterogeneity. Further, upon sub-group analysis to reveal the cause of heterogeneity we excluded Frazzitta *et al.*[106] because the patients in their study had on average a longer disease duration (13.2 ± 4.1 years) than the patients from other studies. Additionally, Dalla Bella *et al.*[99] was excluded from further analysis. The study's training regime differed from the other studies i.e. rhythmic auditory cueing with ±10% modulation of pace according to preferred cadence. Moreover, the training included a hand tapping task concurrently with gait training. The analysis after excluding these studies revealed a positive *medium* effect size with moderate heterogeneity (g: 0.64, 95% C.I: 0.37 to 0.92, I^2: 36.08%, $p = 0.34$). Moreover, an additional analysis of training duration was performed (more or less than 45 min). The analysis for thirteen studies included a treatment duration for less than 45 minutes (Supplementary Figure 9) revealed a positive *medium* effect size with substantial heterogeneity (g: 0.61, 95% C.I: 0.48 to 0.74, I^2: 69.3%, $p < 0.01$). Further, exclusion of Chaiwanichsiri *et al.*[85], Frazzitta *et al.*[106] was done as both the studies incorporated treadmill training and a training duration of 20 minutes, and Harro *et al.*[113] as the authors only included only one training session per week, whilst the others included more than 3 sessions per week. The analysis for 30–45 min of duration (Supplementary Figure 10), revealed a positive *medium* effect size with moderate heterogeneity (g: 0.52, 95% C.I: 0.38 to 0.66, I^2: 33.8%, $p > 0.05$). The analysis for 20 min of duration (Supplementary Figure 11), revealed a positive *large* effect size with substantial heterogeneity (g: 1.09, 95% C.I: 0.7 to 1.47, I^2: 80.9%, $p < 0.01$). The studies however differed considerably from one another as, Frazzitta *et al.*[106] included parkinsonian patients in advanced stage of disease, as compared Chaiwanichsiri *et al.*[85] where patients were in early stages. The two studies analyzing the effects of training in ling duration i.e. more than 45 minutes were considerably different as del Olmo and Cudeiro[112] utilized rhythmic auditory cueing with an instruction to perform faster gait, and while carrying out a manual task, whereas del Olmo *et al.*[102] did not incorporate such technique. A sub-group analysis based on the number of weeks the patients received treatment i.e. less or more than 5 weeks was performed. Analysis for patients receiving treatment for less than 5 weeks (Supplementary Figure 12) revealed a positive *medium* effect size with substantial heterogeneity (g: 0.73, 95% C.I: 0.31 to 1.14, I^2: 21.3%, $p > 0.05$). Likewise, for patients receiving treatment for more than 5 weeks (Supplementary Figure 13) revealed a positive *small* effect size with negligible heterogeneity (g: 0.46, 95% C.I: 0.2 to 0.72, I^2: 0%, $p > 0.05$).

Randomized controlled trials. A sub-group analysis on the included randomized controlled trials was performed (Supplementary Figure 14). Two studies analyzed early and late intervention groups[96,117]. Three studies involved a training regime with rhythmic auditory cueing[88,98,113]. One study analyzed immediate effects of rhythmic auditory cueing on gait[121]. The analysis revealed a positive *small* effect for the group with substantial heterogeneity (g: 0.25, 95% C.I: 0.11 to 0.40, I^2: 73.5%, $p = 0.001$).

A sub-group analysis between "early" and "late" treatment groups revealed a positive *small* effect size for "early" group (Supplementary Figure 15) with negligible heterogeneity (g: 0.11, 95% C.I: −0.16 to 0.39, I^2: 0.0%, $p = 0.88$), and similar *small* effect size for "late" group (Supplementary Figure 16) with negligible heterogeneity (g: 0.11, 95% C.I: −0.16 to 0.39, I^2: 0.0%, $p = 0.\ 45$). A sub-group analysis between de Bruin *et al.*[98] and Harro *et al.*[110] revealed a positive *large* effect size with substantial heterogeneity (g: 0.97, 95% C.I: 0.29 to 1.66, I^2: 93.35%, $p < 0.01$). The training program differed between the studies, de Bruin *et al.*[98] trained their patients for at least 3 sessions per week, whereas Harro *et al.*[113] performed only one training session per week. Gait velocity under dual-task condition was analyzed amongst nine studies. The specifics of dual-tasks have been mentioned (Supplementary Table 1). The analysis (Supplementary Figure 17) revealed a positive *small* effect size (g: 0.38, 95% C.I: 0.09 to 0.66, I^2: 9.95%, $p > 0.05$) with negligible heterogeneity.

Stride length. Stride length was analyzed amongst thirty-four studies. Additional sub-group data was extracted from fourteen included studies. A positive effect here refers to enhancement in stride length, and a negative effect refers to reduction in stride length. The combined analysis revealed (Fig. 5) a positive *small* effect size (g: 0.42, 95% C.I: 0.35 to 0.5, I^2: 85.05%, $p < 0.01$) with substantial heterogeneity. A sub-group analysis in between "off" and "on" medication groups was performed among three studies[71,107,110]. The analysis for "on" group (Supplementary Figure 18), revealed a *large* effect size in positive domain (g: 0.77, 95% C.I: 0.45 to 1.1, I^2: 43.6%, $p = 0.16$) with moderate heterogeneity. Likewise, analysis for "off" group (Supplementary Figure 19), revealed a *large* effect size in positive domain (g: 0.85, 95% C.I: 0.49 to 1.2, I^2: 51%, $p = 0.12$) with marginally moderate heterogeneity. This heterogeneity could possibly be attributed to Chester *et al.*[110], as the authors utilized a different tempo for rhythmic auditory cueing as compared to the other two counterparts. Post exclusion the meta-analysis revealed *large* effect size for both "on" and "off" in positive domain (g: 0.86, 95% C.I: 0.52 to 1.2, I^2: 0%, $p = 0.64$), (g: 0.96, 95% C.I: 0.59 to 1.34, I^2: 0%, $p = 0.39$), with negligible heterogeneity, respectively.

A further analysis differentiated fast and slow-paced stimuli with respect to the patient's preferred cadence. Seven studies compared the effects between fast and slow paced rhythmic cueing[86,93,104,105,109–111], whereas four studies analyzed the effects of only fast paced cueing[31,91,112,114]. Analysis for fast-paced stimuli among eleven studies (Supplementary Figure 20), revealed a positive *small* effect size (g: 0.27, 95% C.I: 0.09 to 0.4, I^2: 69%, $p < 0.01$) with substantial heterogeneity. Chester *et al.*[110] was excluded from further analysis as the authors evaluated the effects of fast and slow-paced stimuli on patients with different stages of severity. Likewise, Lopez *et al.*[91] utilized a tempo faster than the other studies i.e. +25% of preferred cadence, hence was also excluded. Thereafter, a positive *small* effect size (g: 0.3, 95% C.I: 0.08 to 0.52, I^2: 0%, $p = 0.7$) with negligible heterogeneity was observed. Similarly, for the slow-paced stimuli five studies were evaluated (Supplementary Figure 21) a positive *small* effect size (g: 0.43, 95% C.I: 0.18 to 0.69, I^2: 83.2%, $p < 0.01$) with substantial heterogeneity was observed. After excluding (Chester *et al.*, 2006) we observed a positive *medium* effect size (g: 0.69, 95% C.I: 0.35 to 1.03, I^2: 20.03%, $p = 0.29$)

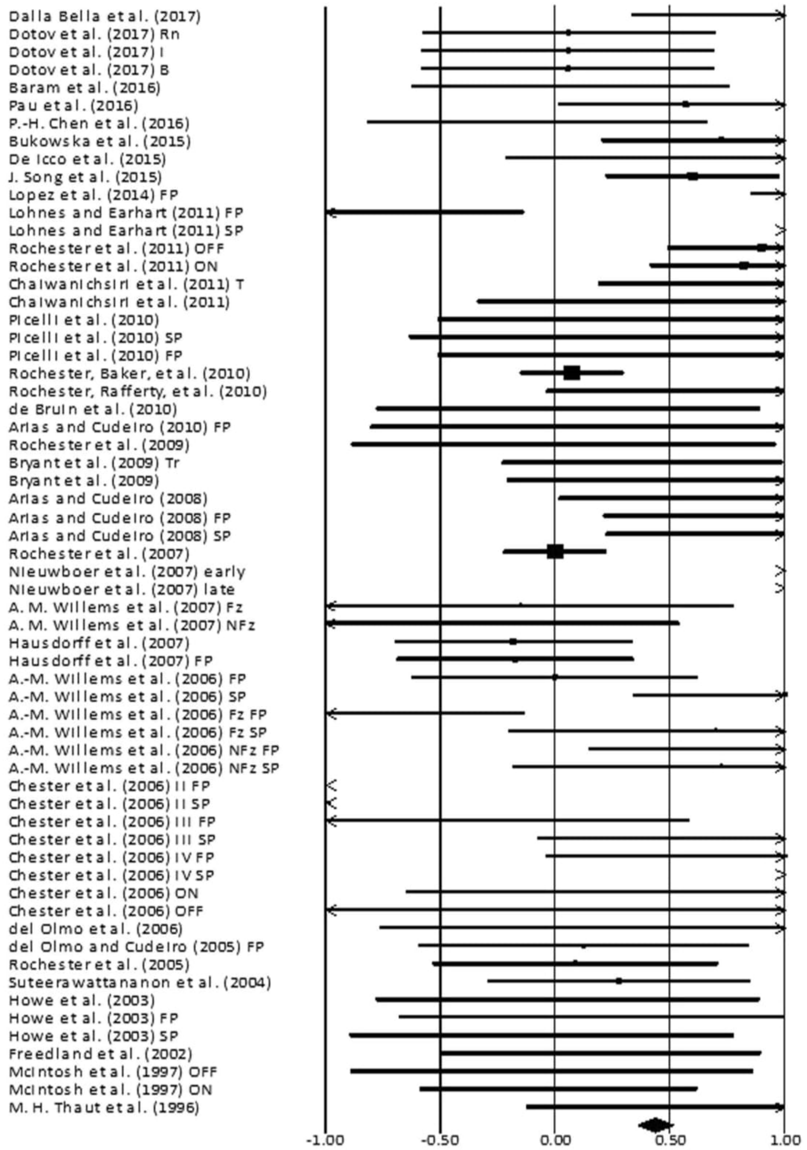

Figure 5. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among parkinsonian patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. (FP: Fast paced, SP: Slow paced, Fz: Freezers, NFz: Non-Freezers, ON: with medications, OFF: without medications, INC: Inclined training, T: Treadmill training, FP T: Fast paced training, I: Isosynchrounous cueing, Rn: Random, BL Biological variability, RAC: Rhythmic auditory cueing).

with negligible heterogeneity. Studies analyzing only the effects of un-modulated rhythmic auditory cueing were analyzed on twenty-three studies (Supplementary Figure 22) and they revealed a positive *small* effect size (g: 0.35, 95% C.I: 0.22 to 0.48, I^2: 35.3%, p = 0.04) with moderate heterogeneity. Studies were then separated based on training or direct application of rhythmic auditory cueing. A sub-group analysis for nine studies analyzing direct application of rhythmic auditory cueing among nine studies (Supplementary Figure 23), revealed a positive *small* effect size (g: 0.12, 95% C.I: −0.11 to 0.35, I^2: 0%, p = 0.72) with negligible heterogeneity. Moreover, for the training group thirteen studies (Supplementary Figure 24) were evaluated and the analysis revealed a positive *small* effect size (g: 0.37, 95% C.I: 0.23 to 0.51, I^2: 26.2%, p = 0.16) with moderate heterogeneity. For training group with 30 minutes of training (Supplementary Figure 25), the analysis revealed a positive *small* effect size (g: 0.36, 95% C.I: 0.21 to 0.51, I^2: 42.5%, p = 0.07) with moderate heterogeneity. Three studies with different training regimes

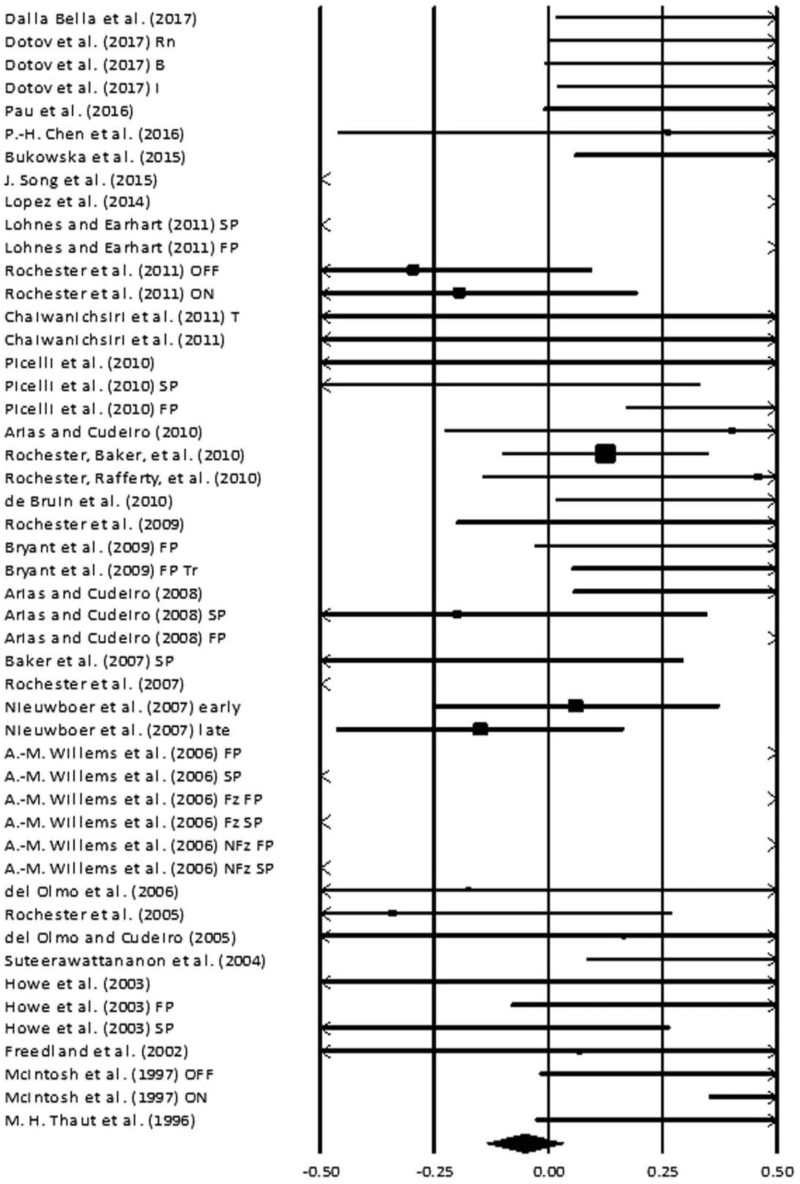

Figure 6. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence among parkinsonian patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in step frequency; a positive effect size indicated enhancement in step frequency. (FP: Fast paced, SP: Slow paced, Fz: Freezers, NFz: Non-Freezers, ON: with medications, OFF: without medications, INC: Inclined training, T: Treadmill training, FP T: Fast paced training, I: Isosynchrounous cueing, Rn: Random, BL Biological variability, RAC: Rhythmic auditory cueing, step frequency: number of steps/minute).

i.e. 20 minutes[85], and 1 hour duration were excluded[102,112]. A further analysis determining treatment duration across more than or less than 5 weeks revealed *medium* positive effect size (g: 0.61, 95% C.I: 0.44 to 0.78, I^2: 71.2%, $p > 0.1$) with substantial heterogeneity. Further sub-group analysis for less than 5 session per week of training revealed *small* positive effect size (g: 0.39, 95% C.I: 0.08 to 0.7, I^2: 0%, $p < 0.11$) with negligible heterogeneity[122,123]. For studies analyzing training for more than 5 sessions per week (Supplementary Figure 26), revealed *small* positive effect size (g: 0.4, 95% C.I: 0.1 to 0.68, I^2: 0%, $p > 0.5$) with negligible heterogeneity.

Randomized controlled trials. A sub group analysis for 4 randomized controlled trials (Supplementary Figure 27) revealed a positive *medium* effect size (g: 0.56, 95% C.I: 0.42 to 0.69, I^2: 98.04%, $p < 0.01$) with substantial heterogeneity. A sub group analysis for two randomized controlled trials analyzing the effects of rhythmic auditory cueing without training revealed no effect (g: 0.0, 95% C.I: −0.28 to 0.3, I^2: 0%, $p = 0.9$) with negligible heterogeneity. Stride length under dual-task condition was analyzed amongst eight studies (Supplementary Figure 28). The analysis revealed a positive *small* effect size (g: 0.31, 95% C.I: 0.14 to 0.48, I^2: 0%, $p = 0.8$) with negligible heterogeneity.

Cadence. Cadence was analyzed amongst thirty studies (Figure 6). Additional sub-group data was extracted from eleven included studies. The analysis of studies revealed a negative *small* effect size (g: −0.05, 95% C.I: −0.13 to 0.03, I^2: 93.6%, $p < 0.01$) with substantial heterogeneity. A positive effect here refers to enhancement in step frequency i.e. number of steps per minute, and a negative effect refers to reduction in step frequency.

Two studies compared the effects of "on" and "off" phase of medications on the patient's affected from parkinsonism[71,107]. A sub-group analysis for "off" treatment groups (Supplementary Figure 29) revealed a negative *small* effect size (g: −0.1, 95% C.I: −0.46 to −0.25, I^2: 81.97%, $p = 0.01$) with substantial heterogeneity. Likewise, for "on" treatment group (Supplementary Figure 30), a positive *small* effect size (g: −0.13, 95% C.I: −0.20 to 0.46, I^2: 89.69%, $p < 0.01$) with substantial heterogeneity was observed. The heterogeneity could be attributed to the use of different tempi i.e. at preferred cadence, at tempo faster than preferred cadence, during rhythmic auditory cueing training by McIntosh *et al.*[107]. Moreover, sub-groups analyses were performed for gait performance with "fast" and "slow" paced tempi with respect to patient's preferred cadence. Five studies compared effects of fast and slow paced stimuli[86,93,104,105,109], whereas two studies evaluated the effects of only fast paced stimuli on gait performance[111,115]. Further, seven studies analyzed only fast-paced stimuli (Supplementary Figure 31), a positive *large* effect size (g: 1.0, 95% C.I: 0.78 to 1.34, I^2: 87.05%, $p < 0.01$) with substantial heterogeneity was observed. A sub-group analysis lead to exclusion of three studies based on the severity of patients included i.e. >9 years of disease duration[85,104,109]. The analysis of fast-paced stimuli in less severe patients revealed a positive *medium* effect size (g: 0.61, 95% C.I: 0.25 to 0.94, I^2: 0%, $p = 0.49$) with negligible heterogeneity. In severe patients, we observed a positive *large* effect size (g: 1.75, 95% C.I: 1.31 to 2.18, I^2: 74.6%, $p = 0.01$) with substantial heterogeneity. However, we excluded Willems *et al.*[86], from further analysis as the authors incorporated a faster tempo i.e. + 20% as compared to + 10% in the other studies[104,109]. We observed a positive *large* effect size (g 1.4, 95% C.I: 0.89 to 1.91, I^2: 27.6%, $p = 0.24$) with marginally moderate heterogeneity. Six studies analyzed the effects of slow-paced stimuli on gait performance in patients (Supplementary Figure 32). We observed a negative *large* effect (g −1.25, 95% C.I: −1.59 to −0.92, I^2: 89.34%, $p < 0.01$) with substantial heterogeneity. Further, on dividing the studies into two categories i.e. >9 years of disease duration (severe and less severe). We observed a negative *medium* effect (g −0.5, 95% C.I: −0.97 to −0.04, I^2: 0%, $p = 0.93$) with negligible heterogeneity, in less severe group. Whereas, a negative *large* effect (g −2.05, 95% C.I: −2.53 to −1.57, I^2: 92.45%, $p < 0.01$) with substantial heterogeneity was observed in the more severe group. Further, we excluded Willems *et al.*[86] because the patients differed considerably in terms of age, disease duration and treatment. We then observed a negative *large* effect (g −1.54, 95% C.I: −2.06 to −1.02, I^2: 0%, $p = 0.37$) with negligible heterogeneity. Twenty studies analyzing rhythmic auditory cueing at preferred cadence revealed a positive *small* effect size (g 0.17, 95% C.I: 0.01 to 0.32, I^2: 90.5%, $p < 0.01$) with substantial heterogeneity (Supplementary Figure 33). On further sub-group analysis nine studies analyzing only rhythmic auditory cueing (Supplementary Figure 34), implementation without training revealed a positive *small* effect size (g 0.30, 95% C.I: 0.07 to 0.53, I^2: 0%, $p = 0.45$) with negligible heterogeneity. Thereafter, studies analyzing only rhythmic auditory cueing implementation with training (Supplementary Figure 35), revealed a *small* negative effect size (g: 0.04, 95% C.I: −0.1 to 0.2, I^2: 93.6%, $p < 0.01$) with substantial heterogeneity. Studies analyzing only rhythmic auditory cueing implementation with 30 min (Supplementary Figure 36), of training revealed a *small* effect size (g: 0.09, 95% C.I: −0.06 to 0.25, I^2: 95.5%, $p < 0.01$) with substantial heterogeneity. Further, we excluded Song and Ryu[124], Pau *et al.*[122], and de Bruin *et al.*[98] as the authors included the training for 8, 12 and 13 weeks, respectively. Furthermore, two studies differing considerably in training regimes were excluded from further analysis[88,125]. Studies analyzing only rhythmic auditory cueing implementation with training for a few sessions in less than 5 weeks (Supplementary Figure 37), revealed a positive *medium* effect size (g: 0.65, 95% C.I: 0.33 to 0.96, I^2: 0%, $p = 0.94$) with negligible heterogeneity. An analysis of studies evaluating rhythmic auditory cueing with training more than 5 days per week (Supplementary Figure 38) revealed a negative *small* effect size (g: −0.22, 95% C.I: −1.16 to 0.71, I^2: 23.6%, $p > 0.05$) with negligible heterogeneity.

Randomized controlled trials. We analyzed three randomized controlled trials which evaluated the effects of rhythmic auditory cueing on cadence (Supplementary Figure 39). Upon analysis, we observed a *small* effect (g 0.07, 95% C.I: −0.08 to 0.22, I^2: 44.6%, $p = 0.13$) with moderate heterogeneity. Cadence under dual-task condition was analyzed amongst nine studies (Supplementary Figure 42). The analysis revealed a positive *small* effect size (g: 0.11, 95% C.I: −0.06 to 0.8, I^2: 0%, $p = 0.8$) with negligible heterogeneity.

Double limb support phase. Double limb support phase was analyzed amongst eight studies[56,86,110,111,114,120,122,126]. Additional sub-group data was extracted from three included studies[86,89,110]. A positive effect here refers to increase in total duration when both feet are in contact with the ground, and vice versa for the negative effect. The analysis (Supplementary Figure 43) revealed a positive *medium* effect size (g: 0.5, 95% C.I: 0.34 to 0.67, I^2: 93.46%, $p < 0.01$) with substantial heterogeneity. With a fast-paced stimulus the rhythmic auditory cueing (Supplementary Figure 44), reveals a *small* effect size in positive domain (g: 0.46, 95% C.I: 0.05 to 0.87, I^2: 92.3%, $p < 0.01$) with negligible heterogeneity. Two studies with slow-paced stimuli (Supplementary Figure 45) yielded *small* positive effects (g: 0.33, 95% C.I: −0.18 to 0.85, I^2: 92.8%, $p < 0.01$) with substantial heterogeneity. This heterogeneity could possibly be attributed to the range of severity i.e. stage II, III and IV of parkinsonism in[110]. Finally, analysis with rhythmic auditory cueing at preferred cadence (Supplementary Figure 46), revealed reduction in double limb support phase with *medium* effect size in negative domain (g: −0.56, 95% C.I: −0.9 to −0.22, I^2: 0%, $p = 0.72$) with negligible heterogeneity.

Turn time. Three studies analyzed the effects of rhythmic auditory cueing on turn time[86,110,111]. A positive effect here refers to increase in total duration for performing a turn during gait, and vice versa for the negative effect. The analysis revealed a negative *large* effect size (g: −2.2, 95% C.I: −2.49 to −1.94, I^2: 83.8%, $p < 0.01$) with substantial heterogeneity. Arias and Cudeiro[31] were excluded from further analysis as the authors utilized a rhythmic auditory cueing with faster tempo. The studies were then segregated according to their patient's characteristics as freezers and non-freezers. The meta-analysis for freezers revealed negative *large* effect size (g: −2.08, 95% C.I: −2.5 to −1.66, I^2: 93.7%, $p < 0.01$) with substantial heterogeneity. Further, an analysis for non-freezers revealed negative *large* effect size (g: −2.3, 95% C.I: −2.71 to −1.88, I^2: 87.67%, $p < 0.01$) with substantial heterogeneity. The heterogeneity cannot be further explained here.

Discussion

The primary objective of this present systematic review and meta-analysis was to develop a current state of knowledge for the effects of rhythmic auditory cueing on gait stability in parkinsonian patients. Out of fifty-included studies 88% studies reported beneficial effects of rhythmic auditory cueing on gait parameters. Further, the meta-analysis yielded significant small-to-large standardized effects for the benefits of rhythmic auditory cueing on spatiotemporal gait parameters for parkinsonian patients. Previous studies have reported substantial negative effects of parkinsonism on spatial parameters of gait for instance, stride length, and gait velocity. The current analysis revealed that both stride length (g: 0.48) and gait velocity (g: 0.27) can be enhanced by rhythmic auditory cueing. However, a generalized negative effect of rhythmic auditory cueing was observed on cadence (g: −0.13). Generally, patients with parkinsonism are characterized with reduced gait velocity, stride length, foot clearance, increased cadence, narrowed base of support, festination and in advanced cases freezing of gait[127,128]. The primary underlying physiological reason being inability to generate a substantial amplitude of motor movements[128], possibly due to deficits in internal timing of movements[45,129–131].

From a neurophysiological aspect, Spaulding *et al.*[43] suggested discrepancies in sensory-motor interactions which might lead to such autonomic disruptions. Nombela *et al.*[45] reattributed and mentioned the dysfunction of an internal cueing system which is associated with coordinating a information exchange between basal ganglia and supplementary motor area. Moreover, studies have also suggested degeneration of a widespread neural network in Parkinson's disease including cerebellum, basal ganglia, somatosensory area and pre-somatosensory area during the degenerative process[45,131]. Kotz and Schwartze[132] reported that during the preclinical stage, hyperactivity in pre-somatosensory area might be a compensatory mechanism for cerebellar dysfunctions. Likewise, in advanced stages selective loss of pyramidal neurons in pre-somatosensory area might result in its underactivity, followed by deficits in temporal processing[45,132], possibly leading to motor block or freezing instances during gait.

The use of rhythmic auditory cueing has been discussed widely in published literature[20,43,45,53,60,74]. This medium of entrainment transfer has been speculated to bypass the affected basal ganglia network (pallidal-supplementary motor area) via another alternative pathway[114,133,134]. Moreover, Fujioka *et al.*[65] reported modulation of neuromagnetic β oscillations with rhythmic auditory stimuli in auditory cortex, cerebellum, inferior frontal gyrus, somatosensory area and sensorimotor cortex. The stimuli has been suggested to activate inferior colliculi[135], cerebellum, brainstem[114,136], sensorimotor cortex[137,138], further instigating reorganization in cortico-cerebellar circuits[70]. Rhythmic auditory cueing has also been suggested to reap the benefits of the preserved neural centres[139], involved in perceiving externally cued and goal directed movements amongst parkinsonian patients (see also "kinesia paradoxica"[140]). The authors proposed that motor activities directed by external sensory cueing evoke pathways via cortical, premotor areas[141], effectively bypassing the affected basal ganglia region[95]. Studies have suggested that rhythmic sensory cues can also replace deficient pallidal-cortical projections, activate the supplementary motor area and aid in motor tasks by mimicking feedforward input, thereby reducing bradykinesia, and associated motor deficits[142]. Similarly, the external cueing can supplement critical spatio-temporal information which is necessary for initiation or facilitating motor activities[30,89], such as during gait or arm movements[69,143]. In context of gait execution the external rhythm can guide the patients to synchronize their ground contact and lift-off times[144]. The auditory patterns might also assist the planning of a motor command before executing a movement[145]. Moreover, the periodicity in rhythmic auditory cueing has also demonstrated to effectively reduce variability in musculoskeletal activation patterns, thereby allowing more economical and consistent motor unit recruitment[46], further smoothing the velocity and acceleration profiles of joint motions by scaling movement time[46].

Typical pharmacological interventions for controlling motor symptoms in parkinsonism include levodopa, dopamine agonists and monoamine oxidase type B inhibitors[40]. Rochester *et al.*[71] interestingly mentioned the limitations of dopaminergic medications on gait dysfunctions associated with degeneration of non-dopaminergic pathways[88]. The medications allow only symptomatic relief and offer no relief from the underlying pathology[146]. Moreover, their benefits in terms of enhancement of gait performance is still debatable. Benefits in turn time[147], stride length, gait speed[148], have been reported in some studies. While some studies report no effects on gait speed[149], cadence[150], stride time variability[151], double limb support duration[152], and reduction in postural stability[147]. The current meta-analysis observed beneficial effects of concurrent application of medications and rhythmic auditory cueing. The analyses reported marginally larger effect sizes for stride length (g: 0.96) and gait velocity (g: 0.55) during the "on" phase of medications, in comparison to the "off" medication group for stride length (g: 0.86) and gait velocity (0.43). However, such differences were not found for cadence, where small negative effect sizes were observed in both "on" (−0.13) and "off" (−0.10) conditions. It is important to note that this analysis shows the compensatory role of rhythmic auditory cueing for counteracting motor deficits in the absence of medications. Although, studies have reported the benefits of the medications in short-term[40], a long term cost concerning motor dysfunction has also been reported[146]. Long-term consumption of medications i.e. both levodopa and levodopa sparring therapy has been associated with severe consequences on health and quality of life such as dyskinesis, loss of drug efficacy and toxicity[40,146]. This is possibly due to levodopa associated decline in dopamine transported integrity located in nigrostriatal nerve terminals[153]. Likewise, the progression of disease has shown to reduce the effectiveness of medications[154], especially on gait characteristics[148]. Therefore, the findings in the present review strongly suggest the use of rhythmic auditory cueing as an adjunct therapy with medications to curb the motor deficits in Parkinson's disease. Moreover, we suggest future studies to analyse the long-term effects of rhythmic auditory cueing with withdrawal of parkinsonian medications, to observe whether the enhancements obtained are resilient and are retained, or not.

Another crucial factor in rhythmic auditory cueing that might significantly influence the rehabilitation progress of a parkinsonian patient is "change in tempo". For instance, change in tempo has been associated with various neurophysiological changes such as, increased neuronal activation in fronto-occipital networks[155], excitability of the spinal motor neurons by reticulospinal pathways, which might possibly reduce the response time for a motor task. Likewise, variation in tempo during training is suggested to be beneficial for maintaining a healthy gait pattern, as constant rhythmic pattern for longer durations have shown to decrease fractal scaling of stride times from healthy 1/f structure, possibly because of organization of stride time variability around a single frequency[156–158]. Additionally, Buchecker *et al.*[159] demonstrated beneficial effects of enhanced variability within training on posture and electromyographic activity (see more from "dynamic system theory"[160]). This might serve to be beneficial for parkinsonian patients to learn how to regulate gait, when passing through fall-prone environments. Moreover, the induction of variability can also be subjected subliminally (for instance changes in tempo, frequency, timbre, interstimulus interval, see also[161]). This might maintain variability in the rehabilitation protocol and simultaneously prevent any conscious stress to excessively speed up, or slow down the gait. Future studies can elucidate these effects by evaluating variability in both the auditory and environmental components within training paradigms. In the current analyses, our aim was to determine the extent of tempo shift which might be beneficial in a rehabilitation protocol. Previous studies have shown that healthy participants can easily modulate gait parameters to changes such as ±20%[162,163], however parkinsonian patients have failed to demonstrate such effects[86]. Supposedly, an exceedingly fast tempo might surpass patient's physiological capabilities and could possibly promote the patient in a high-stress situation[20]. Further this increased tempo associated enhancement in gait velocity, cadence, and double limbs support parameters can lead to a speed-accuracy trade off[86,164]. On the contrary, too slow tempo, for instance might allow the participant more time than required to execute a movement, possibly promoting movement specific re-investment[1,24]. Therefore, the extent of tempo shift should be tailor made according to the patients' capabilities.

Fast pace stimuli i.e. $\leq +10\%$ has been suggested to effectively counteract reduction in gait velocity, cadence, stride length[109]. We observed enhancement in gait velocity (g: 0.7), cadence (1.0), and stride length (0.30). Likewise, use of fast paced tempo is to be encouraged during the early phase of disease. Willems *et al.*[86] suggested an association between tempo reduction and enhanced stride length, but also with reduced cadence and gait velocity. This could possibly be attributed to a speed-accuracy trade-off mechanism, where reduction in gait velocity but enhancement in stride length offers slow, but stable gait performance[165]. The present meta-analysis with the application of slow-paced tempo i.e. $\geq +$ 10% reported benefits in stride length (g: 0.69), reduction in cadence (−1.25), and gait velocity (−0.24). Thereby, suggesting an efficient manoeuvre to counteract the shuffling gait characteristic in parkinsonian patient i.e. short stride length with faster cadence[164,166], especially during the advanced stages of disease where rehabilitation aims should focus more on mobility with stability. Gait training with rhythmic auditory cueing at preferred cadence also has shown to allow benefits in gait velocity (g: 0.43), stride length (0.6), cadence (0.46), reduction in turn time (−2.2), and double limb support phase (−0.56). However, a regular use of the same tempo at preferred cadence might impact recovery in terms of fractal scaling. Therefore, in terms of practical application of different tempo in rehabilitation protocols we suggest utilization of preferred, slow and fast tempi (±10% of preferred cadence), to maintain variability in gait during training.

As per the training dosage that should possess most beneficial effects, we observed fourteen studies analysing the effects of rhythmic auditory training with 30 minutes duration, two studies each analysed the training for 20, 45 minutes and 1 hour. Beneficial enhancements in gait parameters were observed in all the studies analysing the effects during a 30 minutes gait training session. These effects were also evident during a 45 minutes session, and for 20 minutes sessions. However, one study analysing the effects of training for long sessions (1- hour) revealed beneficial effects with a fast paced stimuli[112], while the other revealed no effects[112]. We believe, both mental and physical fatigue could have played a crucial aspect for affecting the gait parameters[167] during the long sessions. Nevertheless, more evidence from training studies is required to ascertain the negative effects of long training sessions. Based on the current evidence we strongly suggest limiting the treatment duration between 25–40 minutes/session. Likewise, a minimum of at least 3–5 sessions of rehabilitation are suggested per week, because highest enhancement in stride length (g: 0.39), cadence (0.65) and gait velocity (0.73) were observed during this period. However, this analysis of training dosage must be carefully interpreted as substantial heterogeneity was observed within studies, due to difference in severity and training regimes. These suggestions are in line with the findings of Nascimento *et al.*[168] where the authors reported application of rhythmic auditory cueing for 30 minutes and for 4 times a week for stroke patients.

It is important to note that the retention of enhancements in gait parameters relies not only on the training received in the clinic but also depends largely on how much the patient follows the treatment protocol at home. The patient usually spends limited amount of time in a rehabilitation setting. Therefore, performing and re-executing the tasks effectively and regularly at home is vital for enhancements in motor performance and quality of life[112]. Lim *et al.*[11] for instance, reported enhancement in walking activity to 35 minutes per day (qualifying the 30 minutes criteria by centres for disease control and prevention[169]) post home-based gait training with rhythmic auditory cueing. In addition, a home-based training device allowed a 4.2% increase in posture and gait score, 5.5% reduction in freezing instances, 4 cm increase in step length and a 5 cm increase in walking speed[120]. This type of home-based intervention could possibly be beneficial for people lacking proper exposure to medical interventions in developing countries[125]. For instance, parkinsonian patients lacking effective treatment can utilize smartphone devices with dynamic metronome apps such as Walkmate[157], Listenmee[91], which with proper medical guidance might allow curbing the motor deficits associated with Parkinson's disease[170]. In addition, combining the use of external rhythmic entrainment process with different treatment strategies might be a useful tool in rehabilitation as Post *et al.*[171] suggested the most effective rehabilitation protocol for parkinsonian patients to be multidisciplinary. We included studies analysing the beneficial effects of co-joint application of treadmill and rhythmic auditory cueing. Combining treadmill in gait training sessions offered additional benefits as compared to conventional over ground sessions[38]. For instance, Bello *et al.*[172], reported improvements in stride length, gait speed, time up and go performance and static postural stability, with retention evitable one-month post training. The current meta-analysis revealed beneficial effects of treadmill training in gait velocity (g: 1.0).

Additionally, using the rhythmic entrainment factor with music, could possibly provoke benefits in both psycho-physiological domains[173–177]. For instance, regulating stress levels, mediating arousal, emotions, internal motivation, memory, attention, executive functions[178,179], muscle power[180], and endurance[178]. Modifications in the types of auditory cueing can also impart differential effects on psycho-physiological aspects of performance. For instance, timbre of an auditory input at a higher intensity merged in a broad ascending melody and a rich harmony can possibly motivate a patient to exert more power[182,183]. Also, parkinsonian and associated ageing changes in patients often characterize a higher threshold for action relevant acoustic input, therefore using ecologically valid action related sounds convening spatio-temporal information can possibly enhance saliency of sensory information, transferring spatio-temporal information effectively and therefore providing more benefits[94,95,184,185]. This was also demonstrated by Dotov *et al.*[94], and[95,185]. These authors demonstrated beneficial effects on spatio-temporal gait parameters with biologically variable rhythmic auditory cueing as compared to isosynchronous cueing. Thereby, suggesting potential for modification of auditory signal characteristics for enhancing motor performance in parkinsonian patients. Further methods providing real-time auditory information could possess considerable benefits for enhancing gait performance. One of these methods is movement sonification[73]: here movement parameters are transformed in real-time to sound with an aim to enhance motor perception and performance by targeting areas associated with biological motion perception[66,186,187]. Although few research has been carried out to analyse its effects on parkinsonian gait performance[95,188], yet, several studies highlight its impact on motor performance and its potential for motor rehabilitation[189,190]. Schmitz and Effenberg[190] have shown that the synchronization of cyclic movement patterns with movement sonification reduces variability and increases constancy of movements as compared to discrete auditory stimuli. Furthermore, listening to sonified human movements in contrast to or in addition to non-human auditory stimuli seems to influence movement timing and strengthen entrainment effects[191], possibly by activating mechanisms of biological motion processing in the human brain[66,192]. Moreover, listening to sonification might allow parkinsonian patients to identify their own movement amplitudes and compare their sound with the sound of an auditory movement model, thereby creating a new auditory reference frame. This reference framework might allow a comparison between instructed and intended movement, possibly amplifying the internal representation of movements[193]. This might then induce effects on motor behaviour beyond rhythmic adjustments[58].

Moreover, counteracting alleviation in conscious attention towards autonomic control, in parkinsonian patients is very critical. Several studies have tried to co-jointly analyze the effects of dual-tasks and rhythmic auditory cueing i.e. to analyze the robustness of auditory-motor coupling with higher information processing constraints[109,116]. Dual-tasks are expected to protect the automaticity of the motor tasks, by possibly engaging information processing resources necessary for conscious control (see also constrained action hypothesis, [27]). This present analysis observed small effects on gait parameters with dual task application i.e. gait velocity (g: 0.38), stride length (0.31), and cadence (0.11). Beneficial effects on age related controls have been reported during similar interventions[109]. Nevertheless, rhythmic auditory cueing both with and without training reduced the constraining effects of a manual dual task over gait[88,121]. Interpretations from our results however suggest that rhythmic auditory cueing counteracts cognitive constraints imposed by cognitively demanding dual-tasks such as carrying a tray, and that this external cueing might be useful in counteracting fall prone situations such as escalators, traffic signals (see more cross-modal overload substitution[194]). Moreover, dual-task training has been suggested to impart beneficial impacts on stability, as the training phase might allow smoothing of cognitive abilities[195]. Possibly, including dual-task training regimes with different complexities with rhythmic auditory cueing might enhance functional rehabilitation progress, self-dependence for instance while carrying out activities of daily living. Lastly, patients with Parkinson's have been shown to demonstrate considerable rigidity in trunk motions[196], possibly leading to asymmetry, reduction in arm swing amplitude[197], and trunk rotation during gait[198]. Son and Kim[199] reported beneficial effects of rhythmic auditory cueing for increasing arm swing amplitude (36.4° ± 3° vs 25.2° ± 2.8°) and trunk rotation (7° ± 1.3° vs 6.6° ± 0.9°). Thereby, suggesting the beneficial effects of rhythmic auditory cueing beyond the spatiotemporal parameters of gait for enhancing stability.

Our results are consistent with the findings of previous meta-analysis by Spaulding *et al.*[43], stride length (g: 0.49) and gait velocity (0.54), and cadence (g: 0.55). However, the review did not analyse the quality of included studies, and abstained from performing a heterogeneity analysis. Moreover, Rocha *et al.*[42] included only seven studies and reported moderate-to-substantial heterogeneity in between studies and abstained from performing sub-group analysis to evaluate the reason for heterogeneity. Therefore, this present literature review for the first time bridges the gap in parkinsonian literature concerning the effects of presence/absence of medications, tempo variations, dual-task settings, and training dosage for improving gait performance with rhythmic auditory cueing.

In conclusion, this review strongly suggests the early incorporation of rhythmic auditory cueing for enhancing gait performance in patients affected from parkinsonism. The results based on meta-analysis suggests training with rhythmic auditory cueing should include tempo variations of ±10% with respect to the preferred cadence, for a minimal period of 20–45 minutes per day, for at least 3–5 days per week. However, in the absence of such facilities as in developing countries, smartphone based apps should be promoted by medical practitioners for home based therapy.

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Author Contributions

S.G. conceptualized the study, carried out the systematic-review, statistical analysis, and wrote the paper. I.G. assisted in statistical analysis. I.G., G.S. and A.O.E. acted as additional reviewers and assisted in the review of the final manuscript. A.O.E., G.S. conceptualized the application of real-time movement sonification approach on parkinsonian patients.

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Chapter 3: Effect of (music-based) rhythmic auditory cueing training on gait and posture post-stroke: A systematic review and dose-response meta-analysis

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Effects of (music-based) rhythmic auditory cueing training on gait and posture post-stroke: A systematic review & dose-response meta-analysis

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Gait dysfunctions are common post-stroke. Rhythmic auditory cueing has been widely used in gait rehabilitation for movement disorders. However, a consensus regarding its influence on gait and postural recovery post-stroke is still warranted. A systematic review and meta-analysis was performed to analyze the effects of auditory cueing on gait and postural stability post-stroke. Nine academic databases were searched according to PRISMA guidelines. The eligibility criteria for the studies were a) studies were randomized controlled trials or controlled clinical trials published in English, German, Hindi, Punjabi or Korean languages b) studies evaluated the effects of auditory cueing on spatiotemporal gait and/or postural stability parameters post-stroke c) studies scored $\geq$4 points on the PEDro scale. Out of 1,471 records, 38 studies involving 968 patients were included in this present review. The review and meta-analyses revealed beneficial effects of training with auditory cueing on gait and postural stability. A training dosage of 20–45 minutes session, for 3–5 times a week enhanced gait performance, dynamic postural stability i.e. velocity (Hedge's g: 0.73), stride length (0.58), cadence (0.75) and timed-up and go test (−0.76). This review strongly recommends the incorporation of rhythmic auditory cueing based training in gait and postural rehabilitation, post-stroke.

Stroke is the second main cause of disability across the world[1,2]. Stroke related disability substantially affects activities of daily living[3], promotes dependency[4], social isolation[5], and a poorer quality of life[6]. Physical manifestations in patients affected from stroke are usually exhibited on the contralateral side of the affected brain region[7]. However, independent to the site of lesion paralytic changes, cognitive dysfunctions, and sensory impairments are also observed in most of the cases[8]. Despite advancements in modern rehabilitation approaches poor prognosis for motor recovery post-stroke is still prevalent[9], especially for recovering gait[10], and postural stability[11]. Studies suggest that gait functionality is an important predictor for determining the health status outcome and quality of life in stroke patients[12].

Best practice principles in stroke rehabilitation indicate that effective stroke interventions should be individually-tailored, meaningful, task-specific, involve sufficient repetition and challenge to induce recovery[13–15]. Training with rhythmic auditory cueing has the potential to meet such guidelines while yielding improvements in motor function[16,17]. Literature suggests that the efficacy and specificity of training with auditory cueing relies on the reinforcement of auditory-motor functional connectivity in related brain systems[16–19]. Consequentially, increased motor cortex excitability in the affected hemisphere and enhancement of motor recovery on the affected side is observed[20–22]. Likewise, neuroimaging studies outlining a time frame for establishing auditory-motor co-activations have suggested that such training can utilize the intricate auditory-motor functional connectivity and instigate motor (re)learning efficiently as compared to conventional approaches[23–26]. A recent dose-response meta-analysis by Ghai[17] has also substantiated these findings. The author reported considerable enhancements in arm function post-stroke after training with auditory cueing in in sessions lasting between 30 min to 1-hour.

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Despite this compelling evidence, a joint consensus concerning the influence of auditory cueing-based therapy and effective training dosages for recovering gait post-stroke are still warranted.

To the best of our knowledge, five systematic reviews and meta-analyses till date, have evaluated the effects of rhythmic auditory cueing on gait recovery post-stroke[27–31]. Even though, all of the included reviews reported beneficial effects of auditory cueing on gait performance, we observed substantial methodological limitations in these reviews: a) A limited number of controlled clinical trials were included b) The search for the studies was performed across few academic databases c) Ambiguity in the meta-analysis approach was observed i.e. no sub-group analysis or heterogeneity tests were performed d) The search for relevant literature was limited to few languages. Therefore, interpretation of results from these reviews from both a qualitative and quantitative perspective might indicate a bias. Moreover, till date, no meta-analysis has synthesized the current state of literature for determining specific training dosages with rhythmic auditory cueing for recovering gait and postural stability post-stroke. Therefore, in this present systematic review and meta-analysis an attempt has been made to address these shortfalls, by focusing on two main objectives:

1. Analyze the influence of training with rhythmic auditory cueing on spatiotemporal gait and postural stability parameters in individuals post-stroke.
2. Determine appropriate training dosages with auditory cueing that allows substantial enhancements in gait and postural stability.

Findings from this review shall help augment the predictive power concerning a patient's response to auditory cueing interventions, thereby guiding researchers, clinicians and patients themselves in their choice of an optimal rehabilitation intervention.

Methods

This review was conducted according to the guidelines outlined by Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA statement[32]. A PRISMA checklist has been provided in Supplementary Table 3.

Data sources and search strategy. Nine academic databases were searched from inception until December 2017: Web of science, PEDro, EBSCO, Scopus, MEDLINE, Indian citation index, Cochrane central register of controlled trials, EMBASE and PROQUEST. A sample PICOS search strategy for EMBASE academic database has been provided (Table 1).

An inclusion criterion was determined by two reviewers (S.G, I.G) for the systematic review procedure. The inclusion criterion for the studies were (i) The studies were either randomized controlled trials, cluster randomized controlled trials or controlled clinical trials (ii) The studies evaluated music-based auditory cueing interventions (any training duration, treatment setting) (iii) The studies evaluated spatiotemporal gait parameters (gait velocity, cadence, stride length, stride time, single/double-limb support duration)[33] (iv) The studies evaluated static or dynamic aspects of postural stability (Berg balance scale, Fugl-Meyer lower body assessment, Timed-up and go test, Timed sit-to-stand test, Activity-specific balance confidence scale)[34] (v) The studies included a subjective analysis of stroke outcome (optional) (vi) The studies scored $\geq$4 points on PEDro quality scale (studies scoring $<$3 considered of "poor" quality with high risk of biasing excluded[35]) (vii) The studies were conducted on human participants affected from stroke (any age, disease duration and type) (viii) The studies were published in peer-reviewed academic journals or conference proceedings (un-published "grey" literature was not included) (ix) The studies were published in English, German, Hindi, Punjabi or Korean languages.

The two reviewers (S.G, I.G) duplicated the study selection, data extraction and quality assessment of the included studies. After selection of the articles, following data were extracted from each study i.e. author, journal name, publication year, selection criteria for participants, total sample size, description of the participants (gender, age, health status, duration of stroke, comorbidities), applied treatment intervention, characteristics of applied auditory stimuli, treatment interventions for the control group, dual-task application (if any), outcome measures, results, conclusions and special notes by authors. The data were then summarized and tabulated (Supplementary Table 2). In case of lack of quantitative data in the manuscript, the reviewers (S.G, I.G) made attempts to contact respective corresponding authors for data.

Quality and risk of bias assessment. The quality of the reviewed studies was assessed using the PEDro methodological quality scale[36]. This quality scale consists of 11 items which address external validity, internal validity, and interpretability. The scale can effectively detect potential bias with fair to good reliability[37], and validity[36]. A rating of the methodological quality of the studies was carried out by both the primary (S.G) and secondary (I.G) reviewer. Ambiguous issues were discussed between the reviewers and a consensus was reached. The interpretation of the rated studies were that studies scoring 9–10 were considered of "excellent", 6–8 of "good", 4–5 of "fair", and <3 of "poor" quality[38].

Data Analysis. A within-group i.e. pre-post meta-analysis approach was incorporated in the review to develop a quantitative interpretation of the auditory cueing interventions[39]. The meta-analyses were conducted using CMA (Comprehensive meta-analysis V 2.0, USA). The data in this analysis was distributed and separately analyzed for each outcome measure such as gait velocity, stride length, cadence, and timed-up and go test. Here, the use of either random/fixed effect meta-analysis was dependent upon the presence/absence of heterogeneity during the group analysis, respectively[40]. Moreover, forest plots with 95% confidence intervals were plotted. The effect sizes were adjusted and reported as weighted Hedge's g[41]. A positive effect size would represent a favorable outcome of the intervention and vice versa for the negative effect. Further, the thresholds for the interpretation of

	Databse	**Embase**
	Date	**10/12/2017**
PICOS	**Strategy**	**#1 and #2 and #3 and #4 and #5 and #6**
P	**#1**	('Stroke' OR 'Apoplexy' OR 'CVA' OR 'Cerebral Stroke' OR 'Cerebrovascular accident' OR 'Cerebrovascular Accident, Acute' OR 'ABI' OR 'Acquired brain injury' OR 'Cerebrovascular Apoplexy' OR 'Cerebrovascular Stroke' OR 'Stroke, Acute' OR 'Stroke, sub-acute' OR 'Stroke, chronic' OR 'Vascular Accident, Brain' OR 'Hemiplegia, Crossed' OR 'Hemiplegia, Flaccid' OR 'Hemiplegia, Spastic' OR 'Hemiplegia, Transient' OR 'Monoplegia' OR 'Lower Extremity Paresis' OR 'Muscular Paresis' OR 'Muscle Paresis' OR 'Monoparesis' OR 'Hemiparesis')/de OR (Stroke OR Apoplexy OR CVA OR Cerebral Stroke OR Cerebrovascular accident OR Cerebrovascular Accident, Acute OR ABI OR Acquired brain injury OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Stroke, Acute OR Stroke, sub-acute OR Stroke, chronic OR Vascular Accident, Brain OR Hemiplegia, Crossed OR Hemiplegia, Flaccid OR Hemiplegia, Spastic OR Hemiplegia, Transient OR Monoplegia OR Lower Extremity Paresis OR Muscular Paresis OR Muscle Paresis OR Monoparesis OR Hemiparesis):ti,ab
I	**#2**	('rhythmic auditory cueing' OR 'rhythmic auditory cueing' OR 'rhythmic acoustic cueing' OR 'rhythmic auditory entrainment' OR 'metronome cueing' OR 'metronome' OR 'rhythmic metronome cueing' OR 'acoustic stimulus' OR 'acoustic cueing' OR 'acoustic cueing' OR 'external stimuli' OR 'external cueing' OR 'external cueing' OR 'music therapy' OR 'Neurological music therapy' OR 'tempo' OR 'beat' OR 'rhythm' OR 'RAC' OR 'NMT' OR 'real-time auditory cueing' OR 'sonification')/de OR (rhythmic auditory cueing OR rhythmic auditory cueing OR rhythmic acoustic cueing OR rhythmic auditory entrainment OR metronome cueing OR metronome OR rhythmic metronome cueing OR acoustic stimulus OR acoustic cueing OR acoustic cueing OR external stimuli OR external cueing OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT OR real-time auditory cueing OR sonification)ti,ab
C	**n/a**	n/a
O	**#3**	('walking' OR 'gait' OR 'locomotion' OR 'range of motion' OR 'ROM' OR 'ambulation' OR 'mobility' OR 'treadmill gait' OR 'balance' OR 'stability' OR 'stride' OR 'gait training' OR 'gait rehabilitation' OR 'postural stability' OR 'posture' OR 'dynamic posture' OR 'dynamic balance' OR 'static posture' OR 'static balance' OR 'balance')/de OR (walking OR gait OR locomotion OR range of motion OR ROM OR ambulation OR mobility OR treadmill gait OR balance OR stability OR stride OR gait training OR gait rehabilitation OR postural stability OR posture OR dynamic posture OR dynamic balance OR static posture OR static balance OR balance);ti,ab
S	**#4**	('intervention study' OR 'cohort analysis' OR 'longitudinal study' OR 'cluster analysis' OR 'crossover trial' OR 'cluster analysis' OR 'randomized trial' OR 'major clinical study')/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab
	#5	('rehabilitation' OR 'treatment' OR 'rehab' OR 'management' OR 'therapy' OR 'physiotherapy' OR 'physical therapy' OR 'prevention' OR 'risk prevention')/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
	#6	('age groups' OR 'adolescent' OR 'young' OR 'elderly' OR 'old' AND ('gender' OR 'male' OR 'female')/de OR (age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female));ti;ab

Table 1. Sample search strategy EMBASE.

weighted effect sizes are as follows: an effect size of 0.2 is considered as a small effect, 0.5 as a medium effect and 0.8 as a large effect[42]. Further, heterogeneity between the studies was computed using I^2 statistics[42,43]. The interpretation of heterogeneity via I^2 statistics is as follows: 0–25% is considered as negligible heterogeneity, 25–75% as moderate heterogeneity and $\geq$75% as substantial heterogeneity, respectively. In cases where substantial heterogeneity was observed sensitivity analysis were performed to elucidate the "significant" cause of heterogenity[44]. In this analysis, the results were compared by either including or excluding results from studies that used inadequate randomization methods and/or differed in terms of applied intervention.

In the included studies rhythmic auditory cueing was subjected to patients according to their comfortable cadence. The evaluated parameters were spatiotemporal parameters of gait i.e. gait velocity, stride length and cadence. Furthermore, sub-group analyses were also performed to determine specific training dosages for application of rhythmic auditory cueing in a gait rehabilitation protocol. The main emphasis was laid to determine the duration of a training session and the number of days for which these sessions were performed during a week. Likewise, sub-group analyses were also conducted to analyze joint effects of treadmill training together with rhythmic auditory cueing on gait performance in stroke patients. This analysis was performed to analyze the joint influence of adjunct treadmill training with auditory cueing.

Details of weighted effect size, 95% confidence intervals, significance and heterogeneity have been reported for each outcome measure. Additionally, an analysis for publication bias was performed by Duval and Tweedie's trim and fill procedure[45]. This method involves imputation of the asymmetric studies from the left side to locate the unbiased effect and then re-fills the plot by reinserting the trimmed studies on the left and their imputed counterparts on the right to the mean effect[46]. The graph plots the evaluated weighted effect size i.e. Hedge's g values against standard error on a random effect model. The alpha level was set at 5%.

Results

Characteristics of included studies.

The initial search across the academic databases, department's collection of articles and university's library repository (additional sources) yielded a total of 1,471 studies, which on implementing our inclusion/exclusion criteria, were reduced to 38 (Fig. 1). Thereafter, quantitative data was extracted from 25 studies. In the remaining studies where quantitative data was either mentioned in figures or not mentioned at all, attempts were made by the reviewers (S.G, I.G) to contact respective authors for relevant data. Qualitative data from the included studies have been summarized in (Supplementary Table 2). Of the 38 included studies, 11 were randomized controlled trials and 27 were controlled clinical trials. All the included studies reported that the stroke patients also received conventional physical therapy in addition to auditory cueing.

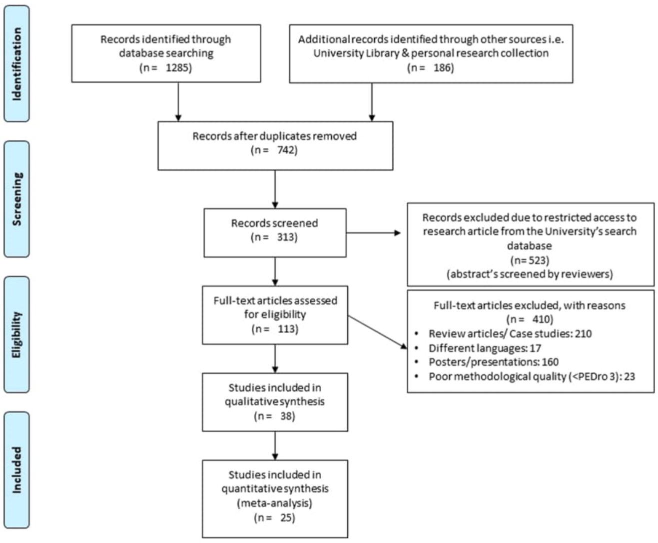

Figure 1. PRISMA flow chart for the inclusion of studies[32].

Participants. A total of 968 participants were analyzed in the 38 studies. All the studies included mix gender patients affected from stroke. The included studies provided data on 322 females, and 529 males. Five studies did not specify the gender of the included patients[47–51]. Descriptive statistics relating to the age (mean ± standard deviation) of the participants were tabulated across the studies. Disease duration of stroke patients were also extracted (see Supplementary Table 2), however, five studies did not mention these details[47–51].

Risk of bias. Individual scores attained by the studies using the PEDro scale for each factor has been mentioned (Supplementary Tables 1, 2). The average PEDro score for the 38 included studies was computed to be Median (1st, 3rd quartile): 5.5 (5, 7) out of 11, indicating on an average a "fair" quality of the studies. During the methodological rating two studies scored eight, nine studies scored seven, nine studies scored six, twelve studies scored five, and six studies scored four (Supplementary Tables 1, 2). Risk of biasing across the studies has also been demonstrated in Fig. 2.

According to the Trim and Fill method 12 studies are missing (Fig. 3). Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.66 (0.50 to 0.83). Using Trim and Fill method the imputed point estimate is 0.80 (0.64, 0.95).

Meta-Analysis. *Outcomes.* The current qualitative and quantitative evidence from the review suggests beneficial effects of rhythmic auditory cueing on gait and postural stability performance post-stroke. All 38 studies included in the review reported significant enhancements in gait performance and dynamic postural stability for post-stroke patients with rhythmic auditory cueing (Supplementary Table 2).

Meta-analysis report. *Gait velocity.* Gait velocity was assessed among 25 studies. Additional data concerning different types of auditory stimulations[52], and lesion sites[53], in stroke patients was retrieved from two studies (Fig. 4). The analysis of studies revealed (Fig. 4) a medium effect size in the positive domain (g: 0.68, 95% C.I: 0.42 to 0.93) with negligible heterogeneity (I^2: 7.54%, $p > 0.05$). Further, a sub-group analysis was performed to evaluate the joint effects of auditory cueing and treadmill gait training (Supplementary Figure 1) among three studies. A small effect size in the positive domain (g: 0.15, 95% C.I: −0.34 to 0.64) was observed with moderate heterogeneity (I^2: 31.3%, $p > 0.05$).

Furthermore, we evaluated the effects of training with rhythmic auditory cueing. Based on the current included studies and previous findings[19,27,54], a training dosage of 20–45 minutes of training session for 3–5 sessions a week was determined. Here, 16 studies with a similar training dosage were included in a sub-group analysis. The analysis of studies revealed (Supplementary Figure 2) a medium effect size in the positive domain (g: 0.73, 95% C.I: 0.39 to 1.08) with no heterogeneity observed in between the studies (I^2: 0%, $p > 0.05$). A comparative analysis for a smaller training dosage i.e. 8–10 minutes could not be included in this analysis due to the presence of heterogeneity between the studies. Here, two studies performed gait training with a duration ranging from 8–10 minutes[48,55]. There were differences in between the studies concerning the characteristics of the delivered auditory stimulations. Hayden, *et al.*[55] for instance, delivered rhythmic auditory cueing according to a patient's

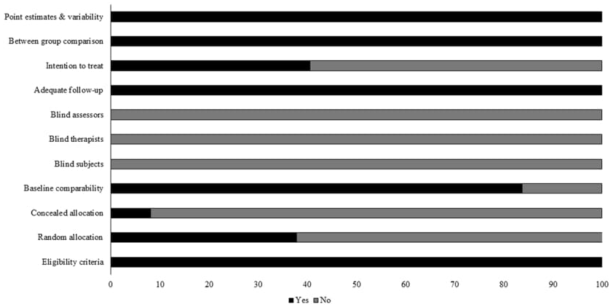

Figure 2. Risk of bias across studies.

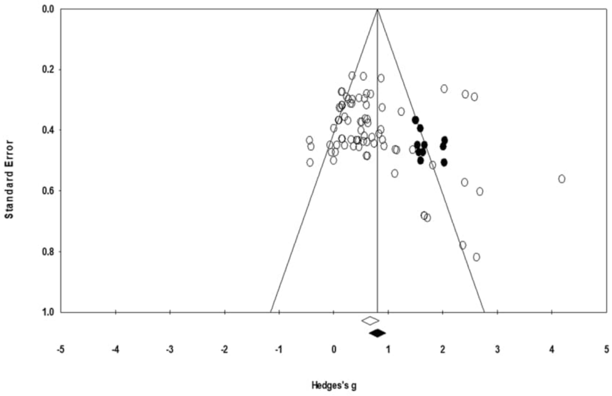

Figure 3. Trim and Fill funnel plot for Hedge's g and standardized effect for each value in the meta-analysis. Each of the effect is represented in the plot as a circle. Imputed studies are represented by darkened circles. Funnel boundaries represent area where 95% of the effects are expected to lie if there were no publication biases. The vertical line represents the mean standardized effect of zero.

preferred cadence and only allowed increments in tempo ranging from 1–3 bpm. On the contrary, Kim and Oh[48] subjected their participants to fixed tempo ranging from 20–100 bpm (Supplementary Table 2). Therefore, a comparison of different training dosages was not performed.

Additionally, a comparative sub-group analysis for five studies analyzing effects of rhythmic auditory cueing without training (Supplementary Figure 3) revealed a comparatively smaller medium effect size in the positive domain (g: 0.33, 95% C.I: 0.12 to 0.54) and here as well no heterogeneity was observed in between the studies (I^2: 0%, $p > 0.05$).

Stride length. Stride length was assessed among 20 studies. Additional data concerning different: types of auditory stimulations[52], and lesion sites[53], in stroke patients was retrieved from two studies. The combined analysis of studies revealed (Fig. 5) a medium effect size in the positive domain (g: 0.50, 95% C.I: 0.26 to 0.73) with no heterogeneity (I^2: 0%, $p > 0.05$). Further, a sub-group analysis for two studies evaluated the effects of treadmill gait training with auditory cueing (Supplementary Figure 4). A medium effect size in the positive domain (g: 0.45, 95% C.I: -0.15 to 1.07) was observed with no heterogeneity (I^2: 0%, $p > 0.05$).

Also, to determine specific training dosage sub-group analyses were again conducted. Here, 11 studies with a similar training dosage i.e. (20–45 minutes of training session for 3–5 sessions a week) were included in the sub-group analysis. The analysis of studies revealed (Supplementary Figure 5) a medium effect size for this training duration in the positive domain (g: 0.58, 95% C.I: 0.17 to 0.98) and no heterogeneity was observed in between the studies (I^2: 0%, $p > 0.05$). Additionally, a comparative sub-group analysis for four studies analyzing effects of rhythmic auditory cueing without training (Supplementary Figure 6) revealed a comparatively smaller medium effect size in the positive domain (g: 0.25, 95% C.I: 0.02 to 0.48) with no heterogeneity (I^2: 0%, $p > 0.05$).

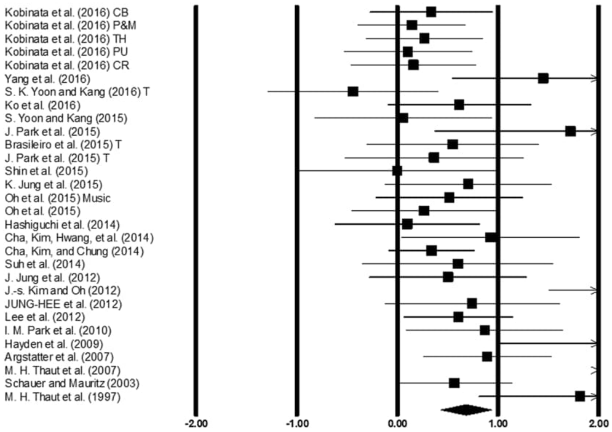

Figure 4. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill).

Cadence. Cadence was assessed among 23 studies. Additional data was retrieved from one study, concerning a different type of auditory stimulation[52]. The analysis of studies revealed (Fig. 6) a large effect size in the positive domain (g: 0.86, 95% C.I: 0.50 to 1.22) with negligible heterogeneity between the studies (I^2: 16.7%, $p > 0.05$). Further, a sub-group analysis for four studies evaluated the effects of treadmill gait training with auditory cueing (Supplementary Figure 7). A medium effect size in the positive domain (g: 0.39, 95% C.I: -0.33 to 1.13) with negligible heterogeneity was observed (I^2: 14.4%, $p > 0.05$).

For evaluating effects of specific training dosage further sub-group analyses were conducted. Here, 11 studies with a similar training dosage i.e. (20–45 minutes of training session for 3–5 sessions a week) were included in the sub-group analysis. The analysis of studies revealed (Supplementary Figure 8) a medium effect size in the positive domain (g: 0.75, 95% C.I: 0.34 to 1.10) with moderate heterogeneity (I^2: 32.8%, $p > 0.05$). Additionally, a comparative sub-group analysis for four studies analyzing the effects of rhythmic auditory cueing without training (Supplementary Figure 9) revealed a smaller medium effect size in the positive domain (g: 0.52, 95% C.I: 0.17 to 0.87) and no heterogeneity was observed in between the studies (I^2: 0%, $p > 0.05$).

Timed-up and go test. Time up and go test was assessed among 6 studies. A negative effect size represented enhancement in the performance on timed-up and go test and vice versa for the positive effect size. The analysis of studies revealed (Supplementary Figure 10) a medium effect size in the negative domain (g: −0.76, 95% C.I: −1.36 to −0.16) with moderate heterogeneity in between the studies (I^2: 25.1%, $p > 0.05$).

Discussion

The primary objective of this present systematic review and meta-analysis was to synthesize the current state of knowledge and determine the effects of rhythmic auditory cueing on gait performance and postural stability in stroke patients. The findings from the current meta-analyses suggest positive, *medium*-to-*large* standardized effects (pre vs post intervention effects) of rhythmic auditory cueing to enhance gait performance and dynamic postural stability post-stroke. The main findings are:

1. Spatiotemporal gait parameters were considerably enhanced after training with rhythmic auditory cueing i.e. gait velocity (g: 0.68), stride length (g: 0.50), and cadence (g: 0.86).
2. Dynamic postural stability was considerably enhanced after training with rhythmic auditory cueing i.e. duration of timed-up and go test performance was reduced (g: −0.76).
3. The enhancements in spatiotemporal gait parameters were substantial in studies following a training regime as compared to studies analyzing a direct application of auditory cueing i.e. gait velocity (training: 0.73, no training: 0.33), stride length (training: 0.58, no training: 0.25) and cadence (training 0.75, no training: 0.52).
4. A dose-response analysis revealed that gait and balance training with auditory cueing for 20–45 minutes session, for 3–5 times a week provided maximum increments in spatiotemporal gait and dynamic postural stability performance.

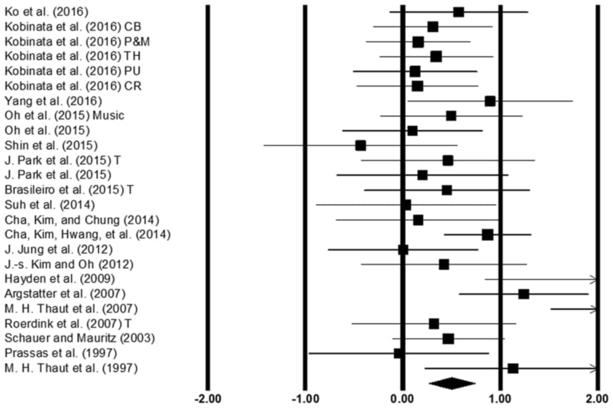

Figure 5. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on stride length amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill).

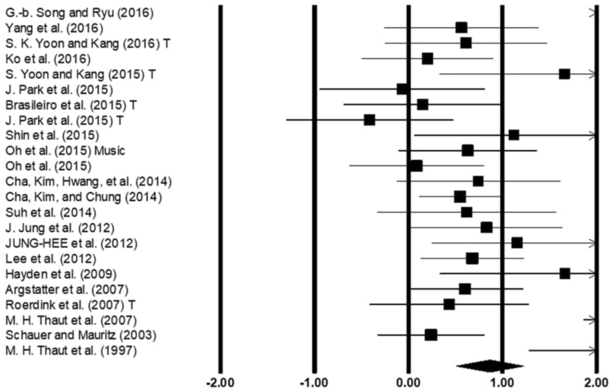

Figure 6. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on cadence amongst post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. (T: Treadmill).

Several reasons can be affirmed to these observed gait and postural performance enhancements after training with auditory cueing. Firstly, from a neurophysiological perspective we presume that auditory cueing could have facilitated the deficit internal neural timing in stroke patients by bypassing the deficit fronto-striatal networks[56], and the basal ganglia-somatosensory area motor loop[57], through alternate pathways (see)[58–60]. Moreover, the enhanced sensorimotor synchronization developed between the perception of auditory cueing and gait execution might be due to enhanced periodic/phase corrections[61]. This development of enhanced temporal template/prediction with the auditory stimulations could be due to pre-attentive "micro-timing", attentive "timescale" processing capabilities of the neural networks mediating phase, periodic corrections, respectively[62]. Secondly, training with auditory cueing could have facilitated re-organization of the deficit neural structures for instance, the stimulation could have increased the motor cortex excitability in the affected hemisphere further resulting in the motor recovery[21,29,63]. Thirdly, based on the findings of Fujioka, *et al.*[64] we expect that the auditory-motor co-activations could have facilitated neuroplasticity. According to the authors, auditory-motor training could facilitate neuromagnetic β band oscillations (a functional measure representing auditory motor coupling and neuroplasticity[65]) thereby assisting in motor recovery.

In addition to these neurophysiological changes, rhythmic auditory cueing can impart multifaceted effects on musculoskeletal system as well[66–71]. Thaut, *et al.*[72] suggested that the recruitment and firing rate of motor neurons is determined by the firing rate of auditory neurons (central audiospinal facilitation[73]), which in turn are stimulated with rhythmic entrainment. Likewise, in an electromyographic analysis during gait performance for post-stroke patients, Thaut, *et al.*[74] revealed that training with auditory cueing reduced muscular co-activation on the paretic side.

Moreover, we observed considerable enhancements in gait performance in studies incorporating training with auditory cueing as compared to direct application of auditory cueing in a single session i.e. gait velocity (training: 0.73, no training: 0.33), stride length (training: 0.58, no training: 0.25) and cadence (training 0.75, no training: 0.52). We presume that these enhancement in performance with training are due to an "entrainment effect" generated as a result of auditory-motor training[68,72]. This effect has been reported to facilitate movement regularity with repetitions (in this context cyclic movements of gait) further resulting in an enhanced "smoothened" learning pattern[26,75–77]. Upon further sub-group analysis we observed differences in terms of performance because of shorter or longer training durations. Here, in a dose-response analysis we observed that a training duration of 20–45 minutes per session provided substantial increments in both the gait and postural performance as compared to shorter training sessions lasting for 8–10 minutes. These dose related findings are in line with a previously published review study reporting beneficial effects of auditory cueing on arm recovery following stroke[16]. Moreover, in light of recent neuroimaging and clinical studies these findings seem plausible[18,24,26]. Bangert and Altenmüller[24], for instance reported auditory sensorimotor EEG co-activations after only 20 minutes of auditory-motor training. The authors reported this instantaneous plasticity in the cortex with right hemispheric anterior regions, which ideally represent audio-motor integration[24,25]. The authors further added, that this minimum time frame was vital for establishing stimulus response consistency between audio-motor signals. Similarly, Ghai, *et al.*[17] reaffirmed these findings and revealed enhanced proprioceptive performance[78,79], after at least 30 minutes of auditory-motor training. According to the authors, this time frame is crucial for establishing an auditory-motor interfaced mapping resulting in a robustly learned skill set[80,81].

In addition, we would like to point out some important gaps in the current state of literature which could be addressed by future studies. Firstly, importance of home-based interventions has been emphasized in several studies[70,82,83]. Home-based intervention can allow a patient to enhance their performance for daily life activities, and allow a patient to train for a longer duration in a cost-effective manner as compared to in rehabilitation centers[83]. None of the included studies in the current review elucidated the effects of auditory cueing as a home-based intervention. However, in our sub-group analyses we observed that using treadmill (a common home-based exercise modality) together with auditory cueing was an efficient way for enhancing spatiotemporal gait performance in patients with stroke (gait velocity: 0.15, stride length: 0.45, cadence: 0.39). Moreover, recently published review studies have recommended the positive influence of using auditory cueing as a home based intervention to facilitate gait recovery in neurological disorders such as, cerebral palsy[70], and multiple sclerosis[84]. Therefore, based on the current state of evidence we strongly hypothesize that combining auditory-motor training in both rehabilitation centers and at home will further enhance the prognostic outcome of stroke patients.

Finally, our findings are in line with previously published "high-quality" systematic reviews and meta-analyses reporting *medium*-to-*large* positive effects of training with rhythmic auditory cueing on gait performance in stroke patients. This present study furthers the current state of knowledge concerning the efficacy of auditory cueing intervention for recovering gait, postural performance post-stroke. This review also addresses the limitations of the previously published reviews due to several of the following reasons. Firstly, the present review incorporates a higher number of experimental studies that support our conclusion i.e. 38 studies (968 participants) as compared to previously published reviews including ten (268 participants)[31], eight (242 participants)[29], seven (211 participants)[27], and 2 (40 participants)[29], studies. This large difference in the number of included studies could be affirmed to a higher number of relevant academic databases searched (with multiple languages) i.e. nine, and the inclusion of controlled clinical trials. Here, the inclusion of controlled clinical trials was justified based on the updated Cochrane guidelines for systematic reviews[85]. The guidelines recommend the addition of controlled clinical trials under the circumstances where data from randomized controlled trials is limited[86]. Secondly, this present review suggests specific training dosages with rhythmic auditory cueing for allowing enhancements in gait performance and postural stability. Thirdly, the present review provides evidence for the beneficial effects of auditory cueing training on dynamic postural stability i.e. timed-up and go test performance. Fourthly, this review provides evidence for the beneficial effects of direct application of rhythmic auditory cueing i.e. no training on gait performance in stroke patients. Lastly, this study provides evidence for the beneficial effects of adjunct training strategies like, treadmill training with rhythmic auditory cueing on gait performance in stroke patients.

Furthermore, we strongly recommend the reader to consider that it is not our intention to disregard the previously published reviews and meta-analyses. These reviews have addressed different factors in stroke recovery (quality of life, arm recovery, cognitive training, gait kinematics, applications by music therapist vs health care practitioner and more), which were not the objectives of the present review. Therefore, in our opinion interpretations should be drawn simultaneously from all the reviews to develop a better understanding of the influence of auditory cueing-based training strategies for stroke recovery.

There are four major limitations in this present review. First, this present systematic review and meta-analysis was not pre-registered in an international prospective register for systematic reviews, such as PROSPERO. Second, lack of descriptive statistics prevented us from including 13 studies in our meta-analysis i.e. out of 38 studies 25 were included. In order to address this limitation multiple attempts were made by the reviewers (S.G and I.G) to retrieve the data from the authors of the respective studies. Thirdly, this meta-analysis evaluated the effectiveness of auditory cueing training from a "pre-post intervention perspective". This is a major limitation of this study. We refrained from including a comparative analysis with the respective control groups due to limited data for the controlled groups mentioned in the studies. Fourthly, in the present meta-analysis a sensitivity analysis was performed to explore causes of heterogeneity instead of a meta-regression or stratified meta-analysis approach. The choice of this approach could raise concerns regarding the appropriateness to pinpoint the "significant" source of heterogeneity. We justify the choice of sensitivity analysis because it allowed us to simultaneously evaluate three moderators of training i.e. length of training session, number of training sessions per week and number of weeks for which training was performed. This however, was not possible with the use of a conventional meta-regression or stratified meta-analysis approach which only allows the evaluation of a single variable at a given instance.

In conclusion, rhythmic auditory cueing provides beneficial effects for enhancing gait performance and dynamic stability post-stroke. The present findings can be reliably interpreted as limited heterogeneity was ensured during the sub-group analyses, and the included studies had a "fair" overall quality i.e. 5.5. This review strongly suggests the incorporation of rhythmic auditory cueing based training post stroke for enhancing gait performance and postural stability. The review suggests a training duration for at least 20–45 minutes and for at least 3–5 times per week[87–94].

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Author Contributions

S.G. conceptualized the study, carried out the systematic-review, statistical analysis, and wrote the paper. I.G. assisted in the systematic-review and meta-analysis procedures. Both the authors reviewed the final draft.

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Chapter 4: Effects of real-time (sonification) and rhythmic auditory stimuli on recovering arm function post stroke: A systematic review & meta-analysis

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SYSTEMATIC REVIEW
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Effects of Real-Time (Sonification) and Rhythmic Auditory Stimuli on Recovering Arm Function Post Stroke: A Systematic Review and Meta-Analysis

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Background: External auditory stimuli have been widely used for recovering arm function post-stroke. Rhythmic and real-time auditory stimuli have been reported to enhance motor recovery by facilitating perceptuomotor representation, cross-modal processing, and neural plasticity. However, a consensus as to their influence for recovering arm function post-stroke is still warranted because of high variability noted in research methods.

Objective: A systematic review and meta-analysis was carried out to analyze the effects of rhythmic and real-time auditory stimuli on arm recovery post stroke.

Method: Systematic identification of published literature was performed according to PRISMA guidelines, from inception until December 2017, on online databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST. Studies were critically appraised using PEDro scale.

Results: Of 1,889 records, 23 studies which involved 585 (226 females/359 males) patients met our inclusion criteria. The meta-analysis revealed beneficial effects of training with both types of auditory inputs for Fugl-Meyer assessment (Hedge's g: 0.79), Stroke impact scale (0.95), elbow range of motion (0.37), and reduction in wolf motor function time test (−0.55). Upon further comparison, a beneficial effect of real-time auditory feedback was found over rhythmic auditory cueing for Fugl-meyer assessment (1.3 as compared to 0.6). Moreover, the findings suggest a training dosage of 30 min to 1 h for at least 3–5 sessions per week with either of the auditory stimuli.

Conclusion: This review suggests the application of external auditory stimuli for recovering arm functioning post-stroke.

Keywords: cueing, stability, rehabilitation, cognitive-motor interference, hemiplegia, spasticity, paresis

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INTRODUCTION

According to World health organization, stroke accounts as the third main cause of disability across the world (1). The incidence of stroke related disability have almost doubled in the developing countries in the past decade (2, 3). The disability affects basic day to day life activities (4), which further increase dependency (5), anxiety, depression (6), social isolation (7), and promote a poor quality of life (8, 9). Moreover, the disability inflicts substantial economic burden on patients (10).

Typically, patients affected from stroke exhibit sensorimotor dysfunctions on the contralateral side of the affected brain region (11). These deficits can be exhibited focally, segmentally, unilaterally, or bilaterally (12). The symptoms are typically characterized by progressive inefficient movement synergy patterns (13), abnormal muscle tone (14), force production (15), compromised dexterity (16), poor coordination (17), and more (18). Moreover, hyper/hypokinetic movement disorders are also common [see Handley et al.,(12)]. Additionally, cognitive and sensory dysfunctions are also common in patients with stroke (19). Despite advancements in rehabilitation, poor prognosis in stroke is still prevalent, especially for recovering arm function (5, 20). Studies suggest that upper limb recovery is an important predictor for determining the health status outcome, and quality of life for stroke patients (21, 22).

The poor gross and fine motor performance in upper extremities can be due to abnormal co-contraction of antagonists/agonists (23), disruptions in force production/adaptation (24), and regulation of stretch reflex (15, 25). Besides, these musculoskeletal dysfunctions can considerably impair joint kinematics (26, 27). According to Hara et al. (28) impaired activation of motor units in terms of firing rate and synchronization might result in such deficits. Furthermore, as the disease progresses, these changes increase fatigue (29), reduce coordination (30), and with the progression of time promote development of joint contractures (31), and subluxations/dislocations (32). Likewise, discrepancies in sensory perceptions, memory, cognition, and behavior further impact the prognostic outcome of a stroke patient (33–35).

Neuroimaging studies suggest site specific lesions and silent infarcts at medial temporal lobe (36), gray (37), and white matter (38), further leading to a wide array of cognitive dysfunctions (39) [see Makin, (40) and Sperber and Karnath (41).] Similarly, deficits in corticospinal (42, 43), thalamocortical (44), superior occipito-frontal (41), and superior-longitudinal pathways (45), might overload the already impaired cognitive-motor pathways. Such a constraining impact on the impaired cognitive pathways might increase "internal" conscious monitoring by the patients to control their movements [see movement re-investment (46–48)]. This increase in attention is aimed to safeguard the stability of a movement (49, 50), it retrospectively impairs autonomic execution of a movement and promotes movement failure (46–48). Likewise, dysfunctions in sensory perception could affect perceptuomotor representations in the brain, thereby affecting motor planning and execution (35). Together, these cognitive and sensorimotor dysfunctions affect the prognosis of a stroke patient.

Common treatment strategies to curb cognitive motor dysfunctions in stroke patients include training with virtual-reality (51), mental imagery (52), biofeedback (53), physical therapy (54), exercise (55), prosthesis (56–58), dual-task priority training, and more (59). Recently studies have tried to enhance the stroke recovery by simultaneously addressing the sensory deficits with motor rehabilitation by applying external sensory stimulation as a neuro-prosthetic (59–62). Studies have analyzed the effects of different sensory stimuli in auditory, visual and tactile domain on motor performance (59, 61, 62). However, the literature predominantly supports the beneficial role of auditory stimuli (50, 63, 64). The main reasons which underlie the beneficial effects are thought to be multifaceted. Firstly, rich neuroanatomical interconnectivity has been reported between auditory and motor cortex (65–67). Here, inference can be drawn from literature evaluating auditory startle reflex on animal models (68, 69). Studies using Double-labeling experiments have revealed that cochlear root neurons in the auditory nerve can project bilaterally to sensorimotor paths, including synapsing on reticulospinal neurons (65, 68, 70). Likewise, patterns of thalamocortical and corticocortical inputs unique to auditory cortex have also been reported [for a detailed review see (71)]. In humans, neuroimaging data confirms the presence of cortico-subcortical network involving putamen, supplementary motor area, premotor cortex, and the auditory cortex especially for perceiving and processing rhythmic auditory stimuli (72–75). Secondly, the human auditory system can consistently perceive auditory cues 20–50 ms faster as compared to its visual and tactile counterparts (76–78). Thirdly, the auditory system has a strong bias to identify temporal patterns of periodicity and structure as compared to other sensory perceptual systems (78–80). For instance, auditory rhythmic perception has been reported to exist well beyond the limits of temporal resolution of visual modalities i.e., when periodicities are presented at a rate of $\sim$300–900 ms (80, 81).

In the literature, however, rhythmic auditory cueing (67), and real-time kinematic auditory feedback (82), also termed as sonification, are the most widely studied approaches in upper limb stroke rehabilitation. Both the methods possess differential influence over neurophysiological and musculoskeletal domains. Firstly, rhythmic auditory cueing can be defined as repetitive isosynchronous stimulations applied with an aim to simultaneously synchronize motor execution (83, 84). Here, neuroimaging data for rhythmic auditory stimuli suggests facilitated activations in premotor cortex, insula, cuneus, supplementary motor area, cerebellum, and basal ganglia (73, 80, 85–87). Moreover, training with rhythmic auditory cueing has been reported to modulate neuromagnetic β oscillations (88, 89), biological motion perception (82, 90), auditory-motor imagery (91–93), shape variability in musculoskeletal activation patterns (94), cortical reorganization, neural-plasticity (95, 96), and also movement specific re-investment (97). Real-time kinematic auditory feedback on the other hand is a comparatively new approach. Such type of an intervention involves mapping of movement parameters on to the sound components, such as pitch, amplitude with a very minimal or no latency (82). The feedback has been reported to alleviate sensory perceptions like proprioception (98), by enhancing sensorimotor representation while facilitating activations in action observation system (90), and inducing neural plasticity (99). Moreover, the feedback has been reported by Effenberg et al. (82) to extend the benefits of discrete rhythmic auditory cueing stimuli. Here, the authors suggest that the continuous flow of information might allow a participant to better perceive their movement amplitudes and positioning, thereby resulting in development of both feedback and feed-forward models (82). Moreover, by allowing additional influence over the action observation system the real-time auditory stimuli might also enrich the internal stimulation of the executed movement (50, 82, 90). This methodology involves delivering action relevant auditory feedback, where the characteristics of stimuli (e.g., frequency, amplitude) are mapped to the specific joint kinematics in real-time, for an example see (98). Schmitz et al. (90) in a neuroimaging study reported that observation of a convergent audio (sonification)-visual feedback led to enhanced activations in fronto-parietal networks, action observation system i.e., superior temporal sulcus, Broadman area 44, 6, insula, precentral gyrus, cerebellum, thalamus and basal ganglia (90). The authors mentioned that the multimodal nature of the stimuli can enhance the activation in areas associated with biological motion perception and in sub-cortical structures involving striatal-thalamic frontal motor loop. This then might improve perceptual analysis of a movement thereby resulting in efficient motor planning and execution (90).

Till date, no study has analyzed the influence of real-time auditory feedback on upper limb recovery post-stroke. Moreover, no study has compared the influence of rhythmic and real-time auditory stimuli on upper limb recovery post stroke. This information might serve to be an important source of information for future research and for developing efficient rehabilitation protocols in stroke community. Only four systematic reviews have analyzed the influence of rhythmic auditory stimulations on arm recovery post stroke (100–103), in which only two reviews included a statistical meta-analysis (102, 103). In these studies limitations persisted in terms of meta-analysis approach i.e., no heterogeneity analysis. Therefore, interpretation of results from the statistical analyses might indicate biasing. Therefore, the aim of the present systematic review and meta-analysis is to develop a state of knowledge where both qualitative and quantitative data for different auditory stimuli delivery methods can be interpreted for the use of stroke patients and medical practitioners alike. Moreover, a meta-analysis approach will be used to determine specific training dosage for auditory stimuli in recovering arm function post-stroke.

METHODS

This systematic review and meta-analysis was conducted according to the guidelines outlined by PRISMA statement: Preferred Reporting Items for Systematic Reviews and Meta-analysis (104).

Data Sources and Search Strategy

Academic databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane central register of controlled trials, EMBASE, and PROQUEST were searched from inception until December 2017. A sample search PICOS strategy for the review has been provided in (**Table 1**) (105).

Data Extraction

Upon selection for review, the following data were extracted from each article; author, date of publication, selection criteria, sample size, sample description (gender, age, health status, duration of stroke), applied intervention, characteristics of auditory stimuli i.e., rhythmic/real-time, applied dual-task (if any), outcome measures, results, and conclusions. The data were then summarized and tabulated (**Table 2**).

The inclusion criteria for the studies was (i) The experimental studies were either randomized controlled trials, cluster randomized controlled trials or controlled clinical trials; (ii) The included studies reported reliable and valid measures to analyse arm function, and/or kinematic parameters; (iii) The included studies analyzed subjective analysis of stroke outcome; (iv) The included studies scored ≥ 4 score on the PEDro methodological quality scale; (v) The experiments conducted on human participants; (vi) The included studies were published in a peer-reviewed academic journal, conference proceeding; (vii) The included studies were published in English, Hindi, Punjabi, and German languages.

Quality and Risk of Bias Assessment

The quality of the included experimental studies was assessed using the PEDro methodological quality scale (127). This scale consists of 11 items which address both external, internal validity. Moreover, its interpretation can effectively detect potential bias with fair to good reliability, and validity (127). A blinded scoring for the methodological quality was carried out by the primary reviewer (S.G). If any ambiguous issues were there concerning rating of the studies. These issues were discussed with a second reviewer (Dr. Ishan Ghai). Included studies were interpreted according to a scoring of 9–10, 6–8, and 4–5 considered as "excellent," "good," and "fair" quality, respectively (128).

Data Analysis

For a better interpretation of the intervention effects, a meta-analysis was included (129). The absence of presence of heterogeneity asserted the use of either fixed or random effect meta-analysis (130), respectively. A narrative synthesis of the findings structured around the intervention, population characteristics, duration of stroke, auditory signal characteristics, methodological quality, and type of outcome are provided (**Table 2**). A meta-analysis was conducted between pooled homogenous studies using CMA (Comprehensive meta-analysis V 2.0, USA). Heterogeneity between the pooled studies was assessed and interpreted using I^2 statistics. The data in this present review was systematically distributed and pooled for each variable. Thereafter, forest plots with effect size and 95% confidence intervals were plotted. The effect sizes were weighted

TABLE 1 | Sample search strategy EMBASE.

PICOS	DATABSE	EMBASE
	DATE	**10/12/2017**
	STRATEGY	**#1 AND #2 AND #3 AND #4 AND #5 AND #6**
P	#1	("Stroke" OR "Apoplexy" OR "CVA" OR "Cerebral Stroke" OR "Cerebrovascular accident" OR "Cerebrovascular Accident, Acute" OR "Cerebrovascular Apoplexy" OR "Cerebrovascular Stroke" OR "Stroke, Acute" OR "Vascular Accident, Brain" OR "Hemiplegia, Crossed" OR "Hemiplegia, Flaccid" OR "Hemiplegia, Spastic" OR "Hemiplegia, Transient" OR "Monoplegia" OR "Upper Extremity Paresis" OR "Muscular Paresis" OR "Muscle Paresis" OR "Monoparesis" OR "Hemiparesis")/de OR (Stroke OR Apoplexy OR CVA OR Cerebral Stroke OR Cerebrovascular accident OR Cerebrovascular Accident, Acute OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Stroke, Acute OR Vascular Accident, Brain OR Hemiplegia, Crossed OR Hemiplegia, Flaccid OR Hemiplegia, Spastic OR Hemiplegia, Transient OR Monoplegia OR Upper Extremity Paresis OR Muscular Paresis OR Muscle Paresis OR Monoparesis OR Hemiparesis):ti,ab
I	#2	("rhythmic auditory cueing" OR "rhythmic auditory cueing" OR "rhythmic acoustic cueing" OR "rhythmic auditory entrainment" OR "metronome cueing" OR "metronome" OR "rhythmic metronome cueing" OR "acoustic stimulus" OR "acoustic cueing" OR "acoustic cueing" OR "external stimuli" OR "external cueing" OR "external cueing" OR "music therapy" OR "Neurological music therapy" OR "tempo" OR "beat" OR "rhythm" OR "RAC" OR "NMT" OR "real-time auditory feedback" OR "sonification")/de OR (rhythmic auditory cueing OR rhythmic auditory cueing OR rhythmic acoustic cueing OR rhythmic auditory entrainment OR metronome cueing OR metronome OR rhythmic metronome cueing OR acoustic stimulus OR acoustic cueing OR acoustic cueing OR external stimuli OR external cueing OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT OR real-time auditory feedback OR sonification)ti,ab
C	n/a	n/a
O	#3	("Range of Motion" OR "Passive Range of Motion" OR "Joint Range of Motion" OR "Joint Flexibility" "elbow" OR "shoulder" OR "wrist" OR "Fugl Meyer Assessment" OR "Fugl-Meyer assessment for upper extremity" OR "FMA" OR "Wolf motor assessment" OR "WMA" OR "Wolf motor test" OR "Nine hole peg test" OR "NHPT" OR "9HPT" OR "Action reach arm test" OR "ARAT" OR "Stroke index scale" OR "SIS" OR "BATRAC" OR "Bilateral arm training with rhythmic auditory cueing" OR "Unilateral arm training with rhythmic auditory cueing" OR "Arm reach training" OR "BBT" OR "Box and block test" OR "Motor activity log" OR "MAL" OR "Cincinnati Stroke Scale" OR "Los Angeles Prehospital Stroke Scale" OR "ABCD Score" OR "Canadian Neurological Scale" OR "European Stroke Scale" OR "Hemispheric Stroke Scale" OR "NIH Stroke Scale" OR "Modified Rankin Scale" OR "Stroke Specific Quality of Life Measure" OR "Health Survey SF-36" OR "Health Survey SF-12")/de OR (Range of Motion OR Passive Range of Motion OR Joint Range of Motion OR Joint Flexibility elbow OR shoulder OR wrist OR Fugl Meyer Assessment OR Fugl-Meyer assessment for upper extremity OR FMA OR Wolf motor assessment OR WMA OR Wolf motor test OR Nine hole peg test OR NHPT OR 9HPT OR Action reach arm test OR ARAT OR Stroke index scale OR SIS OR BATRAC OR Bilateral arm training with rhythmic auditory cueing OR Unilateral arm training with rhythmic auditory cueing OR Arm reach training OR BBT OR Box and block test OR Motor activity log OR MAL OR Cincinnati Stroke Scale OR Los Angeles Prehospital Stroke Scale OR ABCD Score OR Canadian Neurological Scale OR European Stroke Scale OR Hemispheric Stroke Scale OR NIH Stroke Scale OR Modified Rankin Scale OR Stroke Specific Quality of Life Measure OR Health Survey SF-36 OR Health Survey SF-12);ti,ab
S	#6	("intervention study" OR "cohort analysis" OR "longitudinal study" OR "cluster analysis" OR "crossover trial" OR "cluster analysis" OR "randomized trial" OR "major clinical study")/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab
	#4	("rehabilitation" OR "treatment" OR "rehab" OR "management" OR "therapy" OR "physiotherapy" OR "physical therapy" OR "prevention" OR "risk prevention")/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
	#5	("age groups" OR "adolescent" OR "young" OR "elderly" OR "old" AND ("gender" OR "male" OR "female")/de OR [age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female)];ti;ab

and reported as Hedge's g (131). Thresholds for interpretation of effect sizes are as follows; a standard mean effect size of 0 meant no intervention effect, negative effect size meant a negative intervention effect, and a positive effect size meant a positive intervention effect. Further, a mean effect size of 0.2 was interpreted as a *small* effect, 0.5 interpreted as a *medium* effect, and 0.8 interpreted as a *large* effect (132). Interpretation of heterogeneity made from I^2 statistics was as following: 0–0, 25, 75% was interpreted as negligible, moderate, and substantial heterogeneity, respectively. The alpha level was set at 95%.

RESULTS

Characteristics of Included Studies

A detailed search criterion has been demonstrated in **Figure 1.** Out of 1,889 studies, only 23 studies qualified our inclusion criteria. A total of 385 studies could not be included in the manuscript due to limitations in access by University's search database. The author (S.G) made attempts to contact the respective corresponding authors for retrieving the manuscripts. Although these studies could not be included in the review, the abstracts for all the studies were individually screened by

TABLE 2 | Effects of auditory stimuli on arm function post-stroke.

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Bang (106)	Effect of R-af on arm function in patients affected from stroke	Exp: 4F, 6M (61.3 ± 4.8) Ct: 5F, 5M (58.2 ± 5.1)	9	Exp: 8.9 ± 3.1 years Ct: 10.3 ± 3.7 years	ARAT, FMA, motor activity log (quality of movement, amount of use) and modified Ashworth scale	Pre-test, modified constraint induced movement therapy with/without R-af for 1 h/day, 5 days/week for 4 weeks, post-test	R-af (proportional to reduced pressure by shoulder on the sensor) Frequency faded off with progression from every 1/3rd trial	Significant enhancement in ARAT, FMA, motor activity log (quality of movement, amount of use), modified ashworth scale after training with R-af and in Exp as compared to Ct
Scholz et al. (107)	Effects of R-af on gross motor functions on participants affected from stroke (right hemiparesis).	Exp: 1F (59), 1M (85) Ct: 2M (61.5 ± 3.5)	4	–	FMA, ARAT, BBT, 9-HPT, and SIS	Patients moved their arms in a 3D R-af space, for 9 days of training with R-af (30 min/day)	X axis: Brightness mapped, increased from left to right Y axis: Pitch mapped, increased from bottom to up Z axis: Volume, increased when closed to the participant	Exp: Enhancements were observed for participants in FMA, ARAT, 9-HPT, and SIS Ct: No enhancements were observed for, but minimally for one participants in FMA, and the other in SIS
Malcolm et al. (108)	Effect of RAC on arm kinematics in patients affected from stroke	5M (72.8 ± 6.5)	4	0.7 ± 0.4 years	Movement time, reach velocity, wolf motor function test, FMA, and motor activity log	Pre-test, 1-h session followed by 2 h of home training, 3 times/week for 2 weeks with RAC and reaching performed in sagittal, frontal and diagonal planes, post-test	RAC at patients preferred pace of movement	Significantly enhanced reaching velocity, FMA, and motor activity log after training with RAC Significantly reduced reaching time, wolf motor function test performance time after training from RAC
Speth (109)	Effect of RAC on arm reaching in patients affected from stroke	8 stroke patients	4	–	BBT for (paretic/non-paretic side)	BBT performance with/without RAC i.e., waltz music, metronome	RAC (200 bpm), waltz music (200 bpm) cueing	Enhanced performance for BBT with waltz music>RAC>no feedback for both paretic and non-paretic arms
	Effect of RAC on robot-assisted arm reaching in patients affected from stroke	11F, 22M (51.6 ± 15.9), severe: 18, moderate: 8, mild: 8 Exp: 14 [A; severe (11), moderate (4), mild (4)] [B: 2–6 months' post stroke (8), >12months post stroke (9)] Ct: 14 [A: severe (6), moderate (4), mild (4)] [B: 2-6 months' post stroke (9), >12months post stroke (5)]		1.2 ± 1.3 years	BBT, 9-HPT, and intrinsic motivation inventory	Pre-test, robot assisted arm training "Amadeo" with (Exp)/without (Ct) RAC (polymetric music, game-related action feedback) for 45 min for 9 times for 3–4 weeks, post-test, retention measurement after 8 weeks' post-test	RAC by polymetric music (rhythmic adaptability to multi-joint movements in hand and finger movement e.g., first 3/4 m containing 2 bars, second 2/4 m containing 3 bars, 3rd 3/8 m containing 4 bars: all sounds played in one absolute time frame) and game related sounds (error feedback, natural sounds) together	Significant enhancement in mean BBT for moderate and mild affected patients, for Exp as compared to Ct Significant reduction in mean box and block test for severely affected patients, for Ct as compared to Exp Enhancement in 9-HPT for Exp as compared to Ct Significant enhancement in intrinsic motivation inventory for (interest/enjoyment, perceived competence, relaxation, perceived choice) for Exp as compared to Ct
Scholz et al. (60)	Effects of R-af on gross motor functions on participants affected from stroke (right hemiparesis).	Exp: 7F, 8M (68.8 ± 13.6) Ct: 4F, 6M (72.2 ± 8.4)	6	Exp: 32.5 days Ct: 28 days	FMA, ARAT, BBT, 9-HPT, and SIS	Patients moved their arms in a 3D sonification space, for 10 days of sonification training (30 min/day).	X axis: Brightness mapped, increased from left to right Y axis: Pitch mapped, increased from bottom to up Z axis: Volume, increased when closed to the participant	Exp: Significant enhancements were observed for participants in movement smoothness, FMA, SIS as compared to Ct Enhancements were observed in ARAT, BBT and 9-HPT Ct: No significant enhancements were observed post sham training
van Delden et al. (110)	Effects of RAC on arm reaching in patients affected from stroke	Exp: 8F, 11M (62.6 ± 9.8) Ct I: 3F, 16M (56.9 ± 12.7) CT II: 8F, 14M (59.8 ± 13.8)	7	Exp: 7.8 ± 4.9 weeks Ct I: 9.2 ± 6.8 weeks Ct II: 11.1 ± 6.8 weeks	ARAT, motricity index, FMA, 9-HPT, Erasmus modification of Nottingham sensory assessment, motor activity log test and SIS	Pre-test, BATRAC (Exp), modified constrained induced movement therapy (Ct I), conventional therapy (Ct II), for 60 min session, 3 times/week, post-test, 6 weeks follow up post-test	RAC (rhythmic flexion-extension at the wrist joint)	Significant enhancement in ARAT with BATRAC No differences in between Exp, Ct I, Ct II

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Schmitz et al. (111)	Effect of R-af on reaching task in patients affected from stroke	Exp: 1F, 3M (65 ± 14.8) Ct: 3F (56 ± 5.3)	4	-	ARAT, 9HPT, and BBT	I: Reaching and retraction task by affected arm. II: Patients repositioned a ball on objects of different shapes. Training for 5 days for 5 sessions of 20 min each	Arm velocity: modulates amplitude of sound Elevation angle: modulates frequencies between 133.3 and 266.6 Hz. Radial arm amplitude: modulates brightness	Significant enhancements were observed in BBT for Exp as compared to Ct. Enhancements were observed in 9HPT and ARAT. Ct: No significant enhancements were observed
Kim et al. (112)	Effects of RAC on arm reaching performance in patients affected from stroke	7F, 9M (49.2 ± 17.6)	4	1.9 ± 2.2 years	Movement time, movement unit, elbow extension range of motion by 3D motion detection, triceps, biceps brachii muscle activation and co-contraction ratio from EMG	Repetitive reaching task performed with/without RAC from affected arm	RAC at patients preferred pace of movement	Significant enhancement in elbow range of motion, tricpes brachii activation with RAC Significant reduction in co-contraction ratio, movement time and movement unit with RAC
Shahine and Shafshak (113)	Effect of RAC on arm function in patients affected from stroke	Exp: 19F, 21M (61.4 ± 5.5) Ct: 17F, 19M (62.7 ± 3.1)	9	Exp: 2.6 ± 1.8 years Ct: 2.9 ± 0.7 years	FMA and transcutaneous magnetic stimulation eliciting motor evoked potential in paretic abductor pollicis brevis (motor evoked potential resting threshold, central motor conduction time)	Pre-test, BATRAC for 1-h session/day, 3seesions/week, for 8 weeks, post-test	RAC at patients preferred pace of movement (frequency 0.25–1/s)	Significant enhancement in FMA, motor evoked potential amplitude ratio after BATRAC Significant reduction in motor evoked potential resting threshold, central motor conduction time after bilateral arm training with RAC, and in Exp as compared to Ct
Dispa et al. (114)	Effect of RAC on arm reaching in patients affected from stroke	1F, 9M (66 ± 11.1)	8	2.3 ± 2.6 years	Grip lift parameters (preloading-loading phase, maximum grip force, hold ratio, cross correlation coefficient, time shift), digital dexterity, activity limitation manual ability, satisfaction in activities, and participation	Pre-test, post-test after 4 weeks of no-training, unilateral-bilateral (modified BBT) repetitive grip lift task oriented training with RAC for 1-h session, 3 days/week for 4 weeks, post-test at 4 weeks after training, retention measurement after 4 weeks	RAC at patients preferred pace of movement	Reduction in preloading phase of grip lift parameters for the paretic hand after 4 weeks of training and during retention measurement. Enhancement in loading phase of grip lift parameters for the paretic hand after 4 weeks of training and during retention measurement. No effect on grip lift parameters (maximum grip force, hold ratio, cross correlation coefficient, time shift), digital dexterity, activity limitation manual ability, satisfaction in activities, and participation after 4 weeks of training or during retention measurement.
Whitall et al. (115)	Effect of RAC in arm reaching patients affected from stroke	Exp: 16F, 26M (59.8 ± 9.9) Ct: 26F, 24M (57.7 ± 12.5) fMRI: Exp: 10F, 7M (61.2 ± 13.8) Ct: 10F, 11M (54.8 ± 13.1)	6	Exp: 4.5 ± 4.1 years Ct: 4.1 ± 5.2 years	FMA, wolf motor test (time, weight, function, SIS (emotion, hand, strength), isokinetic strength (elbow flexion-extension nonparetic side, elbow extension paretic side) and isometric strength (shoulder extension, wrist flexion-extension nonparetic side, shoulder extension, wrist extension, elbow flexion paretic side)	Pre-test, BATRAC for 1-h session, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, wolf motor test (weight, function), SIS (hand, strength), isokinetic strength (elbow extension nonparetic side, elbow extension paretic side), isometric strength (shoulder extension, wrist extension nonparetic side, shoulder extension) assessment in Exp after training with RAC Significant reduction in wolf motor test (time) in Exp after training with RAC Significant enhancement in isokinetic strength (elbow flexion nonparetic side), isometric strength (wrist flexion, nonparetic side, wrist extension paretic side) in Exp as compared to Ct

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
		Exp: 3.9 2.7 Ct: 3.3 2.1						Significant enhancement in activation for ipsilesional precentral, anterior cingulate, postcentral gyri, supplementary motor area in Exp after training with RAC as compared to Ct. Significant enhancement in contralesional superior frontal gyrus in Exp after training with RAC, as compared to Ct
Chouhan and Kumar (116)	Effect of RAC on gait and arm reaching in patients affected from stroke	Exp: 3F, 12M (56.7 ± 5.9) Ct I: 3F, 12M (58.1 ± 4.1) Ct II: 3F, 12M (57.3 ± 5.5)	5	–	Dynamic gait index and FMA	Pre-test, gait, reaching task training with RAC (0% of preferred cadence initially, increased by +10% every week if comfortable for patient: for gait) (Exp) or visual feedback (Ct I) for 2 h training, 3 time/week session for 3 weeks, post-tests at 7, 14, 21, 28 days	RAC at 0% and +10% on following weeks of preferred movement pace, and gait (cadence)	Significant enhancements in FMA, dynamic gait index (14, 21, 28 days only) after 7, 14, 21, 28 days of training with RAC and in Exp as compared to Ct II
Secoli et al. (117)	Effect of RAC on tracking task in patients affected from stroke.	Exp: (affect left hemisphere) 8F, 6M (56.3 ± 12.3) Ct: (affect right hemisphere) 1F, 4M (61.8 ± 5) Healthy: 2F, 12M (27 ± 7.5)	4	4.6 ± 1 years	Arm movements with robot assisted force production to execute task in Z dimension Positioning error in Z dimension	Patients performed tracking task with robot assisted device in with/without visual distractor task and/or with/without RAC	Tonal beeps sampled at frequency of 800 Hz and lasting for 0.1 s Frequency manipulated proportionally to vector magnitude of position tracking error within dead-zone. Error direction determined by left and right channel of auditory input	Significant reduction in robot assisted force in Exp when auditory input was delivered, suggesting significant enhancement in arm functioning Significant reduction in robot assisted force for the paretic side as compared to healthy side with RAC No effect on position tracking accuracy
Thielman (118)	Effect of RAC on arm reaching in patients affected from stroke	Exp: 2F, 6M (62.9 ± 6.5) Ct: 4F, 4M (63 ± 9.2)	4	Exp: 2.2 ± 0.7 years Ct: 1.8 ± 1.4 years	Reaching performance scale for near and far targets, FMA, wolf motor function test, shoulder flexion range of motion, motor activity log, grip strength and elbow active range of motion	Pre-test (<5days before training), training for arm reaching with pressure sensor generated auditory feedback (Exp), stabilizer (restrained Ct) on arm reaching for 40-45 minutes' session, 2-3days/week (12 total sessions), post-test (<2days after training)	R-af (proportional to reduced pressure by shoulder on the sensor) Frequency faded off with progression from every 1/3rd trial.	Significant enhancement in reaching performance scale for near-far targets, FMA in Exp after training with R-af Significant reduction in wolf motor function test in Exp after training with R-af Enhancement in shoulder flexion, motor activity log and elbow active range of motion in Exp after training with R-af

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Johannsen et al. (119)	Effect of RAC on arm reaching and gait in patients affected from stroke	Exp I: 3F, 8M (59.5 ± 13.4) Exp II: 3F, 7M (68.1 ± 10.1)	6	5.2 ± 4.2 years	FMA (upper/lower extremity), 10-m walking test, treadmill (step length) and repetitive foot/hand aiming task	Pre-test, BATRAC (arm: Exp I/leg: Exp II) for 45 min session, 2 times/week for 5 weeks, post-test, follow up post-test after 18 weeks	RAC at patients preferred pace of movement (increased at patient's preference) Bilateral training for lower extremities: increased pacing during training from 36.7 ± 6.5 to 45.9 ± 9.5 beats per minute BATRAC: increased pacing during training from 39.8 ± 5.6 to 46.3 ± 5.9 beats per minute	Significant enhancement in treadmill step length on both paretic and non-paretic side after bilateral leg training in Exp II as compared to Exp I (no effects), during immediate follow-up test. No effects in follow up post-test. Enhancement in FMA test for lower extremity in Exp II> Exp I at post-test. No enhancements in follow up post-test Enhancement in fugl meyer motor test for upper extremity in Exp I> Exp II at post-test. No enhancements in follow up post-test Enhancement in treadmill step length on both paretic and non-paretic side after bilateral arm training in Exp I as compared to Exp II for 18 week follow up post-test Enhancement in repetitive foot and arm aiming task on both paretic and non-paretic side after bilateral leg training in Exp II during immediate post-tests. No effects on follow up post-tests
Stoykov et al. (120)	Effects of RAC on arm reaching in patients affected from stroke	Exp I: 3F, 9M (63.8 ± 12.6) Exp II: 5F, 7M (64.7 ± 11.1)	6	Exp I: 9.5±5.4 years Exp II: 10.2±10.1 years	Motor assessment scale (upper arm function, hand movements, upper limb items, advanced hand activities), motor status scale (total, shoulder-elbow, wrist-hand scale), shoulder flexion strength and wrist flexion-extension strength	Pre-test, arm reach training with bilateral (Exp I), unilateral (Exp II) arm training with RAC (for 4 tasks), for 60 minutes' session, 3 times/week for 8 weeks, post-test, RAC (rhythmic flexion-extension at the wrist joint)	RAC at patients preferred pace of movement (0.25-1.5 Hz) incremented gradually during training	Significant enhancement in motor assessment scale (upper arm function, upper limb items) for Exp I Significant enhancement in motor status scale (total, shoulder-elbow, wrist-hand scale), shoulder flexion strength, wrist flexion-extension strength for Exp I and Exp II Enhancement in motor assessment scale (advanced hand activities) in Exp I No differences in motor assessment scale for unilateral arm training for Exp II
Richards et al. (121)	Effects of RAC on arm reaching in patients affected from stroke	5F, 9M (64.4 ± 12.8)	4	5.4±4 years	FMA, wolf motor function test and motor activity log (use, ability)	Pre-test, BATRAC for 1-hour session, 3 times/week, for 6 weeks, post-test	RAC at patients preferred pace of movement	Enhancement in FMA, motor activity log (ability and use) in Exp after training with RAC No effect on wolf motor function test in Exp after training with RAC
Jeong and Kim (122)	Effects of RAC on range of motion, flexibility in patients affected from stroke	Exp: 5F, 11M (58 ± 7.1) Ct: 5F, 12 M (62.2 ± 8.1)	4	Exp: 5.4 ± 4.5 years Ct: 7.2 ± 5.3 years	Shoulder flexion, ankle flexion-extension range of motion and back-scratch test for flexibility upwards/downward the affected arm, profile of mood states, relationship change scale and stroke specific quality of life scale	Pre-test, training for motor activities with RAC for 2 hours/ week for 8 weeks (functional ambulatory training), and self-training at home, post-test	RAC (music) at patients preferred pace of movement	Significant enhancement of range of motion for shoulder flexion, ankle flexion-extension, shoulder flexibility in Exp as compared to Ct, on the affected side Significant enhancement of mood states, interpersonal relationships in Exp Enhancement in quality of life in Exp

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Waller and Whitall (123)	Effects of RAC on arm reaching in patients affected from stroke	Right hemisphere lesion: 2F, 9M (64.3 ± 10) Left hemisphere lesion: 3F, 8M (58.6 ± 17)	5	6.5 ± 4.1 years	FMA, University of Maryland questionnaire for stroke, wolf motor arm test (weight, time), active range of motion elbow flexion, shoulder extension and strength (shoulder extension-abduction-adduction, wrist flexion-extension)	Pre-test, BATRAC for 1-h session, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, University of Maryland questionnaire, active range of motion elbow flexion, shoulder extension (left hemisphere only), strength (shoulder extension (left hemisphere only)-abduction (left only)-adduction, wrist flexion-extension), wolf motor arm test (weight) for stroke for right and left hemisphere lesion patients after training with RAC Significant reduction in wolf motor arm test (time) for patients with left hemisphere lesions as compared right hemisphere lesions after training with RAC Significant enhancement in University of Maryland questionnaire for stroke, wolf motor assessment test (weight, time), active range of motion elbow flexion, shoulder extension, strength (shoulder extension-abduction-adduction, wrist flexion-extension) for patients with left hemisphere lesions as compared to right hemisphere lesions after training with RAC
Luft et al. (95)	Effect of RAC on arm function in patients affected from stroke	Exp: 2F, 7M (63.3 ± 15.3) Ct: 7F, 5M (59.6 ± 10.5)	6	6.2 (3.1–7) years	FMA, shoulder, elbow strength, Wolf motor arm test (weight, time), University of Maryland arm questionnaire for stroke and functional magnetic resonance imaging	Pre-test, BATRAC for 1-h session/day, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement (0.67–0.97 Hz)	After exclusion of 3 patients from Exp: Significant enhancement in FMA in Exp as compared to Ct. Enhancement in shoulder, elbow strength, Wolf motor arm test (weight), University of Maryland arm questionnaire for stroke in Exp as compared to Ct. Reduction in wolf motor arm test (time) in Exp as compared to Ct. Significant enhancements in cerebellum, precentral and postcentral gyri activation after BATRAC
Thaut et al. (124)	Effects of RAC on arm reaching task in patients affected from stroke	8F, 13M (52.7 ± 13.7)	4	–	Wrist trajectory, elbow, shoulder kinematic and optimization model of peak acceleration of wrist joint coordinates	Reaching tasks initiated with/without rhythmic auditory feedback/external time cueing (counterbalanced)	RAC at patients preferred pace of movement 1,000 Hz square wave tone 50 ms pattern	Significant enhancement in elbow range of motion with RAC Significantly reduced trajectory variability of wrist joint, deviation of acceleration curves from optimal coordinates of wrist joint with RAC No effect on arm timing, shoulder joint displacement

(Continued)

TABLE 2 | Continued

Author	**Research question(s)/ hypothesis**	**Sample description, age: (M ± S.D)**	**PEDro**	**Disease duration**	**Assessment tools**	**Research design**	**Auditory stimuli characteristics**	**Conclusion**
Maulucci and Eckhouse (125)	Effects of R-af on reaching task in patients affected from chronic stroke	Healthy: 15F, 9M Exp: 3F, 5M Ct:4F, 4M	4	–	Normal trajectory region for end effectors and reach parameters	Normal participants performed and established generalized repeatability for the experimental groups. Reach trials performed for 42 trials 3 times/week for 6 weeks. Residual performance evaluated post 2 weeks without auditory feedback	Regulated R-af of magnitude and existence of error from normal ellipsoid reach area.	Significant enhancement in trajectory performance for Exp group as compared to Ct group Significant enhancement in both Exp and Ct group for reach trajectory
Whitall et al. (126)	Effects of RAC on arm motor function in patients affected from stroke	6F, 8M (63.7 ± 12.6)	6	5.5 ± 7.9 years	Active, passive range of motion of upper extremity, isometric shoulder, elbow, wrist force (flexion/extension) assessment, FMA, wolf motor function test and modified University of Maryland arm questionnaire for stroke	Pre-test, BATRAC for four 5-min sessions, 3 times a week for 6 weeks, post-test, 8-week retention post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, Wolf motor function test and modified University of Maryland arm questionnaire for stroke with RAC Significant enhancement in elbow, wrist flexion for paretic and non-paretic arm with RAC Significant enhancement in active range of motion for shoulder extension, wrist flexion and thumb opposition and passive range of motion for wrist flexion on the paretic side with RAC Significant enhancements sustained during the 8-week retention post-test across all range of motion, strength variables and qualitative assessment tools with RAC

ARAT, Action reach arm test; 9HPT, 9-hole peg test; FMA, Fugl Meyer assessment for upper extremity; BBT, Box and block test; EMG, Electromyography; RAC, Rhythmic auditory cueing; BATRAC, Bilateral arm training with rhythmic auditory cueing; R-af, Real-time auditory feedback; SIS, Stroke impact scale; Exp, Experimental group; Ct, Control group; F, Females; M, Males.

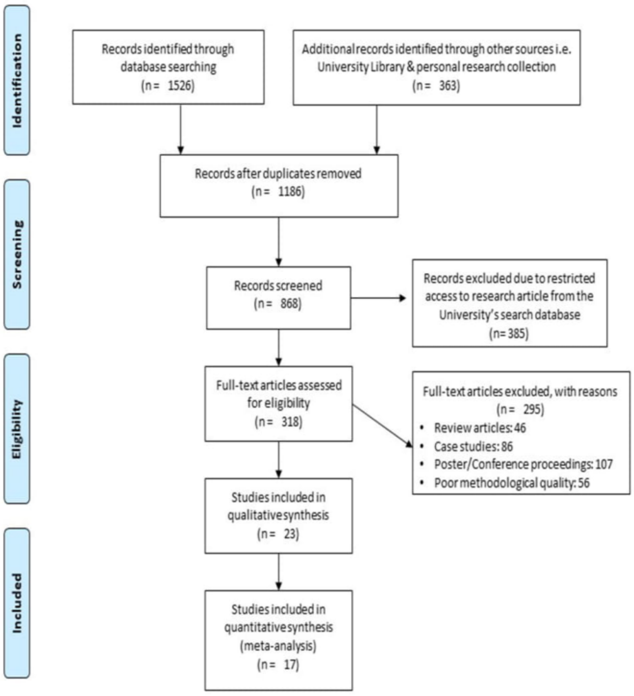

FIGURE 1 | PRISMA flow chart for the inclusion of studies.

the reviewers. The reviewers did not find any counterbalancing data. Data from each included study has been summarized in (**Table 2**). In the included studies, 10 were randomized controlled trials, and 13 were controlled clinical trials. Interventions in all the included studies were performed by either physiotherapists or medical practitioners. However, two studies in addition to training in clinics/laboratories included a phase of self-training administered by the patients themselves, at home (108, 122). Here, in both the studies guidance was provided by the researchers to the patients via telephone.

Participants

In total, the 23 included studies evaluated 585 participants of mixed gender population. The included studies had the gender distribution as follows: 226 females, and 359 males. Descriptive statistics concerning age (mean ± standard deviation) of the participants were tabulated across the studies. Disease duration of stroke patients has also been mentioned for better interpretation of the reader. However, five studies did not mention these details (107, 109, 111, 124, 125).

Risk of Bias

Studies scoring $\geq$4 on PEDro methodological scale were included in the review. Individual scores have been reported (**Table 2**, Supplementary Table 1). The average PEDro score for the 23 included studies was computed to be 5.3 ± 1.6 out of 10, indicating "fair" quality of the overall studies. Here, two studies scored nine (excellent quality), one study scored eight (excellent quality), three studies scored seven (good quality), six studies scored six (good quality), two studies scored five (fair quality), and 11 studies scored four (fair quality) (**Table 2**, Supplementary Table 1). **Figure 2** illustrates risk of bias across the studies. Further, publication bias was analyzed by plotting the evaluated weighted effect size i.e., Hedge's g values against standard error (**Figure 3**). Here, any asymmetry concerning mean in the funnel plot might suggest the presence of publication related bias.

Meta-Analysis

Outcomes

The results clearly suggest a positive influence of training with rhythmic auditory cueing and real-time auditory feedback on arm recovery post-stroke. Out of 23 included studies, significant enhancement was reported in 19 studies, three studies reported enhancements, and only one study reported significant reduction in arm function post training with auditory stimuli (**Table 2**).

Meta-Analysis Report

Application of a strict inclusion criterion was also meant to limit the amount of heterogeneity between the pooled studies (133). Nevertheless, despite these attempts some amount of unexplained heterogeneity was still observed. Thereafter, attempts were made to pool and analyze the studies further in sub-groups. The meta-analysis evaluated arm-functioning parameters, such as Fugl-Meyer assessment scores, Wolf motor time test, Action reach arm test, Stroke impact scale, 9-hole peg test, and elbow range of motion. The reliability and validity of these tests has been proven in the literature (134). Further, sub-group analyses were conducted to analyze specific training dosages, and to compare the effects of rhythmic auditory cueing and real-time auditory feedback. The main reasons for excluding the studies from statistical analysis was either major differences in between assessment methods, for instance considerably different auditory stimuli, disease duration, and/or lack of descriptive statistics within the manuscript. In this case, attempts were made by the primary reviewer (S.G) to contact respective corresponding authors.

Fugl Meyer Assessment Score

Fugl Meyer assessment scores for arm performance were assessed in 11 studies. Here, two studies evaluated the score on stroke patients while using real-time auditory feedback, whereas nine studies utilized rhythmic auditory cueing. The analysis of studies revealed (**Figure 4**) a *large* effect size in the positive domain (g: 0.79, 95% C.I: 0.38–1.09) and moderate heterogeneity was observed in between the studies (I^2: 29.3%, $p > 0.05$). Further, on separating the studies for comparing the effects of rhythmic auditory cueing and real-time auditory feedback, nine studies were analyzed for their effects on rhythmic auditory cueing and three studies for real-time auditory feedback.

An analysis for effects of rhythmic auditory cueing on Fugl Meyer assessment revealed (Supplementary Figure 1), positive

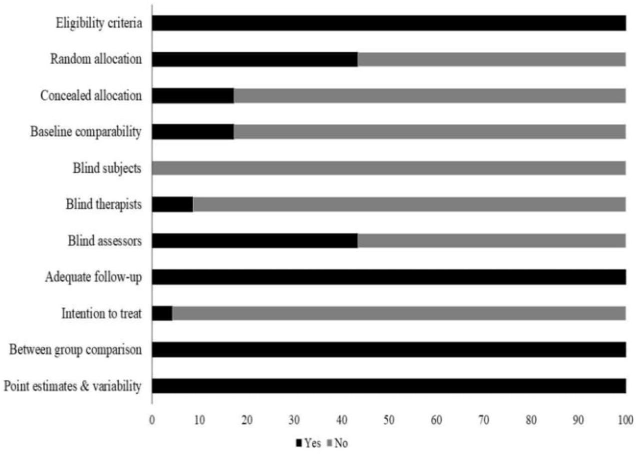

FIGURE 2 | Risk of bias across studies.

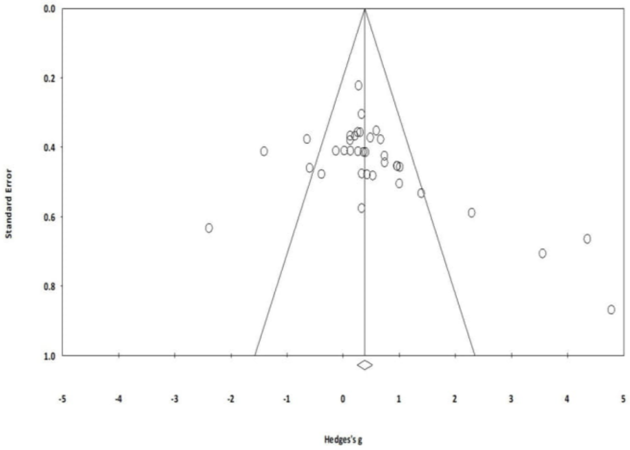

FIGURE 3 | Funnel plot for Hedge's g and standardized effect for each value in the meta-analysis. Each of the effect is represented in the plot as a circle. Funnel boundaries represent area where 95% of the effects are expected to lie if there were no publication biases. The vertical line represents the mean standardized effect of zero. Absence of publication bias is represented by symmetrical distribution of effect's around the mid-line.

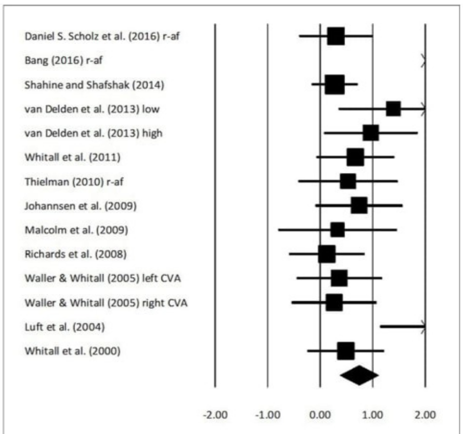

FIGURE 4 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on Fugl Meyer assessment scores on arm function amongst post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in Fugl Meyer scores depicting poor arm functioning; a positive effect size indicated enhancement in Fugl Meyer scores depicting better arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

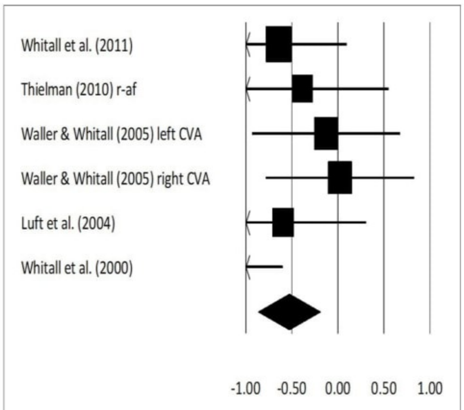

FIGURE 5 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on Wolf motor time assessment scores for arm function amongst post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in Wolf motor scores depicting a better arm functioning; a positive effect size indicated enhancement in Wolf motor scores depicting poor arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

medium effect size with negligible heterogeneity (g: 0.6, 95% C.I: 0.30–0.91, I^2: 10.7%, $p > 0.05$). An analysis for effects of real-time auditory feedback on Fugl Meyer assessment revealed (Supplementary Figure 2), a larger positive *large* effect size with moderate heterogeneity (g: 1.3, 95% C.I: −0.25 to 2.8, I^2: 40.3%, $p > 0.05$).

A further sub-group analysis based on the amount of training dosage (30 min to 1 h, ≥3 sessions per week) for rhythmic auditory cueing revealed (Supplementary Figure 3), positive *medium* effect size with moderate heterogeneity (g: 0.54, 95% C.I: 0.3–0.78, I^2: 43.8%, $p = 0.06$). Only one study (126), performed a training with rhythmic auditory cueing for <30 min, and hence was not included in further analysis. For the real-time auditory feedback Supplementary Figure 2 also illustrates the effects of training dosage for 30–45 min per session, and for >10 sessions of training.

Wolf Motor Time Assessment

An analysis for effects of rhythmic and real-time auditory stimuli on Wolf motor time assessment revealed (**Figure 5**) a negative *medium* effect size with moderate heterogeneity (g: −0.52, 95% C.I: −0.86 to −0.19, I^2: 33.2%, $p = 0.18$). Further, an analysis for only rhythmic auditory cueing revealed (Supplementary Figure 4) a similar negative *medium* effect size with negligible heterogeneity (g: −0.55, 95% C.I: −1.04 to −0.05, I^2: 0%, $p > 0.05$).

A further sub-group analysis based on the amount of training dosage (30 min to 1 h, ≥3 sessions per week) for rhythmic auditory cueing revealed (Supplementary Figure 5), negative *medium* effect size with negligible heterogeneity (g: −0.34, 95% C.I: −0.71 to 0.02, I^2: 0%, $p > 0.05$).

Elbow Range of Motion

Analysis for effects of rhythmic and real-time auditory stimuli on elbow range of motion revealed assessment revealed (**Figure 6**) a positive *medium* effect size with negligible heterogeneity (g: 0.36, 95% C.I: 0.03–0.7, I^2: 0%, $p > 0.05$). Further, a sub-group analysis for only rhythmic auditory cueing revealed a similar positive *medium* effect size with negligible heterogeneity (g: 0.37, 95% C.I: 0.01–0.72, I^2: 0%, $p > 0.05$). Further sub-group analysis was not performed because two studies did not include a training regime (112, 124), and one study analyzed the effects of real-time auditory feedback (118).

Action Reach Arm Test

Analysis for effects of rhythmic and real-time auditory inputs on Action reach arm test revealed (Supplementary Figure 6) a positive *large* effect size with substantial heterogeneity (g: 0.95, 95% C.I: 0.49–1.42, I^2: 87%, $p = 0.01$). Further, a sub-group analysis for only real-time auditory feedback training (30–45 min per session, and for >10 sessions of training) revealed a similar positive *large* effect size with substantial heterogeneity (g: 0.91, 95% C.I: 0.26–1.55, I^2: 95.6%, $p = 0.001$). Here, heterogeneity could be affirmed to considerable differences in the characteristics of real-time auditory feedback provided to the patients (see **Table 2** for details in auditory signal characteristics).

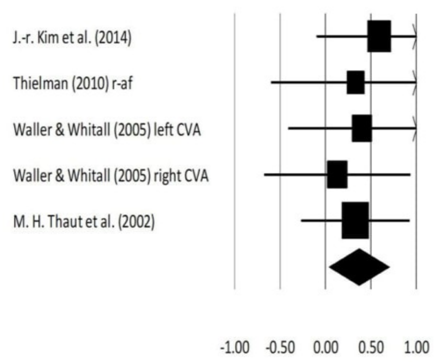

FIGURE 6 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on elbow range of motion among post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in elbow range of motion depicting poor arm functioning; a positive effect size indicated enhancement in elbow range of motion depicting better arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

Nine-Hole Peg Test

Analysis for effects of rhythmic and real-time auditory stimuli on Nine-hole peg test revealed (Supplementary Figure 7) a positive *small* effect size with substantial heterogeneity (g: 0.12, 95% C.I: −0.32 to 0.58, I^2: 85.2%, $p = 0.01$).

Further, a sub-group analysis for only rhythmic auditory cueing training (>30 min training session, 3 sessions per week) revealed a similar positive *small* effect size with substantial heterogeneity (g: 0.12, 95% C.I: −0.32 to 0.58, I^2: 90.15%, $p = 0.001$). Here, heterogeneity could be affirmed to considerable differences in the characteristics of rhythmic auditory cueing provided to the patients (**Table 2**).

Stroke Impact Scale

Analysis for effects of rhythmic and real-time auditory stimuli on Stroke impact scale revealed (Supplementary Figure 8) a positive *large* effect size with substantial heterogeneity (g: 0.95, 95% C.I: 0.49–1.42, I^2: 87%, $p = 0.01$). Further, a sub-group analysis for only rhythmic auditory cueing (>30 min of training, 3 sessions per week) revealed a similar positive *large* effect size with substantial heterogeneity (g: 0.91, 95% C.I: 0.26–1.55, I^2: 95.6%, $p = 0.001$). Here, substantial amount of heterogeneity could be due to considerable differences in the characteristics of real-time auditory feedback provided to the patients (**Table 2**).

DISCUSSION

The objective of this systematic review and meta-analysis was to analyze the current state of knowledge for the effects of rhythmic auditory cueing and real time kinematic auditory feedback for recovering arm function post-stroke. The current meta-analysis reports beneficial *small*-to-*large* standardized effects for both rhythmic auditory cueing and real-time kinematic auditory feedback in this aspect. Normally, patients with stroke exhibit poor spatiotemporal parameters during gross and fine motor skills performance for the upper extremities (135). Research suggests that assessment of arm function from Fugl Meyer test (136), Wolf motor assessment (137), Action reach arm test (138), 9-hole peg test (139), reliably reveal the severity of gross and fine motor function impairment post-stroke (136). In the current meta-analyses, we report beneficial effects of rhythmic auditory cueing on Fugl Meyer test (g: 0.6), Action reach arm test (g: 0.95), Wolf motor time test (g: −0.55), elbow range of motion (0.37), Nine-hole peg test (0.12), and Stroke impact scale (g: 0.91). Similarly, beneficial effects of real-time auditory feedback have also been reported for Fugl Meyer test (1.3), and action reach arm test (0.91). Therefore, indicating beneficial effects of external auditory stimuli for enhancing arm recovery, quality of life post-stroke.

Several reasons ranging from physiological, psychological and cognitive domains can be asserted for the beneficial effects of auditory stimuli on motor performance (64, 67, 83, 140, 141). Firstly, from a neurophysiological aspect, the auditory stimuli could have mediated multifaceted benefits. First and foremost, the stimuli could have facilitated or bypassed the deficit internal cueing system, often impaired in stroke patients exhibiting movement disorders (12). Here, a direct stimuli could have bypassed the deficit putamen directly to thalamus, and then from pre-motor area directly to primary motor cortex (76, 142). Secondly, the external stimuli could have modulated the oscillatory pattern of neuromagnetic β waves (a functional measure of auditory motor coupling) in auditory cortex, cerebellum, inferior frontal gyrus, somatosensory area and sensorimotor cortex (88, 143). Thirdly, enhanced neurological activation in inferior colliculi, cerebellum, brainstem, and sensorimotor cortex post training with rhythmic auditory cueing could have enhanced motor performance. In addition, enhanced neural re-organization especially in cortico-cerebellar circuits, and phase-periodic corrections (144) could have also been important reasons for enhancements in upper limb motor performance. Similarly, external auditory stimuli have also been suggested to facilitate neural plasticity (89, 96). In the present meta-analysis, we report beneficial effects of a training duration of 30 min−1 h with rhythmic and real-time auditory stimuli to result in enhanced performance measures for upper arm. According to the results of, this seems rational. The authors in their research reported enhanced electroencephalographic co-activity in the right hemispheric regions after just 20 min of audio-motor training, thereby implying a timeline for instigating plasticity (96). The authors also suggested the necessity of such time frame for establishing links between the perceptual modalities. Additionally, bilateral training could have also played an integral role in facilitating recovery observed in most of the studies (145). This training strategy has also been reported to facilitate neuroplasticity, cortical reorganization (110). Research suggest that bilateral training can facilitate plasticity by increasing bi-hemispheric activation, disinhibiting motor cortex, and upwardly regulating the descending propriospinal neurons.

In addition to these changes, the external auditory stimuli could also mediate debilitating cognitive dysfunctions commonly observed in patients with stroke (49). Published literature has often reported a direct relationship between the cognitive decline and movement failure (46, 146, 147). Masters and Maxwell (48) suggested that a cognitive decline might predispose patients to internally monitoring their movement patterns. This could then cause interferences with the autonomic functioning of the neural pathways, and might result in information overload (46), which further could lead to movement failure. Here, two explanations have been suggested in literature to counteract this cognitive overload. Firstly, the external auditory stimuli have been suggested to act as an external distractor (148). This could have allowed the patient to direct their focus away from their movements, thereby enhancing automatic control. Choi et al. (149) for instance, analyzed static and dynamic balance in chronic stroke patients during a cognitive-motor dual task. Here, the authors reported balance improvements when auditory cues were used during the dual task. The authors suggested that auditory cues might induce appropriate attention allocation i.e., engage higher attentional resources during auditory perception, which then could have facilitated motor performance. Secondly, enhanced cross modal processing between auditory and proprioceptive signals due to their high spatiotemporal proximity could have circumvented information overload in the native sensory modality by directing task-irrelevant information toward the underused sensory modality (98, 150). Here, inferences can be drawn from the Multiple resource theory (151, 152). The theory states that separate pools of attentional resources exist for different sensory channels and processes. Therefore, utilizing congruent stimuli together through different sensory modalities might reduce attentional interference by distributing the load amongst both the utilized modalities. Research analyzing the influence of cross-modal cueing between sensory modalities for instance audio-tactile domain have reported significant enhancements in performance under dual-task conditions as compared to performances under single sensory modality (150, 153) [for a detailed meta-analysis see (154)].

Moreover, recent research also suggests that in addition to mediating cognitive overload in patients with stroke, the external auditory cueing via music might facilitate, reorganize deficit cortical structures (155–157). For instance, merging the external auditory stimuli with music can allow facilitation of neural network including prefrontal, and limbic cortex this in turn has been associated with cognitive and emotional recovery post-stroke (155). Future research is strongly recommended to address this gap in literature as it might allow in developing of a rehabilitation protocol that focuses not only on motor recovery but also neural re-generation and/or organization (158).

In addition to the cognitive and motor deficits, the external auditory stimuli can also mediate lower sensory perceptual thresholds exhibited in patients in stroke (35). Here, external auditory stimuli might enhance the saliency of the perceptual modalities, which could then support the development of feedback, and feedforward models necessary for motor planning and execution (82, 159–161). Also, cross-sensory impacts between the perceptual modalities due to high spatiotemporal proximity between the sensory modalities might result in the auditory stimuli to support the deficit proprioceptive modality (98). Recent research evaluating the rhythmic auditory cueing suggests that mediating the auditory signal characteristics in terms of ecologically valid action relevant sounds might further enrich the precepted spatio-temporal information and allow extended enhancements in motor execution (142, 162) i.e., as compared to isosynchronous cueing. Patients with stroke due to their sensory impairments usually have higher thresholds for perception of sensory stimuli (35, 163). Therefore, enhancing the saliency of sensory information delivered through ecologically valid action relevant auditory stimuli such as walking on gravel, snow might be beneficial (50, 142, 164). According to Young et al. (165) action relevant auditory stimuli not only specify the temporal but also the spatial information, thereby enriching the feed-forward mechanisms to execute a motor task efficiently (166). The authors also affirmed beneficial effects of action relevant auditory stimuli on gait performance due to putative function of "sensori-motor neurons" (166). Furthermore, it can be expected that modifications in auditory signal characteristics such as modulation of timbre at a higher intensity further merged with a broad ascending melody and rich harmony might motivate a stroke patient to exert more force (50, 142, 167). This however, was not evaluated in any of the studies included in this review and should be a possible topic of research for future studies.

Moreover, research suggests the extended benefits of real-time auditory feedback with respect to rhythmic auditory stimuli. suggested that mapping the movements with real-time auditory feedback could allow a patient to better perceive their self-generated movement amplitudes. Further allowing them to compare it with the sound of a desirable auditory movement model. This could then result in development of an auditory reference framework model, which could amplify internal simulations of movements, and allow a patient to better perceive spatio-temporal parameters as compared to discrete rhythmic component (168). A contextual comparison of neuroimaging data from rhythmic (85, 86), and real-time auditory stimuli (90), suggests a large number of neurological structures having overlapped activation between both the auditory stimuli. However, enhanced activation of the areas associated with action observation such as, superior temporal sulcus, premotor cortex (169, 170), have been reported with real-time auditory feedback in one study (90). Here, the main reasons for the enhanced activation in areas associated with motion perception can be attributed to the findings of Shams and Seitz (171) and Lahav et al. (172). Here, the authors suggested that a convergent audio-visual motion would enhance accuracy of perception and motor performance due to the enhanced multimodal congruent nature (90, 171). Further, Lahav et al. (172) hypothesized that an audio-visual mirror neuron system with the premotor areas might be involved in serving as an "action listening" and "hearing & doing mirror neuron system," with the latter being largely dependent on a person's motor repertoire. Likewise, Vinken et al. (173) demonstrated that mapping real-time auditory feedback with real life activities lead to enhanced accuracy in judgement of actions, thereby demonstrating enhanced potential for improving motor perception, control, and learning. In the present meta-analysis enhanced scores for Fugl Meyer scores with real time kinematic auditory feedback (g: 1.3) were observed as compared to rhythmic auditory cueing (0.60).

The auditory stimuli could have also influenced the musculoskeletal structure of the upper extremities. For example, research suggests that intricate neuroanatomical interconnections between the auditory and motor cortex could allow the auditory stimuli could possibly mediate the firing and recruitment rate of motor units (28). This could then result in smoothening of motor movements, further resulting in enhanced joint kinematics, and movement scaling parameters (174). Likewise, regularized muscle co-activation rate has also been documented in electromyographic studies (175–177). This was also demonstrated in our meta-analysis concerning enhancement in elbow range of motion with rhythmic auditory cueing.

Moreover, the application of these interventions can be promoted in a cost-effective manner due to their high viability (50, 142). The strategies could prove to be efficient in developing countries where higher costs of rehabilitation promote stroke associated morbidity and mortality (178, 179). Here, the medical practitioners or tele-stroke (179), helplines can promote the use of mobile applications which can be utilized by patients at their home. Few smartphone applications have been reported in published literature, however, their feasibility in terms of costs is too high (180, 181). Future studies are recommended to address this gap and develop open source applications for the use of stroke patients. Here, the global position sensors, gyroscope and accelerometers present usually in a smartphone can be utilized to direct kinematic information, which could then assist in projecting either optimal rhythmic cueing pattern or converted/mapped in real-time to produce sonified auditory feedback. Further, applications can be developed to generate different types of ecologically valid sounds.

Finally, as the current review mentions a sole author (S.G), concerns regarding biasing, methodological flaws in the study's design and outcomes could be expected (182). Here, the reader is assured that this present systematic review and meta-analysis was carried out by two authors. Dr. Ishan Ghai (I.G) acted as an additional reviewer and statistician in the current study. His role is duly mentioned in the methodological, and acknowledgment sections. Dr. Ishan Ghai has himself consented to be excluded from this study as a co-author. Moreover, to ensure transparency in the methodological parts of the current review and analyses sufficient description has been provided for reciprocating the search strategy (**Table 1**), and the statistical analysis. Additionally, the corresponding author is willing to share the entire data with any reader upon request.

In conclusion, this present review for the first time analyzed the effects of rhythmic and real time auditory stimuli on arm recovery in post-stroke patients. The present findings are in agreement with systematic reviews and meta-analysis carried out to analyze auditory entrainment effect on aging (50), cerebral palsy (164), stroke (183), multiple sclerosis (184), and parkinsonism (63, 185). This review strongly suggests the incorporation of rhythmic and real-time auditory stimuli with a training dosage of 30 min to 1 h of training, for >3 sessions week for enhancing arm function recovery post-stroke.

AUTHOR CONTRIBUTIONS

SG conceptualized the study, carried out the systematic review, statistical analysis, and wrote the paper.

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SUPPLEMENTARY MATERIAL

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Chapter 5: Effects of rhythmic auditory cueing on gait in cerebral palsy: A systematic review and meta-analysis

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REVIEW

Effect of rhythmic auditory cueing on gait in cerebral palsy: a systematic review and meta-analysis

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Abstract: Auditory entrainment can influence gait performance in movement disorders. The entrainment can incite neurophysiological and musculoskeletal changes to enhance motor execution. However, a consensus as to its effects based on gait in people with cerebral palsy is still warranted. A systematic review and meta-analysis were carried out to analyze the effects of rhythmic auditory cueing on spatiotemporal and kinematic parameters of gait in people with cerebral palsy. Systematic identification of published literature was performed adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and American Academy for Cerebral Palsy and Developmental Medicine guidelines, from inception until July 2017, on online databases: Web of Science, PEDro, EBSCO, Medline, Cochrane, Embase and ProQuest. Kinematic and spatiotemporal gait parameters were evaluated in a meta-analysis across studies. Of 547 records, nine studies involving 227 participants (108 children/119 adults) met our inclusion criteria. The qualitative review suggested beneficial effects of rhythmic auditory cueing on gait performance among all included studies. The meta-analysis revealed beneficial effects of rhythmic auditory cueing on gait dynamic index (Hedge's g=0.9), gait velocity (1.1), cadence (0.3), and stride length (0.5). This review for the first time suggests a converging evidence toward application of rhythmic auditory cueing to enhance gait performance and stability in people with cerebral palsy. This article details underlying neurophysiological mechanisms and use of cueing as an efficient home-based intervention. It bridges gaps in the literature, and suggests translational approaches on how rhythmic auditory cueing can be incorporated in rehabilitation approaches to enhance gait performance in people with cerebral palsy.

Keywords: entrainment, spastic diplegia, hemiplegia, ataxia, rehabilitation, balance

Introduction

Cerebral palsy is a common developmental disorder.[1,2] The global prevalence of cerebral palsy is approximately 1.5–3.5/1,000 children,[3,4] and is supposedly growing in developing countries.[5] Cerebral palsy is primarily characterized by pre/postnatal damage to the brain,[3] often predisposing to grave neuromuscular and psychological disorders.[3,6] The treatment of cerebral palsy inflicts substantial costs[7] and adversely impacts quality of life.[8,9] Typically, motor dysfunction in cerebral palsy is characterized by spastic or extrapyramidal deficits.[10] These neuromuscular dysfunctions might cause dyskinesia, dystonia, ataxia, or hypotonia.[11,12] Further, these might lead to increased fatigue, reduced dexterity/coordination, postural instability, muscle contracture, and joint subluxation. Also, these neuromuscular disorders progress with aging.[11] For instance, lack of mobility and hypertonia often lead to development of muscle and joint contractures and secondary bone deformities. These neuromuscular deficits among both children and older adults with cerebral palsy considerably impair kinetic and kinematic changes, impair locomotion, and predispose to falls. For instance,

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exaggerated anterior stooping posture associated with increased anterior tilt in the pelvis, hip flexion, adduction, and internal rotation[13–15] adversely impact efficiency in energy expenditure[16] and spatiotemporal gait parameters.[17] Bourgeois et al[18] reported reduction in spatiotemporal gait parameters, such as cadence, stride length, and gait velocity associated with considerable enhancement in gait variability, which might predispose severely toward falls.[19]

In addition to these musculoskeletal changes, Rosenbaum et al[2] suggested considerable discrepancies in sensory perceptions, cognition, and behavior. Neuroimaging studies report deficits in the dorsolateral prefrontal cortex, dorsal anterior cingulate gyrus,[20] somatosensory cortex,[21] and cerebellum[22] which might considerably impair intellectual and cognitive performance.[22–24] Likewise, deficits in corticospinal, thalamocortical, superior occipitofrontal and superior longitudinal pathways have also been reported.[12,20,25] Together, these psychological constraints might also impair motor performance, such as in a dual-task scenario. For instance, Hung et al[26] reported drops in gait-performance measures in unilateral cerebral palsy patients while performing a dual task. Studies have suggested that this modification in gait patterns might happen due to an alleviation in "internal" conscious attention toward autonomic control that adversely impacts proprioception and autonomic functioning, possibly because of movement-specific reinvestment.[27–29] The theory suggests that directing attention internally to control autonomic movements, such as gait, can have an adverse impact on performance,[29] especially in high-stress situations.[30] Common treatment strategies to curb motor dysfunctions in cerebral palsy include training with virtual reality,[31] biocueing,[32] physical/occupational therapy,[33] physical exercise,[34] treadmill,[35] and orthosis.[36,37]

Recently, several studies have tried to address the sensorimotor deficits in people with cerebral palsy by applying rhythmic auditory entrainment.[38–41] Cueing aims to counteract sensory deficits, and has been shown to modulate neuromagnetic β-oscillations,[42] cortical reorganization, enhance biological motion perception,[43,44] motor imagery,[45,46] neural plasticity,[48] reduce shape variability in musculoskeletal-activation patterns,[47] and movement-specific reinvestment.[49] Moreover, as a cheap[50] and viable[51] treatment strategy, this approach can provide substantial benefits in developing countries, where prevalence of cerebral palsy due to socioeconomic factors is more prominent.[52,53] We identified high-quality systematic reviews analyzing the effects of external auditory cueing on gait performance among healthy,[121] Parkinsonism[54–56,122] and stroke participants.[57–59] However, to the best of our knowledge, no systematic or narrative analysis has been carried out to analyze the effects of auditory entrainment on gait in people with cerebral palsy. Therefore, we attempted to develop a state of knowledge for the use of cerebral palsy patients and medical practitioners, where both qualitative and quantitative data from high-quality studies can be interpreted.

Materials and methods

This review was conducted according to the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[60] and American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) methodology for systematic reviews.[61]

Data sources and search strategy

The academic databases Web of Science, PEDro, EBSCO, Medline, Cochrane Central Register of Controlled Trials, Embase and ProQuest were searched from inception until July 2017. A sample-search strategy is provided in Table 1.

Data extraction

Upon selection for review, data extracted from each article were study aim, selection criteria, sample size, sample description (sex, age, health status), intervention, characteristics of auditory cueing, dual tasks, outcome measures, results, and conclusions. The data were then summarized and tabulated (Table 2). The inclusion criteria for the studies were: randomized controlled trials, cluster-randomized controlled trials, or controlled clinical trials; reporting reliable and valid spatiotemporal gait and kinematic parameters; including dynamic aspects of gait stability; use of PEDro methodological quality scale (score ≥4); conducted on human participants; published in a peer-reviewed academic journal; and published in English, German, or Korean.

Quality and risk-of-bias assessment

The quality of the studies was assessed using the PEDro methodological quality scale.[62] The scale consists of eleven items addressing external validity, internal validity, and interpretability, and can detect potential bias with high reliability,[63] and validity.[62] A blinded rating of the methodological quality of the studies was carried out by the first (SG), second (IG) and third (AOE) reviewers. Ambiguous issues were discussed between reviewers and consensus was reached. Included studies were rated and interpreted according to scoring of 9–10, 6–8, and 4–5 for "excellent", "good", and "fair" quality,[64] respectively. Inadequate randomization,

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Table 1 Sample search strategy – Embase

Date	**July 10, 2017**
Strategy	**#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7**
#1	("rhythmic auditory cueing" OR "rhythmic acoustic cueing" OR "rhythmic auditory entrainment" OR "metronome cueing" OR "metronome" OR "rhythmic metronome cueing" OR "acoustic stimulus" OR "acoustic cueing" OR "acoustic cueing" OR "external stimuli" OR "external cueing" OR "external cueing" OR "music therapy" OR "Neurological music therapy" OR "tempo" OR "beat" OR "rhythm" OR "RAC" OR "NMT")/de OR (rhythmic auditory cueing OR rhythmic auditory cueing OR rhythmic acoustic cueing OR rhythmic auditory entrainment OR metronome cueing OR metronome OR rhythmic metronome cueing OR acoustic stimulus OR acoustic cueing OR acoustic cueing OR external stimuli OR external cueing OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT)ti,ab
#2	("CP" OR "Cerebral Palsy" OR "Cerebral Palsy athetoid" OR "Cerebral Palsy congenital" OR "Cerebral Palsy Diplegic infantile" OR "Cerebral Palsy dyskinetic" OR "Cerebral Palsy dystonic-rigid" OR "Cerebral Palsy hypotonic" OR "Cerebral Palsy mixed" OR "Cerebral Palsy monoplegic, infantile" OR "Cerebral Palsy quadriplegic infantile" OR "Cerebral Palsy Rolandic type" OR "Cerebral Palsy Spastic" OR "Congenital Cerebral Palsy" OR "diplegia-spastic" OR "Diplegic infantile cerebral palsy" OR "infantile cerebral palsy-diplegic" OR "infantile cerebral palsy-monoplegic" OR "infantile cerebral palsy-quadriplegic" OR "little disease" OR "little's disease" OR "Monoplegic cerebral palsy" OR "Monoplegic infantile cerebral palsy" OR "Quadriplegic infantile cerebral palsy" OR "Spastic diplegia")/de OR (CP OR Cerebral Palsy OR Cerebral Palsy athetoid OR Cerebral Palsy congenital OR Cerebral Palsy Diplegic infantile OR Cerebral Palsy dyskinetic OR Cerebral Palsy dystonic-rigid OR Cerebral Palsy hypotonic OR Cerebral Palsy mixed OR Cerebral Palsy monoplegic, infantile OR Cerebral Palsy quadriplegic infantile OR Cerebral Palsy Rolandic type OR Cerebral Palsy Spastic OR Congenital Cerebral Palsy OR diplegia-spastic OR Diplegic infantile cerebral palsy OR infantile cerebral palsy-diplegic OR infantile cerebral palsy-monoplegic OR infantile cerebral palsy-quadriplegic OR little disease OR little's disease OR Monoplegic cerebral palsy OR Monoplegic infantile cerebral palsy OR Quadriplegic infantile cerebral palsy OR Spastic diplegia):ti,ab
#3	("cognitive task" OR "concurrent task" OR "dual task" OR "dual task paradigm" OR "dual task paradigm" OR "cognitive task training" OR "dual task training" OR "dual task training")/de OR (cognitive task OR concurrent task OR dual task OR dual task OR dual task paradigm OR dual task paradigm OR cognitive task training OR dual task training OR dual task training"):ti,ab
#4	("walking" OR "gait" OR "locomotion" OR "range of motion" OR "ROM" OR "ambulation" OR "mobility" OR "treadmill gait" OR "balance" OR "stability" OR "stride" OR "gait training" OR "gait rehabilitation")/de OR (walking OR gait OR locomotion OR range of motion OR ROM OR ambulation OR mobility OR treadmill gait OR balance OR stability OR stride OR gait training OR gait rehabilitation);ti,ab
#5	("rehabilitation" OR "treatment" OR "rehab" OR "management" OR "therapy" OR "physiotherapy" OR "physical therapy" OR "prevention" OR "risk prevention")/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
#6	("age groups" OR "adolescent" OR "young" OR "elderly" OR "old" AND ("gender" OR "male" OR "female")/de OR (age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female));ti;ab
#7	("intervention study" OR "cohort analysis" OR "longitudinal study" OR "cluster analysis" OR "crossover trial" OR "cluster analysis" OR "randomized trial" OR "major clinical study")/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab

nonblinding of assessors, no intention-to-treat analysis, and no measurement of compliance were considered as major threats for biasing.[65]

Data analysis

This systematic review also included a meta-analysis approach to develop a better understanding of the incorporated interventions.[66] Presence and lack of heterogeneity drove the use of either random- or fixed-effect meta-analysis.[67] A narrative synthesis of the findings structured according to intervention, population characteristics, methodological quality, and type of outcome is provided (Table 2). A meta-analysis was conducted between pooled studies using Comprehensive Meta-Analysis software (version 2.0; Biostat, Englewood, NJ, USA). Heterogeneity among the studies was assessed using I^2 statistics. The data in this review were systematically distributed, and for each available variable pooled, dichotomous data were analyzed and forest plots with 95% CIs reported. Effect sizes were adjusted and reported as Hedge's *g*.[68] Thresholds for interpretation of effect sizes were as follows: standard mean effect of 0 meant no change, negative effect meant a negative change, and a positive effect meant a positive change.

Mean effect of 0.2 was interpreted as a small effect, 0.5 a medium effect, and 0.8 a large effect.[69] Interpretation of heterogeneity via I^2 statistics was 25%, 50%,75% as negligible, moderate and substantial heterogeneity, respectively. 75% as negligible, moderate, and substantial heterogeneity, respectively. Meta-analysis reports, including heterogeneity among studies, were evaluated to determine the reason for heterogeneity, and studies included were then pooled separately and analyzed again in a sub-group analysis. The α-level was set at 95%.

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Table 2 Studies analyzing the effects of RAC on gait

Study	Research aim	Sample description, age (years), mean ± SD/range	PEDro score	Assessment tools	Research design	Auditory cueing	Conclusion
Efraimidou et al[70]	Effects of RAC on gait in people with CP	Exp: 5M (35.2±13) Ct: 5M (38.8±12.2)	5	Timed up-and-go test, 10 m walk test, BBS, center-of-pressure sway, self-esteem scale, profile of mood states	Pretest, 50-minute session twice a week for 8 weeks with RAC at 70 bpm, and posttest at 90 bpm	Rhythmic music cueing (70–90 bpm), with 4/4 music meter	Significant enhancement in timed up-and-go test, normal and fast gait speed in a 10 m walking test in Exp compared to Ct Significant enhancement in BBS score in Exp compared to Ct Significant reduction in center-of-pressure sway and timing of right- and left-foot synchronization in Exp compared to Ct Significant enhancement in self-esteem score and overall scoring of profile and mood states in Exp compared to Ct
Shin et al[38]	Effects of RAC on gait in people with hemiplegia (stroke/CP)	CP: 4F, 3M (30.1±4.1) Stroke: 4F, 7M (44.27)	4	Cadence, gait speed, stride length, stride time, step time, single/double-support time, stance/swing phase (temporospatial deviation and side-to-side comparison), pelvis, hip, knee, ankle, foot kinematics, gait-deviation index	Pretest, gait training with RAC for 30 minutes/session, and three sessions/week for 4 weeks, posttest	RAC by four-chord progression with metronome beat on keyboard at preferred cadence	Significantly reduced ankle plantar flexion at initial contact and push-off Reduced anterior pelvic tilt in sagittal plane after training with auditory cueing Significantly enhanced kinematic improvements in stroke patients compared to CP Significant enhancement in gait-deviation index and kinematics for people with subacute compared to chronic stroke No effect on gait parameters after training from auditory cueing Enhanced side-to-side symmetry after training from auditory cueing Significant enhancement in gait-deviation index, hip adduction in mid-stance, maximal knee flexion in mid-swing, ankle dorsiflexion in terminal stance after training from RAC
Wang et al[73]	Effect of auditory feedback on motor capacity, strength, mobility, and gait in people with CP (spastic diplegia)	Exp: 6F, 12M (9±1.9) Ct: 3F, 15M (8.9±2.6)	7	Gross motor-function measure (dimensions D and E), goal-dimension score, gait speed, PEDI, functional skill scale of PEDI, caregiver-assistance scale, one-repetition-maximum load of a loaded sit-to-stand test, gait speed and gait duration for 10 m walking test	Pretest, sit-to-stand exercise at home three times/week for 6 weeks, posttest at 6, 12 weeks Training load progressed 2 weeks upon evaluation of one-repetition-maximum sit-to-stand test, auditory feedback adjusted every 2 weeks upon reassessment	Auditory feedback as patterned sensory enhancement (spatial, temporal, and force cueing) Pitch variations: ascending and descending melodies indicate directions (range of motion cueing)	Significant enhancement in goal-dimension score during posttest at 6- and 12-week follow-up in Exp compared to Ct Significant enhancement in dimension D score in first posttest and 6-week follow-up posttest in Exp compared to Ct Enhancement in dimension E, dimension D (12 weeks posttest) scores during 6- and 12-week follow-up posttest in Exp compared to Ct

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						Tempo, meter, and rhythmic pattern (speed and timing of movement) Loudness: strength of muscular contraction	Significant reduction in PEDI for caregiver assistance at 12-week posttest Exp compared to Ct Enhancement in gait speed (posttest and 12-week posttest), and one repetition maximum of sit to stand in posttest and 6- and 12-week posttests in Exp compared to Ct
Jiang[75]	Effect of RAC on gait performance in people with CP	5F, 4M (5–12)	7	Gait velocity, cadence, and stride length	Gait training with/without RAC at 0 and +5% of preferred cadence (randomly) for one 30-minute session/week for 3 weeks	RAC by piano, guitar, bass, and percussion, with music in 4/4 beat accented by metronome. Piano superimposed on beat to emphasize rhythm at preferred cadence	Significant enhancement in cadence and gait velocity with training from auditory cueing Enhancement in stride length with auditory cueing Significant enhancement in cadence and gait velocity for people with higher level of gross motor functioning compared to lower levels of gross motor functioning
Varsamis et al[77]	Effect of RAC on gait performance in people with CP with mental disabilities	7F, 11M (18.2±3.8)	4	Duration for gait performance, number of steps, steps/minute, pulse/minute, and steps and pulse (intraindividual Standard deviation)	Pretest, gait performance with/without RAC and instruction "do your best"	Rhythmic metronome cueing at preferred cadence	Significant enhancement in duration, number of steps with auditory cueing Significant reduction in steps/minute, pulse/minute, steps and pulse (intraindividual SD) with auditory cueing
Baram and Lenger[41]	Effect of real-time auditory feedback on gait performance in people with CP	Visual cueing: 7F, 3M (13.3±6.2) Auditory cueing: 6F, 4M (11.1±6.5) Ct, visual cueing: 3F, 4M (12.4±0.5) Auditory cueing: 4F, 4M (12.6±7.4)	4	Pre- and posttest gait analysis; training performed between tests with visual or auditory cueing	Walking speed, stride length, and cadence	Real-time auditory cueing at preferred cadence	Significant enhancement in walking speed and stride length compared to Ct condition and visual condition alone No effect of auditory feedback on healthy Ct
Kim et al[39]	Effect of RAC on gait for people with CP	Exp: 5F, 10M (27.3±2.4) Ct: 6F, 7M (27.3±2.5)	7	Cadence, gait velocity, stride length, step length, stride time, step time, stance phase, swing phase, gait-deviation index, kinematic data for pelvis, hip sagittal plane (anterior tilt/flexion at initial contact, maximal–minimal angle of anterior tilt/flexion), coronal plane (abduction–adduction at initial contact, maximal adduction–abduction angle), transverse plane (internal–external rotation at initial contact, maximal–minimal internal–external rotation),	Pretest, gait training with RAC (Exp), neurodevelopmental therapy/Bobath therapy (Ct) at preferred cadence for 30-minute session three times/week for 3 weeks posttest	Rhythmic metronome cueing at preferred cadence	Significant enhancement in cadence, gait velocity, stride length, step length, swing phase, gait-deviation index in Exp after training with RAC compared to Ct Significant reduction in stride time, step time, stance phase in Exp as compared to Ct Significant reduction in pelvis: sagittal plane (anterior tilt initial contact, maximal angle of anterior tilt) in Exp as compared to Ct Significant enhancement in pelvis: sagittal plane (minimal angle of anterior tilt) and hip joint: transverse plane

(*Continued*)

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Table 2 (*Continued*)

Study	Research aim	Sample description, age (years), mean ± SD/range	PEDro score	Assessment tools	Research design	Auditory cueing	Conclusion
				knee sagittal plane (flexion at initial contact, maximal flexion at swing, minimal flexion at stance), ankle sagittal plane (flexion at initial contact, maximal dorsiflexion at stance, minimal plantar flexion at preswing), foot transverse plane (internal–external rotation at initial contact, maximal–minimal internal–external rotation)			(maximal internal rotation) in Exp as compared to Ct Significant reduction in hip joint: sagittal plane (minimal flexion angle) and coronal plane (abduction–adduction at initial contact, maximal adduction–abduction angle) in Exp as compared to Ct
Kim et al[76]	Effect of RAC on gait in children with CP	Exp I (community ambulators): 3F, 5M (25.1±8.1) Exp II (household ambulators): 2F, 4M (26.3±6.6) Ct: 15F, 15M (21.5±1.7)	4	Cadence, gait velocity, stride length, step length, stride time, step time, stance phase, swing phase, gait-deviation index, kinematic data for pelvis, hip sagittal plane (anterior tilt/flexion at initial contact, maximal–minimal angle of anterior tilt/flexion), coronal plane (abduction–adduction at initial contact, maximal adduction–abduction angle), transverse plane (internal–external rotation at initial contact, maximal–minimal internal–external rotation), knee sagittal plane (flexion at initial contact, maximal flexion at swing, minimal flexion at stance), ankle sagittal plane (flexion at initial contact, maximal dorsiflexion at stance, minimal plantar flexion at preswing), foot transverse plane (internal–external rotation at initial contact, maximal–minimal internal–external rotation)	Gait performance with/without rhythmic metronome cueing at preferred cadence	Rhythmic metronome cueing at preferred cadence	Significant reduction in pelvis: sagittal plane (anterior tilt initial contact, maximal, minimal angle of anterior tilt) and hip: sagittal plane (maximal, minimal flexion angle) and transverse plane (maximal internal–external rotation) in Exp after training with RAC (Exp I > Exp II) Significant enhancement in gait-deviation index with RAC in Exp (Exp I > Exp II) Significant reduction in step length for household-ambulator group with RAC
Kwak[74]	Effect of RAC on gait performance in people with CP	30 (6–20) Exp I: 10 patients Exp II: 10 patients Ct: 10 patients	4	Cadence, stride length, gait velocity, gait cycle, gait symmetry, and foot-contact pattern	Pretest, (Exp I and II) gait training at +5%, +10%, and +15% of preferred cadence in first, second, and third weeks, respectively, training for	RAC at +5%, +10%, and +15% of preferred cadence by music, steady-beat pattern with 4/4 meter, ie, 80-120 bpm	Significant enhancement in stride length, gait velocity, and gait symmetry for Exp I Enhancement in stride length, gait symmetry, and gait velocity for Exp II compared to Ct

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30 minutes/session for 5 days/week for 3 weeks posttest Exp I: therapist-guided gait training with RAC (with drum/clap cueing, pattern sensory enhancement, and therapeutic instrument music playing for muscle strengthening) Exp II: therapist-guided gait training, but self-guided training with RAC Ct: conventional training by a therapist without auditory cueing	Input by drum or clap sound in closed and open tone to differentiate acoustics for right and left foot	Enhancement in cadence for Exp I and II and reduction in cadence for Ct

Abbreviations: BBS, Berg Balance Scale; bpm, beats per minute; CP, cerebral palsy; Ct, control group; Exp, experimental group; F, female; M, male; PEDI, Pediatric Evaluation of Disability Inventory; RAC, rhythmic auditory cueing.

Results

Characteristics of studies included

Our initial search across academic databases yielded a total of 387 studies; 175 studies were included from a personal library. After implementing our inclusion/exclusion criteria, nine studies were left (Figure 1). Data from the studies included have been summarized in Table 2. Of the nine studies included, all were controlled clinical trials.

Participants

A total of 227 participants were analyzed in the incorporated studies. In the studies included, eight studies incorporated mixed-sex patients. Only one study included male participants.[70] The studies provided data on 227 participants (n=119 females/108 males). Moreover, in 108 children, the sex distribution was 57 females to 51 males, and for adults 62 females to 57 males. Descriptive statistics relating to the age (means ± SD) of the participants were tabulated across the studies (Table 2).

Risk of bias

To reduce the risks of bias, studies scoring ≥4 on PEDro were included in the review. Moreover, research protocols to be included in the review were limited to gold-standard randomized controlled trials, cluster-randomized controlled trials, and controlled clinical trials. The individual scores attained by studies using the PEDro scale are reported in Table 2, and Table S1. The average PEDro score for the nine studies was 5 of 10, indicating fair quality for studies overall. Three studies scored 7, and six studies scored 4. Risk of bias across the studies is shown in Figure 2.

Outcomes

The results provided evidence for a positive impact of rhythmic auditory cueing on spatiotemporal and kinematic gait parameters among adults and children with cerebral palsy. In all studies, significant enhancement in primary spatiotemporal and kinematic gait parameters were reported.

Meta-analyses

The evaluation of research studies via meta-analysis requires strict inclusion criteria to limit heterogeneity efficiently.[71] However, among the pooled group of studies after strict inclusion criteria, some unexplained heterogeneity was still observed. Subgroup analyses were then performed for identical studies to evaluate the cause of the heterogeneity. The parameters evaluated were spatiotemporal gait parameters, such as cadence, stride length, gait velocity, and kinematic

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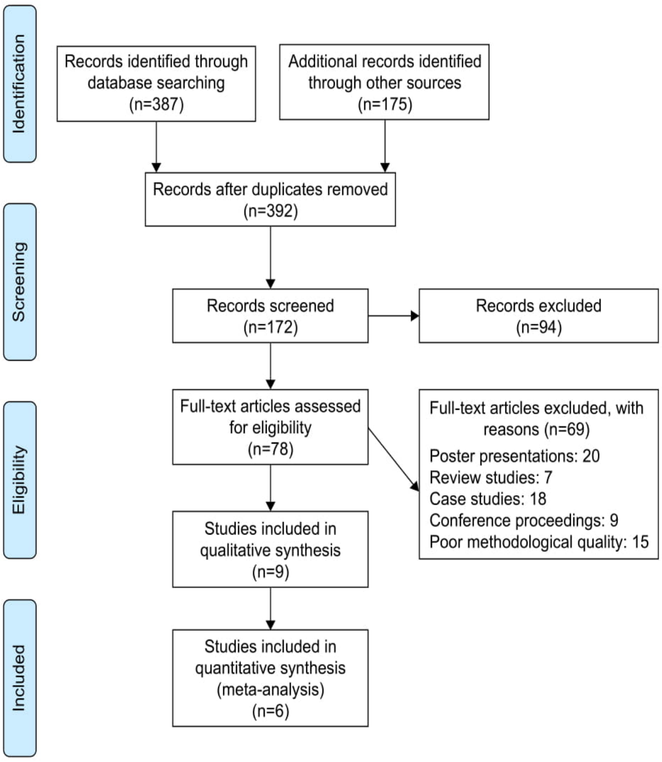

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for inclusion of studies.

parameters. Further analyses were conducted to evaluate the effects of rhythmic auditory cueing at preferred cadence on gait velocity in both adults and children separately. We included a generalized group analysis by first combining all the pooled studies. The studies excluded differed considerably in assessment methods or if descriptive statistics were not mentioned in the manuscript. However, attempts were made to contact the coauthors for the data.

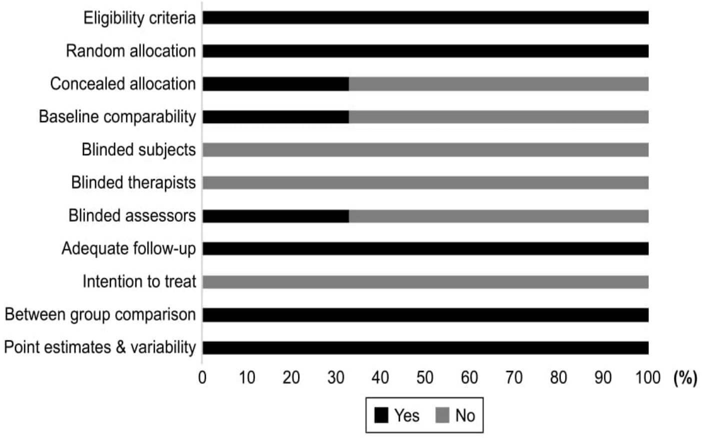

Figure 2 Risk of bias across studies.

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Gait velocity

Gait velocity was analyzed in six studies. Here, two studies evaluated the effects of rhythmic auditory cueing on gait velocity in adults[38,72] and four in children[41,73–75] with cerebral palsy. One study included assessment of gait velocity while using patterned sensory enhancement[73] as the mode of auditory feedback. Analysis of studies revealed (Figure 3) a large positive effect (g=1.13, 95% CI 0.33–1.94). Substantial heterogeneity was observed between studies (I^2=84%, P>0.01). Subgroup analyses were conducted to explore heterogeneity.

An analysis for effects of rhythmic auditory cueing on gait velocity in children revealed (Figure S1), large positive effect with substantial heterogeneity (g=1.24, 95% CI 0.31–2.17, I^2=81%; P<0.01). Here, the heterogeneity could possibly be attributed to different training regimes in the studies, ie, no training was included by one,[41] while others[73–75] had training regimes for ≥3 weeks. Subgroup analysis revealed (Figure S2) a large positive effect with substantial heterogeneity (g=1.53, 95% CI 1.07–1.98, I^2=82%; P<0.01). Moreover, Jiang[75] included only one training session per week. Whereas, others performed training for three (Wang et al.[73]), and five times (Kwak[74]), per week. Subgroup analysis revealed a large positive effect with negligible heterogeneity (g=2.05, 95% CI 1.5–2.6, I^2=0; P>0.05). Finally, subgroup analysis evaluating the effects of rhythmic auditory cueing on gait velocity in adults revealed a large positive effect with negligible heterogeneity (g=0.95, 95% CI –0.95 to 2.85, I^2=0; P>0.05).

Stride length

Stride length was analyzed in five studies. Two and three studies evaluated the effects of rhythmic auditory cueing on stride length in adults[38,72] and children,[41,73–75] respectively. Analysis revealed (Figure 4) a medium positive effect (g=0.58, 95% CI –0.02 to 1.19). Moderate heterogeneity was observed between studies (I^2=65%, P>0.01). Subgroup analyses were conducted to explore the cause of heterogeneity. Analysis for effects of rhythmic auditory cueing on stride length in children revealed (Figure S3) a medium positive effect with negligible heterogeneity (g=0.75, 95% CI 0.01–1.48, I^2=0; P>0.05). Subgroup analysis evaluating the effects of rhythmic auditory cueing on stride length in adults revealed a comparably smaller medium effect with negligible heterogeneity (g=0.3, 95% CI −1.07 to 1.67, I^2=0; P>0.05).

Cadence

Cadence was analyzed in five studies, of which two evaluated the effects of rhythmic auditory cueing on cadence in adults[38,72] and three in children[41,73–75] with cerebral palsy. Analysis of studies revealed (Figure 5) a medium positive effect (g=0.33, 95% CI –0.41 to 1.07). Substantial heterogeneity was observed between studies (I^2=79%, P>0.01). Subgroup analyses were conducted to explore heterogeneity. An analysis for effects of rhythmic auditory cueing on cadence in children revealed a small negative effect with negligible heterogeneity (g=–0.11, 95% CI –0.97 to 0.74, I^2=0; P>0.05). Subgroup analysis evaluating the effects of

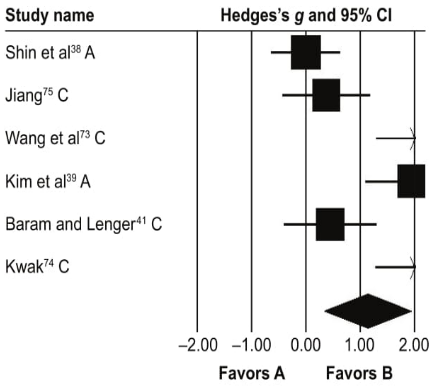

Figure 3 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity in people with cerebral palsy.
Notes: Negative effects indicate reduction in gait velocity, positive effects enhancement in gait velocity. Weighted-effect sizes – Hedge's g (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.
Abbreviations: A, adults; C, children.

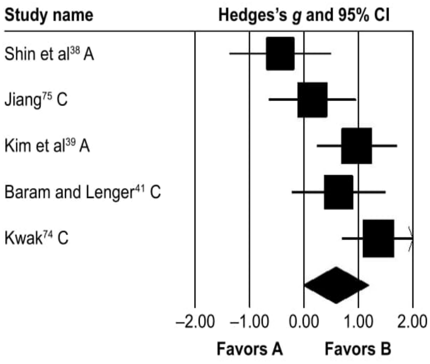

Figure 4 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length in people with cerebral palsy.
Notes: Negative effects indicate reduction in stride length, positive effects enhancement in stride length. Weighted-effect sizes – Hedge's g (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.
Abbreviations: A, adults; C, children.

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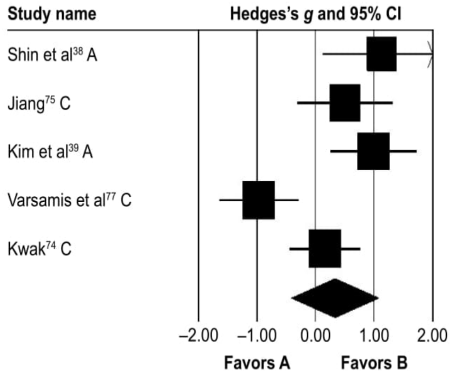

Figure 5 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence in people with cerebral palsy.

Notes: Negative effects indicate reduction in step frequency, positive effects enhancement in step frequency. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

Abbreviations: A, adults; C, children.

rhythmic auditory cueing on cadence in adults revealed a large positive effect with negligible heterogeneity (*g*=1.04, 95% CI 0.44–1.64, I^2=0; *P*>0.05).

Kinematic parameters

Three studies analyzed the effects of rhythmic auditory cueing on gait-dynamic index (a combined measure of lower-limb kinematic performance). Data for subgroup analysis on the gait dynamic index concerning community and household dwellers were extracted from two studies.[38,76] Analysis revealed (Figure 6) a large positive effect (*g*=0.92, 95% CI 0.07–1.76, I^2=0; *P*<0.01) with negligible heterogeneity. Further, an analysis of gait-dynamic index in community dwellers revealed a small positive effect with negligible heterogeneity (*g*=0.07, 95% CI −0.66 to 0.8, I^2=0; *P*>0.05). Comparably, analysis of household dwellers revealed a large positive effect with negligible heterogeneity (*g*=1.11, 95% CI 0.24–1.98, I^2=0; *P*>0.05). Subgroup analysis was also conducted on individual kinematic parameters to specify the magnitude of effects of rhythmic auditory cueing on specific joint kinematics.

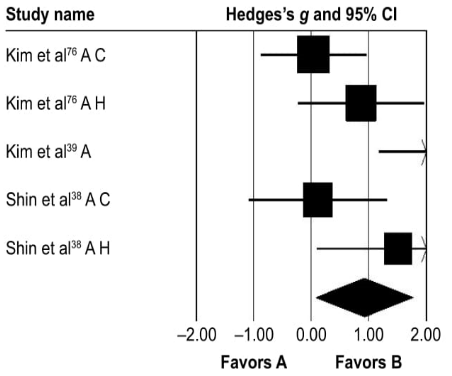

Figure 6 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait-dynamic index in people with cerebral palsy.

Notes: Negative effects indicate reduction in gait-dynamic index, positive effects enhancement in gait-dynamic index. Weighted effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate a favorable outcome for control groups, positive mean differences a favorable outcome for experimental groups.

Abbreviations: A, adults; C, children; H, household dwellers.

Subgroup analysis evaluating changes at the pelvis revealed (Figure S4) small negative effects with negligible heterogeneity (*g*=–0.23, 95% CI −0.68 to 0.21, I^2=0; *P*>0.05). At the hip joint, medium negative effects with moderate heterogeneity (*g*=–0.43, 95% CI −0.89 to 0.01, I^2=33.5%; *P*>0.01) were observed (Figure S5). At the knee joint, medium positive effects with negligible heterogeneity (*g*=0.26, 95% CI −0.18 to 0.71, I^2=0; *P*>0.05) were observed (Figure S6). At the ankle joint, medium positive effects with moderate heterogeneity (*g*=0.36, 95% CI −0.09 to 0.81, I^2=32.7%; *P*>0.01) were observed (Figure S7). Finally, at the foot, small negative effects with moderate heterogeneity (*g*=–0.18, 95% CI −0.62 to 0.26, I^2=0; *P*>0.05) were observed (Figure S8).

Discussion

The primary objective of this systematic review and meta-analysis was to synthesize the current state of knowledge for the effects of rhythmic auditory cueing on gait in people with cerebral palsy. All nine studies reported beneficial effects of rhythmic auditory cueing on gait parameters in children and adults with cerebral palsy. Further, the meta-analysis found significant small–large standardized effects for the benefits of rhythmic auditory cueing on spatiotemporal and kinematic parameters of gait among patients affected with cerebral palsy.

Typically, spatiotemporal parameters of gait may worsen over time in those with cerebral palsy. Deficits in periventricular white matter,[12] gray matter,[78] cerebellum,[79] basal ganglia,[80] and thalamus[81] have been well documented.[12] These neural centers play an integral role in managing stabilization and performance during automated tasks, such as posture and gait.[82,83] In addition, increasing psychological stress might be exerted on automated control for posture, gait, and cognitive processing by deficits reported in corticospinal, thalamocortical, superior occipitofrontal, and longitudinal pathways,[84–86] possibly also explaining the loss of gait rhythmicity.[87] Likewise, increased energy expenditure,[88] associated variability in muscle contraction, and force production

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add to the instability.[89] Rhythmic auditory cueing seems to counter these deficits efficiently. The current meta-analysis reported enhancements in gait velocity (1.24) and stride length (0.75) in children and gait velocity (0.95), stride length (0.3), and cadence (1.04) in adults. Beneficial effects were also observed in gross gait-dynamic index (a combined measure of kinematic variables during gait) for adult patients affected with cerebral palsy (0.92).

Several mechanisms have been suggested for the beneficial effects of rhythmic auditory cueing. For instance, auditory entrainment might aid in reducing errors while executing gait by guiding specific movement patterns.[90,91] External entrainment might act as guidance for "heel-contact" and "push-off" timing and/or muscle contractions.[39] Likewise, such cross-sensory cueing might also reduce information overload in the native sensory modality by directing task-irrelevant information toward the underused sensory modality.[92] The application of auditory entrainment is believed to allow enhancement in gait performance by bypassing or facilitating the frontostriatal pathway via alternative pathways.[93–95] Cunnington et al[96] reaffirmed and suggested that rhythmic cueing might directly serve as an input supplementary motor area, thereby reducing the onset of motor deficits and aiding in performance. Moreover, cueing has been shown to allow modulation of neuromagnetic β-oscillations in the auditory cortex, cerebellum, inferior frontal gyrus, somatosensory area, and sensorimotor cortex[42] and reduce hemispheric asymmetry.[97] Also, enhanced activation in inferior colliculi,[98] cerebellum, brain stem,[94,99] and sensorimotor cortex[100,101] have been reported. This might also suggest the facilitation of corticocerebellar network reorganization.[48] Finally, entrainment has also been shown to reduce variability in electromyographic activity[102] and optimize velocity/acceleration profiles of joint motions by scaling movement time,[103] thereby allowing stable pattern generation.

Studies have shown that rhythmic auditory cueing might also be an efficient tool to counteract dual-task-associated information-processing constraints.[121,122] For instance, Lohnes and Earhart[104] suggested that rhythmic entrainment might allow alleviation in gait performance by possibly freeing up cognitive resources for dual-task execution. Although dual-task performance has been shown to reduce performance in people with cerebral palsy,[26] we did not identify any study analyzing the effects of rhythmic auditory cueing under higher information-processing constraints. We suggest future studies address this substantial gap in the literature. Moreover, recent studies evaluating the effects of rhythmic entrainment have revealed beneficial effects of action-relevant acoustic input on gait performance[105,122,123] as compared to normal isosynchronous cueing.[106] Ecologically valid action-related sounds have been suggested to enhance salience of sensory information concerning spatiotemporal information, thereby aiding movement execution.[105–107] Moreover, recent research has revealed the possibilities of including emotional,[108] motivational,[109] and expressiveness[110] components in auditory entrainment to portray differential effects on gait parameters. Unfortunately, a lack of pertinent literature concerning the specific type of modified auditory cueing in cerebral palsy limits our interpretation of the type of auditory cueing that might be beneficial in rehabilitation. Therefore, we suggest future studies address this gap.

Finally, we believe that auditory entrainment might be efficient because of its economical nature and high viability.[50,51] The rhythmic entrainment factor could be utilized with music in rehabilitation and day-to-day lives. This could allow benefits in psychophysiological domains.[111,112] Moreover, it is important to consider that the retention of enhancements in gait parameters relies not only on the training received in the clinic but also largely on how much the patient follows the treatment protocol at home. In the present meta-analyses, enhancements in kinematic gait parameters observed for household ambulators (1.11) were considerably larger compared to community ambulators (0.07). We believe that delivering this type of home-based intervention could be beneficial for people lacking access to medical interventions in developing countries.[113] The growing number of smartphone devices in developing countries[114] can be used as a delivery tool while using a simple metronome app, such as WalkMate[115] or ListenMee,[116] which with proper medical guidance might allow curbing of motor deficits associated with aging.[117] We also suggest the use of rhythmic auditory cueing as an adjunct to other rehabilitation strategies, eg, assistive devices,[16,124,125] swimming, or other aquatic exercise regimes,[118] as it might enhance stability-associated quality of life[119,120] and rehabilitation progress by focusing on psychophysiological components.

In conclusion, to the best of our knowledge, this review analyzes for the first time the effects of auditory entrainment on adults and children with cerebral palsy. The present findings are in agreement with systematic reviews and meta-analyses carried out to analyze auditory entrainment effects on healthy,[121] stroke[57] and parkinsonism population groups.[54,56,122] This review suggests the incorporation of rhythmic auditory cueing for enhancing gait performance and stability in people with cerebral palsy.

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Author contributions

SG conceptualized the study, carried out the systematic review and statistical analysis, and wrote the paper. IG and AOE were involved in the systematic review process and reviewed the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Chapter 6: Effects of rhythmic auditory cueing in gait rehabilitation for multiple sclerosis: A mini systematic review and meta-analysis

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Effects of Rhythmic Auditory Cueing in Gait Rehabilitation for Multiple Sclerosis: A Mini Systematic Review and Meta-Analysis

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Rhythmic auditory cueing has been shown to enhance gait performance in several movement disorders. The "entrainment effect" generated by the stimulations can enhance auditory motor coupling and instigate plasticity. However, a consensus as to its influence over gait training among patients with multiple sclerosis is still warranted. A systematic review and meta-analysis was carried out to analyze the effects of rhythmic auditory cueing in studies gait performance in patients with multiple sclerosis. This systematic identification of published literature was performed according to PRISMA guidelines, from inception until Dec 2017, on online databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST. Studies were critically appraised using PEDro scale. Of 602 records, five studies (PEDro score: 5.7 ± 1.3) involving 188 participants (144 females/40 males) met our inclusion criteria. The meta-analysis revealed enhancements in spatiotemporal parameters of gait i.e., velocity (Hedge's g: 0.67), stride length (0.70), and cadence (1.0), and reduction in timed 25 feet walking test (−0.17). Underlying neurophysiological mechanisms, and clinical implications are discussed. This present review bridges the gaps in literature by suggesting application of rhythmic auditory cueing in conventional rehabilitation approaches to enhance gait performance in the multiple sclerosis community.

Keywords: rhythm perception, gait, movement disorders, rehabilitation, falls, spasticity

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INTRODUCTION

Multiple sclerosis is a prevalent, progressive demyelinating disease of the central nervous system (1). It is one of the most common causes of non-traumatic progressive disability in younger population groups (2, 3), but is also not uncommon in aged population (4). The main pathological characteristics of multiple sclerosis include progressive demyelination, and disruption of blood brain barrier due to inflammatory changes (5). This eventually affects the functioning of relevant axonal tracts, thereby causing widespread neurological symptoms (1, 6). The clinical manifestations in patients with multiple sclerosis include disruptions in sensory, motor and cognitive functioning. For instance, paresthesia, sensory loss, progressive hemiparesis, ataxia, fatigue, and depression have been widely reported (7, 8).

Gait and postural dysfunctions are also common in patients with multiple sclerosis especially due to the involvement of pyramidal track, cerebellar and spinal cord dysfunctions (9–11).

Prosperini et al. (2) for instance, reported lesions primarily in cerebellar, supratentorial associative bundles to affect the static and dynamic stability in patients with multiple sclerosis. Likewise, pathological involvement of leukocortical, intracortical, and subpial regions have also been reported (7, 12). Together, these sensory, motor and cognitive dysfunctions affect motor control and coordination (13, 14), eventually promoting falls (15), and affecting the quality of life (16). Typical gait characteristics exhibited by patients with multiple sclerosis include reduced gait velocity, stride length, cadence, and increased step width, asymmetric gait, double limb support duration (17, 18) [for a detailed review see (16, 19)]. Kinematic analysis of gait further reports larger range of motion at hip joint (20), increased knee flexion, reducing in ankle plantarflexion (21), and higher pelvic obliquity (22). Furthermore, electromyographic studies report abnormal musculoskeletal co-activation pattern especially at the ankle joint (23). These adjustments in gait kinematics and muscular co-contractions have been affirmed as cautionary measures adopted by patients for promoting stability during gait (24). These gait modifications although are intended to safeguard oneself from falling. Retrospectively, these modifications promote a rather slow, uneconomical, fatigue promoting, and highly fall prone gait pattern (25–28).

Common treatment strategies to curb motor dysfunctions in multiple sclerosis include physical exercise (29, 30), training with virtual-reality (31), physical/occupational therapy (32), hydrotherapy (33), electrical stimulations (16), martial arts (34), dual-task training (28), and external sensory cueing (35, 36). Studies report that sensory dysfunctions in patients with multiple sclerosis primarily play a key role in disrupting motor control and coordination (37). Disruptions in the perception of visual (38), and proprioceptive (39, 40), systems have been well-documented. Therefore, providing additional sensory cueing to support movement execution might serve as a viable option to overcome this loss. Only a handful of studies have analyzed the effects of external sensory stimulations (auditory, visual) on motor performance in patients with multiple sclerosis (35, 36, 41, 42). Nevertheless, the predominant role of auditory cueing as compared to its visual counterpart has been emphasized in literature (43, 44). Predominantly auditory cortex has been reported to perceive rhythmic stimuli by as short as 20–30 ms, which is considerably shorter as compared to visual and tactile thresholds (45–47). Moreover, it utilizes the rich interconnectivity of the auditory cortex to motor centers from spinal cord extending from the brainstem, cortical and subcortical structures (48–50). This also enables the auditory system to operate in a quite fast, precise, and efficient manner (51, 52). Several types of rehabilitation approaches have been reported in the literature for delivering external auditory stimulations, such as rhythmic auditory cueing (50), patterned sensory enhancement (53, 54), and real-time auditory feedback (55, 56). However, rhythmic auditory cueing is the most widely studied treatment strategy with respect to healthy population groups (28), population groups, and patients affected from movement disorders such as parkinsonism (47), stroke (57), and cerebral palsy (58). This type of stimulation can allow enhancements in motor execution in a multifaceted manner (47, 52). For instance, the sensory cueing can enhance biological motion perception (55, 59), promote audio-motor imagery (60, 61), reducing shape variability in muscle co-activation (62), mediate cortical reorganization, neural-plasticity (63), reduce cognitive overload (64), and more (45).

Moreover, recent research suggests increased financial burden on patients with multiple sclerosis (65, 66), especially because of the disease's progressive and relapsing nature (67). Therefore, development of affordable, and convenient rehabilitation strategies must be emphasized. Rhythmic auditory cueing is an effective strategy in these terms as it is viable, cheap, and can also be effectively applied as a home-based intervention (26–28). Therefore, we attempted to develop a state of knowledge by conducting a systematic review and meta-analyses to determine the effects of rhythmic auditory cueing on gait performance in patients with multiple sclerosis.

METHODS

This review was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA statement (68).

Data Sources and Search Strategy

Academic databases such as Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST were searched from inception until December 2017. A sample search strategy has been provided in (**Table 1**).

Data Extraction

Upon selection for review, the following data were extracted from each article i.e., author, date of publication, selection criteria, sample size, sample description (gender, age, health status), intervention, characteristics of auditory cueing, outcome measures, results, and conclusions. The data were then summarized and tabulated (**Table 2**).

The inclusion criteria for the studies was (i) Performed studies were either randomized controlled trials, cluster randomized controlled trials, or controlled clinical trials; (ii) Studies reporting reliable and valid spatiotemporal gait parameters (iii) Studies including dynamic aspects of gait stability (iv) Studies qualified PEDro methodological quality scale ($\geq$4 score); (v) Experiments conducted on human participants; (vi) Published in a peer-reviewed academic journals; (vii) Articles published in English, German and Korean languages.

Quality and Risk of Bias Assessment

The quality of the studies was assessed using the PEDro methodological quality scale (72). The scale consists of 11 items addressing external validity, internal validity, and interpretability and can detect potential bias with fair to good reliability (73), and validity (72). A blinded rating of the methodological quality of the studies was carried out by the primary reviewer. Ambiguous issues were discussed between the 1st (SG) and the 2nd (IG) reviewer and consensus were reached. Included studies

TABLE 1 | Sample search strategy EMBASE.

DATABSE	EMBASE
DATE	10/12/2017
STRATEGY	#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7
#1	(“rhythmic auditory cueing” OR “rhythmic auditory cueing” OR “rhythmic acoustic cueing” OR “rhythmic auditory entrainment” OR “metronome cueing” OR “metronome” OR “rhythmic metronome cueing” OR “acoustic stimulus” OR “acoustic cueing” OR “acoustic cueing” OR “external stimuli” OR “external cueing” OR “external cueing” OR “music therapy” OR “Neurological music therapy” OR “tempo” OR “beat” OR “rhythm” OR “RAC” OR “NMT” OR “real-time auditory cueing” OR “sonification”)/de OR (rhythmic auditory cueing OR rhythmic auditory cueing OR rhythmic acoustic cueing OR rhythmic auditory entrainment OR metronome cueing OR metronome OR rhythmic metronome cueing OR acoustic stimulus OR acoustic cueing OR acoustic cueing OR external stimuli OR external cueing OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT OR real-time auditory cueing OR sonification)ti,ab
#2	(“MS” OR “Multiple sclerosis” OR “Acute fulminating sclerosis” OR “disseminated sclerosis”)/de OR (MS OR Multiple sclerosis OR Acute fulminating sclerosis OR disseminated sclerosis))ti,ab
#3	(“walking” OR “gait” OR “locomotion” OR “range of motion” OR “ROM” OR “ambulation” OR “mobility” OR “treadmill gait” OR “balance” OR “stability” OR “stride” OR “gait training” OR “gait rehabilitation”)/de OR (walking OR gait OR locomotion OR range of motion OR ROM OR ambulation OR mobility OR treadmill gait OR balance OR stability OR stride OR gait training OR gait rehabilitation);ti,ab
#4	(“rehabilitation” OR “treatment” OR “rehab” OR “management” OR “therapy” OR “physiotherapy” OR “physical therapy” OR “prevention” OR “risk prevention”)/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
#5	(“age groups” OR “adolescent” OR “young” OR “elderly” OR old) AND (gender OR “male” OR “female”)/de OR [age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female)];ti;ab
#6	(“intervention study” OR “cohort analysis” OR “longitudinal study” OR “cluster analysis” OR “crossover trial” OR “cluster analysis” OR “randomized trial” OR “major clinical study”)/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab

were rated, and interpreted according to scoring of 9–10, 6–8, and 4–5 considered of “excellent,” “good,” and “fair” quality (74), respectively. Inadequate randomization, non-blinding of assessors, no intention to treat analysis and no measurement of compliance were considered as major threats to biasing (75).

Data Analysis

This systematic review also included a meta-analysis approach even with a few number of studies (76), with an aim to develop a better understanding of the incorporated interventions (77). The presence and lack of heterogeneity asserted the use of either random or fixed effect meta-analysis (78). A narrative synthesis of the findings structured around the intervention, population characteristics, methodological quality (**Table 2**) and the type of outcome are also provided. Likewise, summaries of intervention effects for each study were provided in a tabular form (**Table 2**). A meta-analysis was conducted between pooled studies using CMA (Comprehensive meta-analysis V 2.0, USA). Heterogeneity between the studies was assessed using I^2 statistics. The data in this review was systematically distributed and for each available variable pooled, dichotomous data was analyzed and forest plots with 95% confidence intervals are reported. The effect sizes were adjusted and reported as Hedge’s g (79). Thresholds for interpretation of effect sizes were as follows: a standard mean effect size of 0 means no change, mean effect size of 0.2 is considered as a *small* effect, 0.5 is considered as a *medium* effect and 0.8 as a *large* effect (80). Interpretation of heterogeneity via I^2 statistics was that values from 0-0, 25, 75% were viewed to sustain negligible, moderate, and substantial heterogeneity, respectively. A significance level of 0.05 was adopted.

RESULTS

Characteristics of Included Studies

Our initial search yielded a total of 602 studies, which on implementing our inclusion/exclusion criteria, were reduced to five (**Figure 1**). Data from the included studies have been summarized in (**Table 2**). Of the five included studies, one was a randomized controlled trial, whereas four were controlled clinical trials.

Participants

A total of 188 participants were analyzed in the incorporated studies (144 females/40 males). All the studies evaluated a mixed gender sample size.

Risk of Bias

To reduce the risks of bias, studies scoring ≥ 4 on PEDro were included in the review. Moreover, the limitation of research protocols to be included in the review were limited to gold standard randomized controlled trials, cluster randomized controlled trials and controlled clinical trials. The individual scores attained by the studies using the PEDro scale have been reported (**Tables 2**, **3**). The average PEDro score for the five included studies were computed to be 5.2 out of 11, indicating fair-quality of the overall studies. One study scored 7, one scored 6, one scored 5, and two studies scored 4. Publication bias was analyzed by plotting a Hedge’s g against standard error (**Figure 2**). Asymmetries concerning mean in the funnel plot might suggest bias (either positive or negative), in which case results are published. Risk of bias across the studies has been demonstrated in **Figure 3**.

TABLE 2 | Studies analyzing the effects of rhythmic auditory cueing on gait in patients with multiple sclerosis.

Author	**Research question(s)/hypothesis**	**Sample description, age: (M ± *SD*)**	**PEDro score**	**Assessment**	**Research design**	**Auditory signal characteristics**	**Conclusions**
Shahraki et al. (69)	Effects of auditory cueing on gait in patients affected from multiple sclerosis	Exp: 7F, 2M (40.3 ± 6.6) Ct: 7F, 2M (38.1 ± 12.1)	4	Stride length, stride time, double support time, cadence & gait velocity	Pre-test, gait training with rhythmic auditory cueing at +10% of preferred cadence for 30 min/session, 3 times/week for 3 weeks, post-test	Rhythmic metronome cueing at +10% of preferred cadence	Significant enhancement in stride length, gait speed, cadence in Exp as compared to Ct & after training with auditory cueing. Significant reduction in stride time & double support time after training with auditory cueing. Significantly reduced stride time in Exp as compared to Ct.
Seebacher et al. (70)	Effects of rhythmic auditory cueing and motor imagery on gait in patients affected from multiple sclerosis	Exp I: 25F, 9M (43.8) Exp II: 29F, 5M (45.4) Ct: 31F, 2M (43.1)	7	Timed 25-foot walk test, 6-min walk test, multiple sclerosis walking scale 12, modified fatigue impact scale, short-form 36 health survey, multiple sclerosis impact scale 29 & Euroquol 5D 3L questionnaire	Pre-test, motor imagery training (internal gait simulation with fast gait, wider steps...) with rhythmic auditory cueing for 17 min session, 6 times/week for 4 weeks, post-test	Rhythmic auditory cueing at preferred cadence Exp I: Instrumental music: cueing at 2/4, 4/4 meter, emphasis on 1st & 3rd beat. Exp II: metronome cueing at 2/4, 4/4 meter, emphasis on 1st & 3rd beat. Rhythmic verbal cues by researcher (heel off, toe off...)	Significant enhancement in 6-min walking distance in both Exp I & II after receiving auditory cueing, as compared to Ct. Significant reduction in timed 25-foot walking time, modified fatigue impact scale in both Exp I & II after receiving auditory cueing, as compared to Ct. However, Exp I had better benefits as compared to Exp II. Significant enhancement in short-form 36 health survey, multiple sclerosis impact scale 29 & Euroquol 5D 3L questionnaire i.e., quality of life, in both Exp I & II after receiving auditory cueing, as compared to Ct. However, Exp I had better benefits as compared to Exp II.
Seebacher et al. (71)	Effects of rhythmic auditory cueing and motor imagery on gait in patients affected from multiple sclerosis	Exp I: 10F (47.3) Exp II: 7F, 3M (41.8) Ct: 5F, 5M (46.1)	6	Timed 25-foot walk test, 6-min walk test, modified fatigue impact scale	Pre-test, motor imagery training (internal gait simulation with fast gait, wider steps...) with rhythmic auditory cueing for 17 min session, 6 times/week for 4 weeks, post-test	Rhythmic auditory cueing at preferred cadence Exp I: Instrumental music: cueing at 2/4, 4/4 meter, emphasis on 1st & 3rd beat. Exp II: metronome cueing at 2/4, 4/4 meter, emphasis on 1st & 3rd beat. Rhythmic verbal cues by researcher (heel off, toe off...)	Significant enhancement in 6-min walking distance in both Exp I & II after receiving auditory cueing, as compared to Ct. Significant reduction in timed 25-foot walking time, modified fatigue impact scale in both Exp I & II after receiving auditory cueing, as compared to Ct.
Conklyn et al. (41)	Effect of rhythmic auditory cueing on gait in patients affected from multiple sclerosis	Exp: 3F, 2M (47±10.5) Ct: 4F, 1M (50.2±5.4)	5	Functional ambulation performance, double support percentage (right/left), cadence, stride length (right/left), gait velocity, step length (right & left), norm velocity & timed 25-foot walking test	Exp: Pre-test, gait performance for 20 min per day for 4 weeks with rhythmic auditory cueing increased by 10% of attained cadence on every evaluation of test, post-tests at week 1, week 2, week 3, week 6 Ct: same procedure but rhythmic auditory cueing only for 2 latter weeks	Rhythmic auditory cueing in music at +10% of preferred cadence on each evaluation post-test	Significant enhancement in cadence, stride length (right/left), gait velocity, step length (right & left), norm velocity after training with rhythmic auditory cueing for 1 week. Significant reduction in double support percentage (right/left) in Exp as compared to Ct.
Baram and Miller (42)	Effect of auditory on gait in patients affected from Multiple sclerosis	Exp: 10F, 4M (48.5 ± 8) Ct: 6F, 5M (25.4 ± 1.9)	4	Gait velocity, stride length, 10 m walking test	Pre-test, followed by rhythmic auditory cueing & 10 min follow-up short term residual performance test	Rhythmic auditory cueing modified in real-time with steps	Significant enhancement in gait speed & stride length with rhythmic auditory cueing. Significant enhancement in short-term residual performance with auditory cueing.

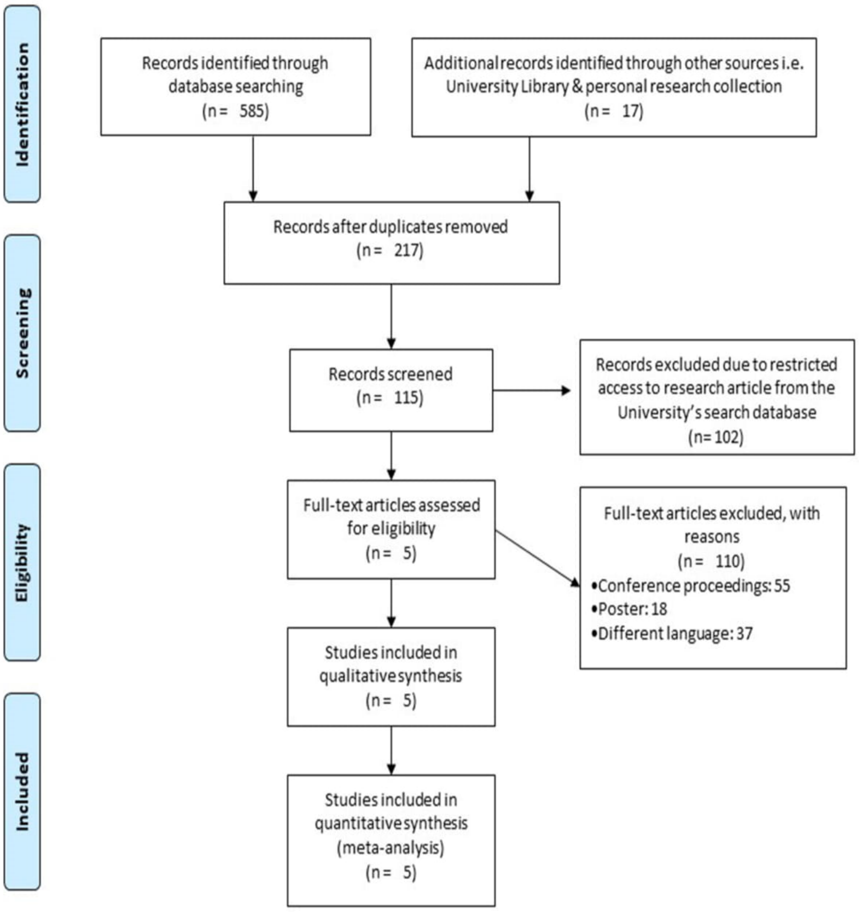

FIGURE 1 | PRISMA flow chart for the inclusion of studies (68).

Meta-Analysis

Outcomes

The results suggest evidence for a positive impact of rhythmic auditory cueing on spatiotemporal gait parameters patients affected from multiple sclerosis. In the five included studies, all the studies reported significant enhancements in gait parameters with application of rhythmic auditory cueing.

Meta-Analyses

The evaluation of research studies via meta-analysis requires a strict inclusion criteria to efficiently limit the heterogeneity (81). However, among the pooled group of studies post a strict inclusion criterion, some amount of unexplained heterogeneity was still observed. Here, the few number of studies included in the meta-analysis limited our capability to perform additional sub-group analysis. The evaluated parameters were the spatiotemporal gait parameters such as gait velocity, cadence, stride length, and Timed-25 feet walking test.

Gait Velocity (Meter per Second)

The meta-analysis on gait velocity for patients with multiple sclerosis revealed (**Figure 4**) a *medium* effect size in positive domain with moderate heterogeneity (Hedge's g: 0.67, 95% CI: 0.14 to 1.20, I^2: 71.6%, $p = 0.02$).

Stride Length (Meters)

The meta-analysis on stride length for patients with multiple sclerosis revealed (**Figure 5**) a *medium* effect size in positive domain with substantial heterogeneity (Hedge's g: 0.71, 95% CI: 0.17 to 1.26, I^2: 82.3%, $p = 0.03$).

Cadence (Number of Steps per Minute)

The meta-analysis on cadence for patients with multiple sclerosis revealed (**Figure 6**) a *large* effect size in positive domain with substantial heterogeneity (Hedge's g: 1.00, 95% CI: 0.24 to 1.76, I^2: 70.3%, $p = 0.06$).

TABLE 3 | Individual Pedro scores for studies (1: point awarded, 0: no point awarded).

Study	Pedro score	Point estimates & variability	Between group comparison	Intention to treat	Adequate follow-up	Blind assessors	Blind therapists	Blind subjects	Baseline comparability	Concealed allocation	Random allocation	Eligibility criteria
Shahraki et al. (69)	4	1	1	0	1	0	0	0	0	0	0	1
Seebacher et al. (70)	7	1	1	0	1	0	0	0	1	1	1	1
Seebacher et al. (71)	6	1	1	0	1	1	0	0	0	0	1	1
Conklyn et al. (41)	5	1	1	0	1	1	0	0	0	0	0	1
Baram and Miller (42)	4	1	1	0	1	0	0	0	0	0	0	1

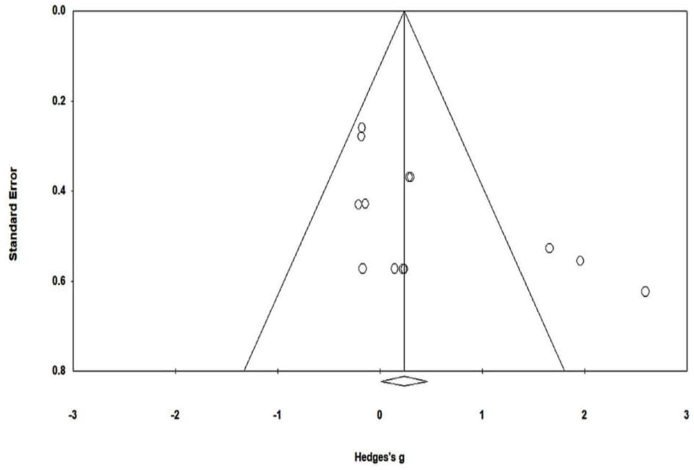

FIGURE 2 | Funnel plot for Hedge's g & standardized effect for each effect in the meta-analysis. Each of the effect is represented in the plot as a circle. Funnel boundaries represent area where 95% of the effects are expected to abstain if there were no publication bias. The vertical line represents mean standardized effect of zero. Absence of publication bias is represented when the effects should be equally dispersed on either side of the line.

Timed 25 Feet Walking Test (Seconds)

The meta-analysis for timed-25 feet walking test for patients with multiple sclerosis revealed (**Figure 7**) a *small* effect size in negative domain with substantial heterogeneity (Hedge's g: −0.17, 95% CI: −0.48 to 0.12, I^2: 0%, $p > 0.05$).

DISCUSSION

The primary objective of this present systematic review and meta-analysis was to develop a current state of knowledge for the effects of rhythmic auditory cueing on gait performance in patients with multiple sclerosis. All the included studies reported significant enhancements in gait performance post training with auditory cueing. The meta-analysis revealed significant small-to-large standardized effects for the beneficial influence of rhythmic auditory cueing on spatiotemporal gait parameters. Previous studies have reported a detrimental effect of multiple sclerosis on spatiotemporal gait parameters (16). For instance, Muratori et al. (82) has conclusively reported that a decrease in gait velocity, cadence, and stride length are important predictors for decreased quality of life, and increased fall related morbidity/mortality. Authors reported that gait velocity had a strong correlation with disease severity i.e., Expanded Disability Status scale and Multiple Sclerosis quality of life-54 scale. Likewise, Community Balance and Mobility scale has a strong relationship with step length and cadence (82). The current systematic review and meta-analysis reveals that training with rhythmic auditory cueing enhances gait velocity (Hedge's g: 0.67), stride length (0.70), cadence (1.0). Similarly, timed 25-foot walk test has been characterized as an important predictor to determine quality of life by focusing on functional independence and its impact on occupation, and social life (83–85). Here as well, a decrease in Timed 25-feet walking test (−0.17) was also reported in the analysis. This therefore suggests potential benefits of rhythmic auditory cueing for directly enhancing the quality of life and reducing morbidity/mortality ratios in patients with multiple sclerosis.

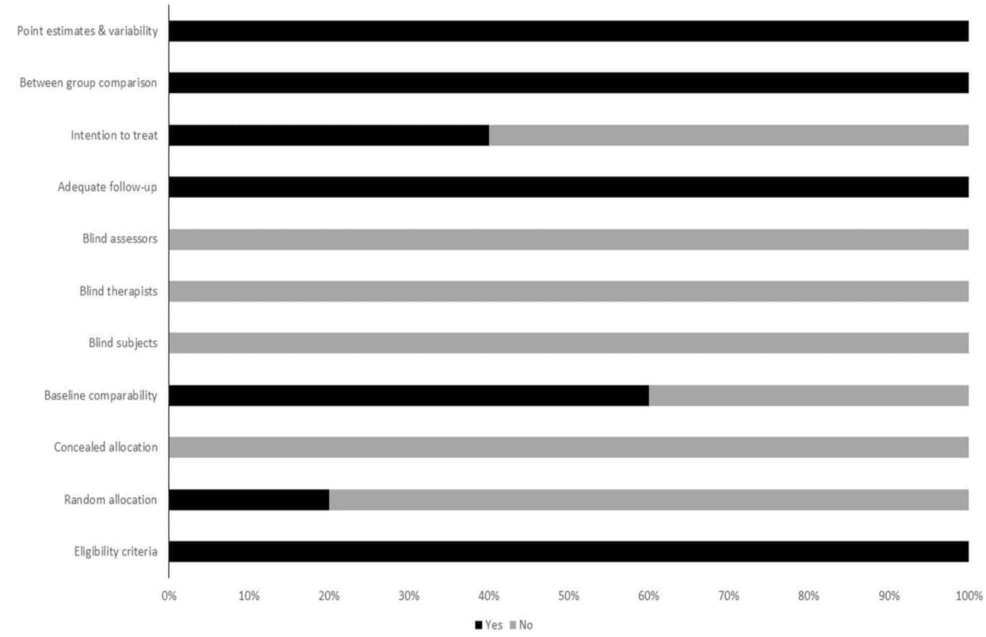

FIGURE 3 | Risk of bias across studies.

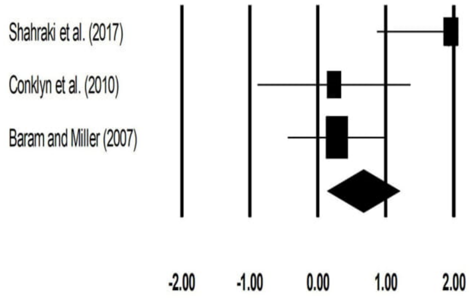

FIGURE 4 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on gait velocity (meter per second) for patients with multiple sclerosis. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI.

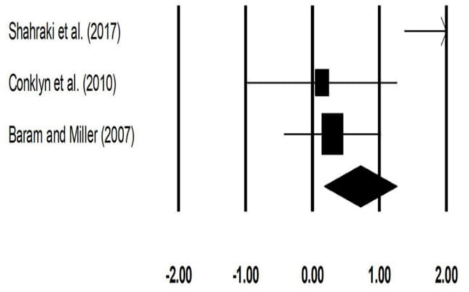

FIGURE 5 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on stride length (meters) for patients with multiple sclerosis. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI.

Neurophysiological mechanisms due to which auditory cueing enhances gait performance in patients with multiple sclerosis are not well-understood (16, 36, 42). In multiple sclerosis the onset of movement disorders is usually due to dysfunctions in white matter regions (16, 36, 86). Here inference can be drawn for the beneficial effects of auditory cueing, from a few studies analyzing the effects of auditory-sensorimotor training on white matter plasticity in musicians (87, 88). Bengtsson et al. (87) reported that auditory-sensorimotor training can increase myelination due to increased neural activity in the fiber tracts during training. The authors reported enhanced Fractional Anisotropy [usually reduced in multiple sclerosis (89, 90)] in corpus callosum, cortico-spinal, cortico-cortical tracts, and the posterior limb of the internal capsule. These neural structures are of critical importance when considering fine motor performance, bimanual coordination, auditory processing and motor learning (91, 92). Therefore, we hypothesize that training with auditory cueing could have enhanced the gait performance by facilitating the deficit white matter regions and/or mediating re-myelination. However, no research till date has analyzed the

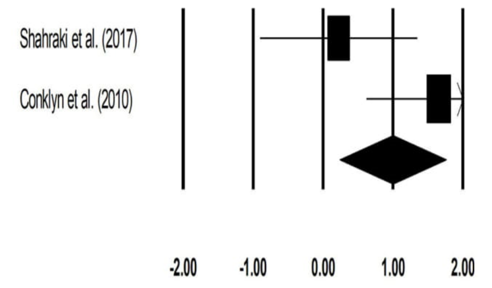

FIGURE 6 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on cadence (number of steps per minute) for patients with multiple sclerosis. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI.

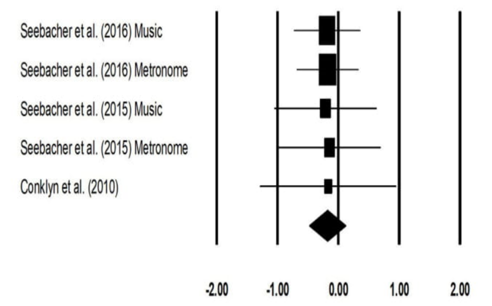

FIGURE 7 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on Timed 25 feet walking (seconds) test for patients with multiple sclerosis. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI.

influence of auditory cueing on white matter plasticity in patients with multiple sclerosis. We strongly recommend future research to analyze the effects of auditory-motor entrainment on white matter plasticity in patients with multiple sclerosis.

Additionally, research in the past decades, for instance by Grimaud et al. (86) has reported that involvement of deep gray matter regions such as basal ganglia is unusual in patients with multiple sclerosis. However, recent evidence suggests that focal lesions and diffused neurodegeneration in deep gray matter regions such as basal ganglia, thalamus are an important precursors for contributing in development of neurological disabilities (1, 93–99), cognitive dysfunctions (97, 100), and the onset of fatigue (101, 102). Interestingly, research has also revealed a strong correlation between the quantitative susceptibility mapping of putamen and caudate nucleus with the severity of disease (97). Thereby suggesting greater involvement of gray matter structures with disease progression. This therefore again in our opinion might offer an additional explanation that application of rhythmic auditory cueing could have targeted the deficit basal ganglia circuitry similarly as in patients with Parkinson's disease to enhance gait performance, reduce the level of depression, anxiety, and fatigue in patients with multiple sclerosis [for a detailed mechanism see (47) and (27)]. Additionally, deficits in cerebellum [both gray and white matter regions (103)] have also been widely reported in patients with multiple sclerosis (104, 105). Here, findings of Molinari et al. (106) can justify the enhancements in gait performance with the application of auditory cueing. Molinari et al. (106) suggests that cerebellar dysfunctions such as in multiple sclerosis might impair the capability to consciously detect rhythmic variations for stabilizing motor response. However, the authors suggest that unconscious effects to entrain movements with external auditory cues might still be preserved in such patients. The authors suggest that in such cases the motor entrainment to auditory cueing might be induced unconsciously, independent of cerebellar processing at either the spinal or the cortical level. The authors proposed that computing of the timing information in such cases can be achieved peripherally i.e., directly in the auditory nerve by neural excitation patterns generated by precise physiological coding. This information can then be transferred directly into adjacent motor structures, which entrain with the neural motor codes and allow enhanced synchronization between the auditory stimuli and motor response (106, 107).

Furthermore, research suggests that application of auditory cueing can facilitate cortical reorganization in patients with multiple sclerosis (50). Till date only one research has analyzed the influence of rhythmic auditory cueing on cortical activation in patients with multiple sclerosis (108). The authors reported enhanced activation in left superior frontal gyrus, left anterior cingulate, and left superior temporal gyrus after gait training with rhythmic auditory cueing (36, 108). The increased activation in these neural centers has been associated with enhancements in executive functioning, auditory-motor entrainment, attention and motivation (50, 53). Similarly, enhanced activations in inferior colliculi (109), cerebellum, brainstem (110, 111), sensorimotor cortex (112, 113), premotor areas (114) have been reported post application of rhythmic auditory cueing in other movement disorders such as stroke and parkinsonism. Furthermore, modulation of neuromagnetic β oscillations (representing functional coordination between auditory-motor systems) with application of auditory cueing has been reported in auditory cortex, inferior frontal gyrus, somatosensory area, sensorimotor cortex and cerebellum (115). This ability of auditory cues has been recently demonstrated by Ross et al. (116) to facilitate immediate neural plasticity by facilitating feedforward mechanisms. Studies also suggest that training with rhythmic auditory cueing might offer reorganization of cortical and cerebellar circuits (63). Schaefer (117) for instance, suggested that auditory cueing infused with regularity and repetition of movement can result in an accelerated learning and neuroplasticity. Patients with multiple sclerosis have been reported to possess similar rapid-onset motor plasticity levels than that of healthy controls (118). Taken together, this evidence suggests strong therapeutic potential of external auditory stimulations to enhance gait performance in patients with multiple sclerosis. However, lack of conclusive evidence limits our interpretations, therefore we recommend future studies to analyse these components in neuroimaging studies.

Furthermore, extending beyond the neurophysiological effects of auditory stimulations Shahraki et al. (69) suggested that external auditory stimulations could also enhanced stability by facilitating the vestibular system via the medial-medial geniculate nuclei and organ of Corti (119). The authors demonstrated enhancements in spatiotemporal gait parameters with the application of rhythmic auditory cueing as compared to conventional physiotherapeutic gait training interventions in patients with multiple sclerosis. Likewise, Baram and Miller (42) too reported the beneficial aspects of external auditory cueing as compared to visual cueing. The authors reported higher gait velocity due to auditory cueing as compared to visual cueing, because of reduced reaction time facilitated by auditory stimulations during voluntary movements. The authors reported significant enhancements in gait velocity (Experimental: 12.8% vs. control: −3.0%) and stride length (8.3 vs. 0.3%) with the application of online rhythmic auditory cueing. Moreover, the authors demonstrated enhanced learning during residual performance (without auditory cueing) for both gait velocity (18.7 vs. 2.4%), and stride length (9.9 vs. 4.0%).

Moreover, we believe that the external auditory cueing could have also guided the gait of the patients' by explicitly synchronizing their ground contact and lift-off times (120). The cueing could have allowed the patients to effectively plan their movements before executing them (121). Likewise, enhanced kinematic efficiency and reduced variability in musculoskeletal activation patterns have been reported post training with rhythmic auditory cueing (26). Moreover, change in tempo of the auditory stimulation could have also played a major role in mediating gait performance. In the current review, only one study (69), trained their participants with a higher tempo (+10%) of rhythmic auditory cueing as compared to their preferred cadence. This "change in tempo" characteristic although not evaluated in the meta-analysis due to lack of data can serve as a crucial factor in rehabilitation of gait. For example, change in tempo has been associated with various neurophysiological changes such as increased neuronal activation in frontal-occipital cortical networks (122), and increased excitability of spinal motor neurons through the reticulospinal pathways (integral for reducing the response time in a motor task). Moreover, it has been reported that prolonged training with a constant pattern of rhythm can decrease fractal scaling of stride times from healthy 1/f structure (123–125). Here, we hypothesize that changing the tempo regularly during training can promote the development of a stable, and adaptable gait pattern. In rehabilitation this might serve as a measure to teach patients on how to regulate gait when passing through different fall prone environments.

Another crucial aspect analyzed in the current review is the effects of auditory cueing induced mental imagery in patients multiple sclerosis (70, 71). Labriffe et al. (126) reported higher activations in primary sensorimotor cortex and secondary somatosensory cortex bilaterally during the imagination of gait. The authors further reported correlated activations in bilateral somatosensory area and right pre-somatosensory area during mental imagery of gait. This training regime seems plausible in patients with multiple sclerosis where physical fatigue is a major concern for medical practitioners (127). Seebacher et al. (70) in their randomized controlled trial, asked the patients to kinaesthetically imagine gait from the first-person perspective with music and metronome induced rhythmic auditory cueing (71). The authors reported that mental imagery, which is usually diminished in patients with multiple sclerosis can be facilitated with rhythmic auditory cueing. Further, their study revealed significant enhancements spatiotemporal gait parameters such as timed 25-foot walking test, and 6-min walking test with the application of metronome/music-cued motor imagery groups. Here, comparable enhancements during 6-min walking test in music-cued (512.6 m), and metronome-cued (533.9 m) groups as compared to control group (471.2 m) clearly demonstrates beneficial effects of training with auditory cueing for enhancing physiological performance i.e., reduced fatigue. Likewise, improvements in multiple sclerosis related quality of life, pain, physical and mental health related quality of life were larger both music/metronome-cued groups as compared to control group. We would like to suggest that the beneficial effects of mental imagery here can also be effectively incorporated in home-based interventions. For instance, physiological fatigue might force the patient to train less at home. However, in such cases the patients can be taught to imagine themselves performing gait, while also imagining auditory cues. Previous studies suggest that the retention of enhancements in rehabilitation is dependent on how much the patient follows the treatment protocol at home (27, 28, 128). Therefore, developing interventions which can be easily followed by patients at home are desired. One of the included studies incorporated a home-based training intervention with external auditory cueing (41). Conklyn et al. (41) utilized a simple mp3 player to deliver rhythmic auditory cueing for practizing gait as a home-based intervention. The authors reported enhancements in spatiotemporal gait parameters and found increased patient adherence to the treatment. This type of home-based intervention could possibly be beneficial for people lacking proper exposure to medical interventions in developing countries (129). For instance, patients lacking effective medical resources can utilize smartphone devices with metronome applications for example Walkmate (124), Listenmee (130), or imagine gait with external stimulations or even imagine gait with auditory stimulations (joint audio-motor imagery).

Finally, a quantitative assessment for analyzing specific training dosage could not be performed in this study because of the limited amount of data and substantial heterogeneity in between the studies. Nevertheless, four of the included studies used a training regime that lasted for more than 17 min per session and was performed for at least three times a week for more than 3 weeks (41, 69–71). Likewise, based on the current evidence of training dosage for other movement disorders this dosage seems viable., for instance suggested a dosage of 25–40 min/session, for 3–5 sessions per week for patients with Parkinson's disease. Moreover, according to the findings of Bangert and Altenmüller (131) this training dosage seems plausible. The authors investigated cortical activation patterns during an audio-motor task and reported auditory-sensorimotor EEG co-activity after at least 20 min of training. Bangert and Altenmüller (131) speculate that this time frame is crucial for sensitive auditory monitoring, forming associations with the auditory target image in the working memory, during motor execution. Therefore, we suggest future studies to design training regimes with external auditory stimulations with at least 20 min training sessions. A limitation of the present review is that a meta-analysis was performed on a limited number of studies. Although, the main aim for conducting a meta-analysis was to allow a better understanding of the effects of auditory cueing over different spatiotemporal gait parameters for medical practitioners, patients and future researchers. This, however, does not rule out the possibility of incurring a type II error. We strongly suggest the reader to carefully interpret the results, while also considering the qualitative description of include studies provided in this review.

This review for the first time synthesized the evidence for effects of training with rhythmic auditory on gait in patients with multiple sclerosis. Our results are consistent with the findings of review studies suggesting the beneficial effects of rhythmic auditory cueing in healthy population (28), and population groups with movement disorders such as parkinsonism (47), stroke (57), and cerebral palsy (58). In conclusion, this review and meta-analysis suggests the incorporation of rhythmic auditory cueing for enhancing gait performance in patients with multiple sclerosis.

FUTURE DIRECTIONS

Extending beyond the beneficial effects of conventional isosynchronous auditory cueing, we recommend future studies to analyse the effects of biologically variable auditory stimulations on gait performance in patients with multiple sclerosis. Due to excessive sensory loss higher than normal threshold for action relevant acoustic input might be beneficial for patients with multiple sclerosis (132). Therefore, using ecologically valid action related sounds (walking on gravel, snow) conveying spatio-temporal information can possibly enhance saliency of sensory information for patients with multiple sclerosis (133–136). Similarly, analyzing the effects of methods providing real-time auditory information could possess considerable benefits for enhancing gait performance as well. This type of feedback allows converting the movement parameters in real-time to sound (mapping with pitch, amplitude). Here, the aim is to enhance motor perception and performance by targeting areas associated with biological motion perception (55, 59, 137). have shown that the synchronization of cyclic movement patterns with real-time auditory feedback can reduces variability and increases consistency of movements when compared with isosynchoronous rhythmic stimulations (56). According to this feedback can enable the patients to identify their own movement amplitudes and compare their produced sound patterns with the sound of an auditory movement model, thereby creating a new auditory reference framework. This then can possibly allow a better comparison between instructed and intended movement while simultaneously amplifying the internal representation of movements (138). In summary, we recommend future studies to focus on mediating auditory signal characteristics (ecologically valid, online feedback) for developing an efficient auditory stimulation, which can allow widespread benefits for patients with multiple sclerosis in both psychophysiological domains.

We also suggest future research to analyse the combined effects of external auditory stimulations with music therapy, as it might yield additional benefits to curb deficits in cognitive and physiological domain. For instance, Thaut et al. (139) demonstrated that musical mnemonics can facilitate a stronger oscillatory network synchronization in prefrontal regions during a word learning task in patients with multiple sclerosis. The authors suggested that musical stimuli might allow a "deep encoding" during a learning task and might also sharpen the timings of neural dynamics in brain which are normally degraded by the demyelination process. The authors also reported that this enhancement in cognitive performance was correlated with higher EDSS scores (139). Thereby, indicating that patients in more severe disease stages also benefited from the music facilitated "deep learning" strategies (139, 140). Likewise, enhanced cortical reorganization and regeneration in areas associated with cognition have been reported post music therapy (141, 142). We strongly recommend future research to analyse these effects in patients with multiple sclerosis. Furthermore, beneficial effects of music therapy in patients with multiple sclerosis has also been reported on respiratory musculature (143, 144). Future studies can focus on developing experimental protocols that use rhythmic cueing during music to facilitate breathing while performing gait. This approach might allow simultaneous strengthening of respiratory musculature while performing physical activities. Finally, it is important to consider the important psychological support that music therapy can offer to the patients with multiple sclerosis by reducing anxiety, depression, improving mood, self-acceptance and motivation (145–147). Future studies can also focus on analyzing these psychological aspects during the training regimes as this might allow in development of a multifaceted rehabilitation approach focusing on psychophysiological recovery of patients with multiple sclerosis.

AUTHOR CONTRIBUTIONS

SG conceptualized the study, carried out the systematic-review, statistical analysis, and wrote the paper. IG assisted in the systematic-review process and reviewed the manuscript.

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Chapter 7: Effects of dual tasks and dual-task training on postural stability: A systematic review and meta-analysis

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REVIEW

Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis

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Abstract: The use of dual-task training paradigm to enhance postural stability in patients with balance impairments is an emerging area of interest. The differential effects of dual tasks and dual-task training on postural stability still remain unclear. A systematic review and meta-analysis were conducted to analyze the effects of dual task and training application on static and dynamic postural stability among various population groups. Systematic identification of published literature was performed adhering to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, from inception until June 2016, on the online databases Scopus, PEDro, MEDLINE, EMBASE, and SportDiscus. Experimental studies analyzing the effects of dual task and dual-task training on postural stability were extracted, critically appraised using PEDro scale, and then summarized according to modified PEDro level of evidence. Of 1,284 records, 42 studies involving 1,480 participants met the review's inclusion criteria. Of the studies evaluating the effects of dual-task training on postural stability, 87.5% of the studies reported significant enhancements, whereas 30% of the studies evaluating acute effects of dual tasks on posture reported significant enhancements, 50% reported significant decrements, and 20% reported no effects. Meta-analysis of the pooled studies revealed moderate but significant enhancements of dual-task training in elderly participants (95% CI: 1.16–2.10) and in patients suffering from chronic stroke (−0.22 to 0.86). The adverse effects of complexity of dual tasks on postural stability were also revealed among patients with multiple sclerosis (−0.74 to 0.05). The review also discusses the significance of verbalization in a dual-task setting for increasing cognitive–motor interference. Clinical implications are discussed with respect to practical applications in rehabilitation settings.

Keywords: multitasking, fall, balance, cognition, rehabilitation, training, coordination

Introduction

Postural stability is an integral component of the motor control and coordination process of the body, which is required for preserving steadiness during static and dynamic activities.[1] This component relies upon proprioceptive afferents and complex sensorimotor actions.[2–4] Posture is mediated by both higher "controlled" and lower "automatic" levels of processing,[5,6] implying the involvement of basal ganglia–cortical loop for higher level processing[7] and brainstem synergies for lower level processing.[8] Studies have suggested that any alleviation in conscious-controlled attention toward postural control increases the likelihood of disrupting coordination and stability,[9,10] possibly, as a consequence of movement-specific reinvestment.[9,11] The theory of reinvestment suggests that directing attention internally to control movement, which is usually automatic, can disrupt its performance.[9,10] The theory also suggests that

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aging[12] and neurological diseases[9] are common conditions that increase reinvestment. Seidler et al[13] reaffirmed these suggestions and associated physiological changes with aging and injury to loss in gray/white matter within the central nervous system, resulting in differential-reorganized cortical activation. Here, the authors suggested that differential cortical activation within the higher neural centers can affect task prioritization, further allowing increased conscious attention while carrying out cognitive or motor tasks.[14]

To resolve this issue, distracting dual tasks have been used in several studies.[9,15–17] A dual task acutely directs the performer's attention toward an external source of attention (eg, n-back, random letter generation tasks), while performing a primary task. According to the constrained action hypothesis, this attentional change might allow motor systems to function in an automatic manner, resulting in more effective performance.[10] Practical applications for enhancing the automation of postural control have been demonstrated in studies evaluating complex motor skills,[18,19] postural stability,[17] and gait.[15]

However, with an increase in complexity, a subsequent increase in cognitive processing and eventually cognitive–motor interference has been reported.[20–23] This increase in central interference adversely affects both cognitive and motor performance.[6,23] Studies speculate that inhibition of cognitive and balance ability post dual-task inclusion can be because of the bottleneck and central sharing model theories.[21,24] According to these theories, functioning of a neurological pathway mediating both cognitive and motor functions might be affected, when a continuous input as in a dual-task setting is directed with a primary task. This might adversely affect cognitive tasks or stability performance.

Similarly, a complexity-related decrease in cortical reciprocal inhibition in fall-prone population groups (elderly, patients with history of fall, with neurological diseases) has been identified as an important factor to promote postural instability.[25,26] Studies suggest reduced gamma-aminobutyric acid B-mediated cortical inhibition[27] and elevated muscular coactivation[26,28] to be the primary reasons for this effect. Boisgontier et al,[6] Ruffieux et al,[26] and Smith et al[29] in their review studies concluded that application of dual task on fall-prone population groups results in postural instability and poor cognitive performance. However, minimal effects of cognitive–motor interference have been reported in a few reviews for diseased fall-prone population groups, which theoretically should exhibit poorer cognitive resources as compared to their healthy older counterparts.[30,31] Therefore, there is a need to determine specific factors that in terms of complexity for a cognitive or motor task might result in differential effects on stability.

Furthermore, studies have extensively mentioned the beneficial effects of motor,[32,33] dual-task training,[34–36] for enhancing cognitive and motor performance even in fall-prone population groups. Another important determinant that is commonly utilized to enhance stability and cognitive performance is physical exercise.[32,33,37] The studies report these training maneuvers to be crucial for smoothening of various cognitive abilities and reducing cognitive–motor interference.[38–40] Müller and Blischke[41] suggested that the training allows modulation of consciousness-dependent motor activities to be more automatic, thereby reducing dual-task costs. Likewise, Bherer et al[42] while reporting the beneficial effects in fall-prone population groups suggested freeing up of cognitive resources meant for monitoring performance to be the primary reason. The change in modulation of motor activity has been suggested to allow automatization by "structural displacement",[43,44] where a shift in the operation control of motor planning and executive control occurs from higher cognitive centers to basic noncognitive centers.[45,46] This training maneuver has recently drawn a lot of interest as compared to its older counterpart and speculations persist as to which protocol overlays beneficial effects on postural stability among different population groups.[47,48] Recent review studies evaluating the effects of dual-task training in elderly[38,49] and population groups with neurological diseases[50,51] conclusively report the beneficial effects of dual-task training for enhancing cognitive abilities and stability, whereas some review studies report no identifiable benefits.[33,52] The studies also mentioned the increased heterogeneity of the training protocols within the studies to cause difficulties in identifying a specific method's effectiveness. Wang et al,[51] for instance, in their meta-analysis reported benefits of dual-task training on static stability, however, with considerable heterogeneity (I^2: 88%). This review was an attempt to extend the efforts of the previous reviews and comparatively examine the effects of dual tasks, dual-task training methodologies on the postural stability of healthy and fall-prone population groups. The review also aimed to conduct meta-analysis across homogeneous groups for determining effective methodologies in terms of complexity and training methodologies for dual task and dual-task training scenarios.

Methods

This review was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[53]

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Data sources and search strategy

The databases Scopus, PEDro, SportDiscus, EMBASE, and MEDLINE were searched from inception until June 2016. The search was limited to the abovementioned databases due to access regulations of the university. Keywords for search strategy were included using medical subject headings (MeSH). An example of the search strategy for EMBASE database has been provided in Table S1. The inclusion criteria for the studies were as follows: 1) studies that were randomized controlled trials (RCTs), cluster RCTs, and controlled clinical trials (CCTs); 2) measurement of postural stability using highly valid and reliable methods (static and dynamic posturographic analyses, center of pressure, center of gravity analysis, sensory orientation test, Berg balance scale, time up and go test, star excursion balance test, modified star excursion balance test, and active movement extent discrimination apparatus); 3) dual tasks performed during the research were reliable and valid; 4) studies that scored ≥4 on the PEDro methodological quality scale; 5) experiments that were conducted on human participants; 6) published in a peer-reviewed academic journal; and 7) articles that were published in English language. Studies evaluating the abovementioned parameters in participants below the age of 18 years were not included, as development of postural control centers has been reported to take place during this developmental phase.[54] Studies were excluded if they analyzed postural stability in a sitting position or while using a picture analysis software. All the studies identified during the search were independently screened (Figure 1) for eligibility by a primary researcher and every effort was undertaken to avoid subjective bias.[55] Preliminary analysis for selection was performed by analyzing titles and abstracts, and, wherever necessary, the entire text of the article was studied. Where further clarification of the published data was required, the

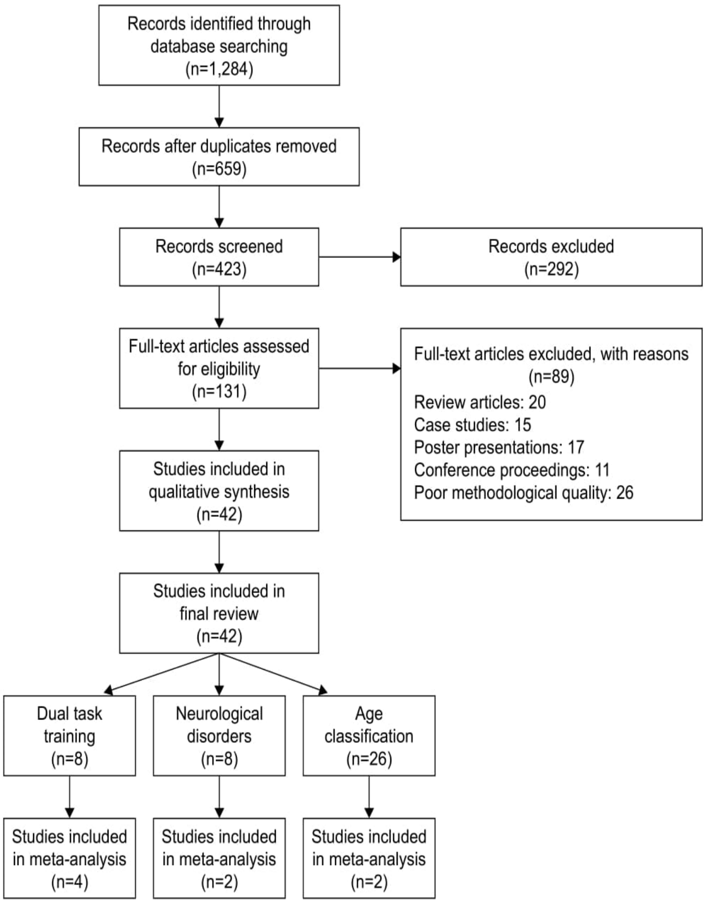

Figure 1 Flow diagram illustrating studies for inclusion in the review study (PRISMA flow diagram).
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

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first researcher attempted to contact the respective authors. Bibliographic sections of all the articles were retrieved for evaluations. Citation search for all the included articles was performed using Web of Science. A classification of studies based on their experimental design[56] and country of origin was also made (Supplementary material).

Data extraction

Upon selection for review, the following data were extracted from each article: author, date of publication, selection criteria, sample size, sample description (gender, age, health status), intervention, dual-task, outcome measures, results, and conclusions. The data were then summarized and tabulated. Furthermore, classification of studies was made based on their experimental application,[56] and the population groups were assessed.

Quality and risk of bias assessment

The quality of the studies was assessed using the PEDro methodological quality scale. The scale consists of eleven items addressing external validity, internal validity, and interpretability. The PEDro scale can detect potential bias with fair to good reliability[57] and is a valid measure of the methodological quality of trials. A blinded rating of the methodological quality of the studies was carried out by the primary reviewer. Ambiguous issues were discussed between reviewers, and consensus was reached. For the included CCTs, a scoring of 9–10, 6–8, and 4–5 was considered to be of "excellent", "good", and "fair" quality,[58] respectively. Likewise, the level of evidence was suggested to be of level 1a (strong) if more than one RCT (≥6), 1b if one RCT (≥6), and 2 if one RCT (<6), or CCTs with similar methodological approaches were consistent with the results.[58] With differential results among paired groups of studies, the result of the study(s) with higher PEDro score was given more consideration. Inadequate randomization, nonblinding of assessors, no intention to treat analysis, and no measurement of compliance were major threats to biasing.[2]

Data analysis

This systematic review also included a random-effect meta-analysis approach to develop a better understanding of the incorporated interventions. A narrative synthesis of the findings structured around the intervention, population characteristics, methodological quality (Table 1), and the type of outcome is provided. Likewise, summaries of intervention effects for each study were provided in a tabular form (Table S1). A meta-analysis was conducted between pooled studies using comprehensive meta-analysis (CMA V 3.0; Englewood, NJ, USA). Heterogeneity between the studies was assessed using I^2 statistics. The data in this review were systematically distributed and for each available variable pooled, dichotomous data were analyzed and forest plots with 95% confidence intervals (CIs) are reported. The effect sizes were adjusted and reported as Hedge's *g*. Thresholds for interpretation of effect sizes were as follows: a standard mean effect size of 0 means no change, negative effect size means a negative change, mean effect size of <0.1 is considered a small effect, 0.1–0.3 a medium effect and >0.30 a large effect.[59,60] Interpretation of heterogeneity via I^2 statistics was as follows: 0–40% might not be significant, 30%–60% represents moderate heterogeneity, 50%–90% represents substantial heterogeneity, and 75%–100% represents considerable heterogeneity. Meta-analysis reports including heterogeneity among studies were evaluated to determine the reason of heterogeneity, and the included studies were then pooled separately and analyzed again. The alpha level was set at 95%.

Results

Characteristics of included studies

The initial search yielded 1,284 studies, which on implementing the inclusion/exclusion criteria were reduced to 42 (Figure 1). Data from the included studies are summarized in Table 1. Of the 42 studies, three were RCTs,[34–36] and 39 were CCTs. Eight studies evaluated the effects of dual-task training on postural stability.[34–36,48,61–64] Eight studies evaluated the effects of dual tasks on participants suffering from neurological diseases, such as degenerative cerebellar disorder, Parkinson's disease, and multiple sclerosis.[21,65,66] Twenty-six studies evaluated the effects of dual tasks on postural stability among healthy young and/or elderly participants.[16,17,20,67–89] Within these 26 studies, 14 studies compared the effects between young and elderly participants, eleven studies evaluated only young and one study evaluated only elderly participants.

Participants

Of the included studies, 33 studies incorporated mixed-gender participant groups.[16–18,20–22,36,61–67,69–78,81–84,87,88,90–94] Four studies incorporated only female participants,[35,79,85,86] and two studies incorporated only male participants.[34,89] Three studies did not specify the gender of the included participants.[48,61,80] The included studies provided data on 1,480 participants (n=796 females/581 males). Descriptive statistics related to the age (mean ± standard deviation) of the participants were tabulated across the studies. Three studies

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Table 1 Studies analyzing the effects of dual-task training and dual tasks on posture

Study	Research aim	Sample description	PEDro score and (level of evidence)	Research design	Postural analysis	Dual-task (C: cognitive, Cm: cognitive–motor and M: motor components)	Conclusion
Dual-task training							
Choi et al (2015)[34]	Assess the effects of DT training on postural stability among participants suffering from subacute stroke	8 F, 12 M (59±12) DT training (10), Ct (10)	5 (1b)	Postural stability assessed post DT training for 30 min, five times a week for 4 weeks	Sway analysis and Berg balance scale	Cm: computer-based cognitive memory test	Significantly enhanced postural stability post DT training DT performance significantly enhanced post DT training
An et al (2014)[48]	Assess the effects of DT training on postural stability among participants suffering from chronic stroke	33 chronic stroke patients Motor (11), cognitive (11), motor–cognitive (12) training group	4 (1b)	Postural stability assessed post DT training for 30 min, three times a week for 8 weeks	Sway analysis, time up and go test and functional reach test	C: mental arithmetic task Cm: Stroop, verbal analogical and counting backward task	Significantly enhanced postural stability in motor–cognitive training group as compared to motor or cognitive alone training group
Kim et al (2013)[62]	Assess the effects of DT training on postural stability among participants suffering from chronic stroke	VUDT: 5 F, 7 M (52±2) VDT: 8 F, 5 M (59±3) UDT: 9 F, 4 M (57±3)	4 (1b)	Postural stability assessed post DT training for 30 min, three times a week for 8 weeks with/without unstable base, visual restriction, dual task	Sway analysis, functional reach test and Berg balance scale	Cm: trial making and Stroop task	Significantly enhanced postural stability post DT training especially in VUDT group DT performance significantly enhanced post DT training in VUDT group
Hiyamizu et al (2012)[36]	Assess the effects of DT training on postural stability among healthy elderly participants	Elderly: DT training – 10 F, 7 M (72±5) DT: 16 F, 3 M (71±4)	7 (1b)	Postural stability assessed post DT training twice a week for 3 months (ST) with/without ST, EO/EC	Berg balance scale, activity-based confidence scale	Cm: visual search, verbal fluency, calculation task and Stroop task M: strength and balance training task	No significant difference in postural sway after DT training DT performance significantly enhanced post DT training
Buragadda et al (2012)[61]	Assess the effects of DT training on postural stability among elderly participants with balance impairments	30 participants	4 (1b)	Postural stability assessed post DT training (variable, fixed priority), 45 min session, three times a week for 4 weeks	Chair stand test, functional reach test, time up and go test	Cm: word spelling task and memory task	Significantly enhanced postural stability post variable priority DT training as compared to fixed priority
Li et al (2010)[63]	Assess the effects of DT training on postural stability among healthy elderly participants	DT training: 7 F, 3 M (74±5) Ct: 6 F, 4 M (77±7)	4 (1b)	Static, dynamic posture, and mobility stability assessed post DT training during five sessions separated by 2 days	Single support balance, sway analysis, and sit to stand test	Cm: n-back task	Significantly enhanced postural stability during single and double support dynamic balance DT performance significantly enhanced post DT training
Silsupadol et al (2009)[35]	Assess the effects of DT training on postural stability among elderly participants	ST training: 7 F (74±7) DT training (fixed): 6 F (74±6) DT training (variable): 4 F (76±4)	6 (1b)	Postural stability assessed post DT training (variable, fixed priority), 45 min session, three times a week for 4 weeks	Berg balance scale, activity-based confidence scale	Cm: random letter generation task	Significantly enhanced postural stability post variable priority DT training as compared to fixed priority DT training

(*Continued*)

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Table 1 (*Continued*)

Study	Research aim	Sample description	PEDro score and (level of evidence)	Research design	Postural analysis	Dual-task (C: cognitive, Cm: cognitive–motor and M: motor components)	Conclusion
Pellecchia (2005)[81]	Assess the effects of DT training on postural stability	9 F, 9 M (18–46)	5 (1b)	Postural stability assessed during single and DT training conditions, within three sessions	Sway analysis	Cm: counting backward in three tasks	Significantly enhanced postural stability post DT training as compared to single task training condition, DT performance significantly enhanced post DT training No difference in DT performance post DT training
Neurological disorder							
Jacobi et al (2015)[91]	Assess the effects of DT on postural stability among healthy and participants suffering from DCD	Healthy: 10 F, 10 M (58±11) DCD: 10 F, 10 M (58±11)	4 (2)	Static and dynamic postural stability assessed while EO/EC, with platform stable/unstable, with/without DT	Sensory organization test	Cm: verbal working memory task	Significantly reduced postural stability in participants with DCD as compared to healthy participants DT performance significantly reduced
Prosperini et al (2015)[66]	Assess the effects of DT on postural stability among healthy and participants suffering from MS	Healthy: 30 F, 16 M (39±9) MS: 60 F, 32 M (39±10)	4 (2)	Postural stability assessed with/without EO/EC, DT	Sway analysis	Cm: Stroop word color task	Significantly reduced postural stability in participants with MS as compared to healthy participants DT performance significantly reduced in MS patients
Andrade et al (2014)[22]	Assess the effects of DT on postural stability among participants suffering from AD, PD, and healthy participants	AD: 9 F, 3 M (72±5) PD: 7 F, 6 M (71±6) Healthy: 7 F, 6 M (66±4)	4 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: counting backward task	Significantly reduced postural stability with ST performance in AD, PD participants as compared to their healthy counterparts DT performance significantly reduced in patients with AD and PD
Boes et al (2012)[21]	Assess the effects of DT on postural stability among participants suffering from MS	MS: mild – 17 F, 2 M (46±13) Moderate: 24 F, 3 M (58±7)	6 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: word list generation task	Significantly reduced postural stability in participants classified in moderate MS as compared to mild MS group
Negahban et al (2011)[65]	Assess the effects of DT on postural stability among healthy and participants suffering from MS	Healthy: 15 F, 8 M (31±7) MS: 15 F, 8 M (32±7)	6 (2)	Postural stability assessed on rigid/foam surface, while EO/EC, with/without DT	Sway analysis	C: silent backward counting task	Significantly enhanced postural stability in MS and healthy participants DT performance not affected in patients with MS as compared to healthy participants

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Holmes et al (2010)[94]	Assess the effects of DT on postural stability among healthy elderly and participants suffering from PD	Healthy: 4 F, 8 M (62±8) PD: 4 F, 8 M (64±9)	5 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: numeral recitation and monologue generation task	Significantly enhanced postural stability observed in participants affected by PD as compared to healthy controls with/without DT, especially in monologue generation task
Marchese et al (2003)[92]	Assess the effects of DT on postural stability among healthy participants and participants suffering from PD	Healthy: 7 F, 13 M (60±7) PD: 8 F, 16 M (66±7)	5 (2)	Postural stability assessed with/without EO/EC, DT	Sway analysis	Cm: calculation task M: thumb opposition task	Reduced postural stability observed in participants affected by PD as compared to healthy controls with/without DT and motor tasks during eyes closed/open. With PD Fa performing significantly poorer
Morris et al (2000)[93]	Assess the effects of DT on postural stability among healthy and participants suffering from idiopathic PD (with/without history of fall)	PD fall: 8 F, 7 M (67±8) PD no fall: 8 F, 7 M (68±7) Healthy: 8 F, 7 M (68±7)	5 (2)	Postural stability assessed with/without internal/external perturbation, with/without DT	Internal and external perturbations to center of mass	Cm: verbal recital task	Significantly reduced postural stability with DT in PD fall-prone > nonfall-prone > healthy participants
Age classification							
Lanzarin et al (2015)[20]	Assess the effects of DT on postural stability among healthy young participants	Young: 10 F, 10 M (25±4)	5 (2)	Postural stability assessed with/without EO/EC, with/without DT	Sensory organization test	C: mental arithmetic task	Significantly reduced postural stability during ST, while EO and EO with oscillating platform
Bergamin et al (2014)[68]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 15 F, 15 M (23±1) Elderly: 15 F, 15 M (72±5)	4 (2)	Postural sway assessed with/without DT	Sway analysis	C: mental arithmetic task Cm: spatial memory and counting backward aloud task	Significantly enhanced postural stability during mental arithmetic, spatial memory task Significantly poor stability during counting backward aloud task
Hwang et al (2013)[77]	Assess the effects of DT on postural stability among healthy young participants	9 F, 11 M (28±4)	5 (2)	Postural stability assessed with/without vibration, with/without DT	Sway analysis	Cm: verbal and nonverbal task with hand-held button press	Significantly enhanced postural stability during nonverbal tasks, but less during verbal tasks
Haggerty et al (2012)[74]	Assess the effects of DT on postural stability among healthy elderly participants	Elderly: 4 F, 6 M (74±4)	5 (2)	Postural stability assessed with/without VTf, DT	Sway analysis and biofeedback	Cm: verbal auditory and push button dual task	Significant enhancement of postural stability when DT performed with VTf as compared to DT alone DT performance significantly reduced
Mak et al (2011)[78]	Assess the effect of delayed visual feedback and DT on posture among healthy young and elderly participants	Young: 10 F, 5 M (24±3) Elderly: 5 F, 10 M (age not specified)	4 (2)	Posture stability assessed with EO, delayed visual feedback, with/without DT	Sway analysis	C: mental arithmetic task	Significantly enhanced postural stability in young participants. Significantly reduced postural stability in elderly participants

(*Continued*)

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Table 1 (*Continued*)

Study	Research aim	Sample description	PEDro score and (level of evidence)	Research design	Postural analysis	Dual-task (C: cognitive, Cm: cognitive–motor and M: motor components)	Conclusion
Resch et al (2011)[17]	Assess the effects of ST on postural stability among healthy young participants	Young: 10 F, 10 M (20±1)	5 (2)	Postural stability assessed by using SOT with/without DT	Sensory organization test	Cm: auditory switch task	Significantly enhanced postural control DT performance significantly reduced
Doumas et al (2008)[73]	Assess the effects of DT on postural stability and vice versa among healthy young and elderly participants	Young: 10 F, 8 M (21±2) Elderly: 10 F, 8 M (71±3)	4 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: n-back task	Significantly reduced postural stability for elderly participants in sway reference somatosensory condition. No difference in postural stability of young participants DT performance significantly reduced in elderly participants during sway reference somatosensory condition
Ramenzoni et al (2007)[82]	Assess the effects of DT on postural stability among healthy young participants	Young: 10 F, 13 M (28–25 y)	5 (2)	Postural stability assessed with/without DT, during encoding and rehearsal with combination of verbal and visual interference	Sway analysis	Cm: verbal and visual cognitive task	Significantly reduced postural stability during encoding of verbal and visual task as compared to rehearsal period DT performance significantly reduced during verbal and visual tasks
Donker et al (2007)[16]	Assess the effects of DT on postural stability among healthy young participants	Young: 20 F, 10 M (19–30 y)	5 (2)	Postural stability assessed while EO/EC and with/without DT	Sway analysis	Cm: uttering name backwards task	Significant enhancement of postural stability when DT performed with eyes closed
Swan et al (2007)[85]	Assess the effects of DT on postural stability among healthy female young participants	Young: 98 F (18–27 y)	4 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: Brook spatial and nonsense memory task	Significant enhancement in postural stability with enhanced DT difficulty. No effect of difficulty enhancement in balance task DT performance significantly reduced with increased complexity of DT
Vuillerme et al (2006)[89]	Assess the effects of DT on postural stability among healthy young participants	Young: 9 M (23±1)	4 (2)	Postural stability assessed with/without EO/EC, ST	Sway analysis	Cm: probe reaction time task	Significantly enhanced postural stability during EO, closed DT as compared to EC
Huxhold et al (2006)[79]	Assess the effects of ST, DT on postural stability among healthy young and elderly participants	Young: 10 F, 10 M (24±2) Elderly: 9 F,10 M (69±3)	4 (2)	Postural stability assessed with/without ST and DT	Sway analysis	Cm: digit choice reaction time, two back digit working memory, two back spatial working memory and watching digit conditions task	Significantly enhanced postural stability in both age groups with simple DT DT performance significantly reduced in elderly participants during digit and spatial two back tasks

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Swan et al (2004)[86]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 18 F (19–25 y) Elderly: 15 F (60–74 y)	5 (2)	Postural stability assessed under, with/without, ST and EO/EC	Sway analysis	Cm: Brooks spatial and nonspatial task	Significantly enhanced postural stability for both age groups DT performance significantly reduced in elderly as compared to young participants
Pellecchia (2003)[76]	Assess the effects of DT on postural stability among healthy young participants	Young: 10 F, 10 M (18–30 y)	4 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: digit reversal task, counting backward in twos and counting backward task	Significantly reduced postural stability with DT DT performance significantly reduced as DT complexity increased
Brauer et al (2002)[69]	Assess the effects of ST on postural stability among healthy young and elderly participants with and without history of fall	Young: 5 F, 10 M (22±5) Elderly: Nfa – 4 F, 11 M (72±6) Fa – 6 F, 7 M (79±6)	5 (2)	Postural stability assessed with sudden movement at the balance platform, with/without DT	Postural recovery via sway analysis	Cm: vocal reaction time task	Reduced postural stability in elderly participants (Fa) and young participants during DT as compared to elderly (Nfa). Also poor recovery by Fa with DT and limited effect of DT on Nfa and young participants DT performance significantly reduced among elderly Fa as compared to elderly Nfa and young participants
Andersson et al (2002)[67]	Assess the effects of DT, calf stimulation, and self-balance focus on postural stability among healthy participants	Exp 1: 17 F, 13 M (27±8) Exp 2: 10 F, 10 M (30±8)	4 (2)	Postural stability assessed with (Exp 1)/without (Exp 2) mental task, ie, focus on balance, with/without DT	Sway analysis	C: silent backward counting task	Significantly reduced postural stability during DT DT performance significantly reduced with balance pertubations
Dault et al (2001)[72]	Assess the effects of DT on postural stability among healthy young participants	Young: 12 F, 12 M (20–40 y)	5 (2)	Static and dynamic postural stability assessed with/without DT	Sway analysis	Cm: Stroop word color task	Significantly reduced postural stability when dynamic stability assessed with ST performance. No significant difference in postural sway during static ST performance DT performance significantly reduced with increased complexity of DT task
Hunter and Hoffman (2001)[75]	Assess the effects of DT on postural stability among healthy young participants	Young: 15 F, 15 M (24 y)	4 (2)	Postural stability assessed with modulation of eye movement and modality of presentation of DT	Sway analysis and video-motion analysis	Cm: visual and auditory cognitive task	Significantly reduced postural stability within visual condition DT performance unaffected

(*Continued*)

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Table 1 (*Continued*)

Study	Research aim	Sample description	PEDro score and (level of evidence)	Research design	Postural analysis	Dual-task (C: cognitive, Cm: cognitive–motor and M: motor components)	Conclusion
Melzer et al (2001)[80]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 20 (26±3) Elderly: 20 (77±2)	5 (2)	Postural stability assessed with/without narrow/wide BoS DT and EMG	Sway analysis	Cm: modified stroop test	Significantly reduced postural stability among elderly participants during DT performance and narrow BoS. Enhancement in stability during DT performance in young participants
Teasdale and Simoneau (2001)[88]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 5 F, 3 M (24±0) Elderly: 2 F, 6 M (68±0)	4 (2)	Postural stability assessed with/without DT	Sway analysis	Cm: probe reaction time task	Significantly reduced postural stability as compared to young participants DT performance significantly reduced in elderly as compared to younger participants
Brauer et al (2001)[70]	Assess the effects of DT on postural stability among healthy young and elderly participants with and without history of fall	Elderly: Nfa – 5 F, 9 M (72±6) Fa – 6 F, 7 M (79±6)	5 (2)	Postural stability assessed with sudden movement at the balance platform, with/without DT	Sway analysis	Cm: vocal reaction time task	Significantly reduced postural stability in elderly participants (Fa) during DT as compared to elderly (Nfa). Also poor recovery by Fa with DT and no effect of DT on Nfa DT performance significantly reduced in elderly Fa participants as compared to Nfa elderly participants
Shumway-Cook and Woollacott (2000)[83]	Assess the effects of DT on postural stability among healthy young and elderly participants with and without history of fall	Young: 3 F, 15 M (34±8) Elderly: Nfa – 4 F, 14 M (74±6) Fa – 3 F, 15 M (85±6)	5 (2)	Postural stability assessed with balance disturbances, with/without EO/EC, somatosensory input, DT	Sway analysis	Cm: choice reaction time auditory task	Significantly reduced postural stability among elderly participants Fa as compared to young and elderly Nfa participants during DT DT performance unaffected, similar in younger and elderly participants
Marsh and Geel (2000)[79]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 14 F (25±2) Elderly: 16 F (71±3)	5 (2)	Postural stability assessed, with EO/EC, with/without DT	Sway analysis	Cm: vocal reaction time task	Significantly reduced postural stability among elderly participants as compared to young participants DT performance significantly reduced in elderly as compared to younger participants
Brown et al (1999)[71]	Assess the effects of DT on postural stability among healthy young and elderly participants	Young: 5 F, 10 M (25±5) Elderly: 3 F, 7 M (78±4)	5 (2)	Postural stability assessed with balance disturbances, with/without DT	Postural recovery via sway analysis and video-motion capturing	Cm: backward digit recall task	Reduced postural stability among elderly as compared to young participants during balance disturbances

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Shumway-Cook et al (1997)[84]	Assess the effects of DT on postural stability among healthy young and elderly participants with and without history of fall	Young: 10 F, 10 M (31±6) Elderly: Nfa – 11 F, 9 M (74±6) Fa – 13 F, 7 M (78±8)	5 (2)	Postural stability assessed on flat and compliant surfaces, with and without DT	Sway analysis	Cm: sentence completion, language processing, visual perception, and judgment of line orientation task	Significantly reduced postural stability in elderly participants (Fa) during dual tasks on both surfaces as compared to young participants No significant effect on young and elderly (Nfa) on flat surface under simple DT DT performance significantly reduced in Fa as compared to young participants
Teasdale et al (1993)[87]	Assess the effects of DT among healthy young and elderly participants	Young: 8 M (24±0) Elderly: 3 F, 6 M (71±0)	4 (2)	Postural stability assessed while making postural adjustments, with/without DT	Sway analysis	Cm: auditory reaction time task	Significantly reduced postural stability among elderly participants as compared to young participants during DT DT performance significantly decreased in elderly as compared to younger participants

Notes: Significant: $P<0.05$; nonsignificant: $P>0.05$. Data presented as mean ± standard deviation.
Abbreviations: AD, Alzheimer's disease; BoS, base of support; Ct, control group; DCD, degenerative cerebellar disorder; DT, acute dual-task application; Exp, experimental group; EMG, electromyography; EO, eyes open; EC, eyes closed; F, female; Fa, history of fall; M, male; MS, multiple sclerosis; Nfa, no history of falls; PD, Parkinson's disease; SOT, sensory orientation test; ST, single task; UDT, unstable base with dual-task; VUDT, visual restriction and unstable base with dual task; VDT, visual restriction with dual task; VTf, vibro-tactile feedback.

provided the median age of participants,[75,87,88] and five studies mentioned the age of participants in range.[16,81,82,85,86]

Risk of bias within studies

In order to efficiently reduce the risks of bias, the studies had to score ≥4 on PEDro scale to be included in the review. The criteria for research studies to be included in the review were limited to gold standard RCTs, cluster RCTs, and CCTs. The individual scores attained by the studies using the PEDro scale are reported in Tables 1 and S2. The average PEDro score for the 42 included studies was computed to be 4.7 out of 10, indicating fair quality of the overall studies. One study scored 7,[36] three studies scored 6,[21,35,65] 20 studies scored 5,[16,17,20,34,69–72,74,77,79–84,86,92–95] and 18 studies scored 4.[22,48,61–63,66–68,73,75,76,78,81,85,87–89,91]

Risk of bias across studies

Common methodological shortfalls observed in this review were inadequate concealment, intention-to-treat, nonblinding of participants, therapists, and assessors. One study reported blinding of assessors and confirmed intention-to-treat the included participants. Furthermore, only two studies confirmed concealed allocation of subjects.[35,36] The authors could not interpret concealed allocation of participants in three studies,[65,82,85] and, therefore, no points were awarded to the studies. The overall risk of bias for quality assessment within studies is illustrated in Figure 2.

Meta-analysis

The evaluation of research studies via meta-analysis requires strict inclusion criteria to efficiently limit the heterogeneity.[96] However, among the pooled group of studies the authors observed unexplained heterogeneity, suggesting incorporation of a random-effect meta-analysis under such conditions. The researchers added that a random-effect meta-analysis involves an assumption that the estimated effects in various studies are unidentical but follow some distribution. Therefore, studies analyzing similar variables were pooled, and a random-effect meta-analysis was conducted across four categories (dual-task training: elderly participants, dual task: multiple sclerosis, young, old). The main reason for not including the statistical approach within the studies was major differences in training duration, assessment methods, age/gender, complexity of dual tasks, and lack of descriptive statistics within the manuscript. The descriptive statistics mentioned within illustrative figures were not included in the study. The authors included ten studies in the meta-analysis which incorporated evaluation of postural

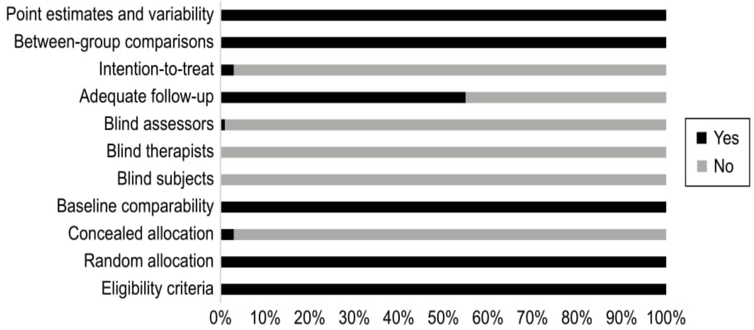

Figure 2 Risk of bias across studies.

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stability in participants similar at baseline and were evaluated with similar methodological approaches, but with different dual tasks. The aim of such analysis was to demonstrate the differential effects of complexity of dual tasks on postural stability. Additionally, the reasons for specific studies are mentioned subsequently.

Dual-task training

Eight studies under this category analyzed the effects of dual-task training on postural stability, whereas four studies, in two different categories, were included in the meta-analysis.[35,48,61,62] From the nonincluded studies, one study analyzed the effects of dual-task training on subacute stroke patients,[34] two studies analyzed the effects on elderly participants,[36,63] and one study on younger participants.[64] The two studies analyzing the effects of dual-task training on elderly participants considerably differed based on training duration and incorporated dual tasks. Hiyamizu et al[36] incorporated Stroop task with a dual-task training duration of two sessions per week for 3 months; however, Li et al[63] used an n-back task with a training duration spread over five sessions with a 2-day gap within each session.

Neurological impairment

Eight studies under this category analyzed the effects of dual task on postural stability of participants affected by neurological disorders. Two studies analyzing the effects of dual task on multiple sclerosis were included in the meta-analysis. However, the third study despite having similar variables could not be included as the descriptive statistics were not available in the text and were not obtained even after contacting the corresponding author. Similarly, three other studies analyzing patients affected by Parkinson's disease could not be included due to lack of descriptive statistics.[22,92,93] Only one study analyzed the effects of dual tasks on postural stability of participants affected from degenerative cerebellar disorder.[91]

Young and elderly participants

Twenty-six studies under this category analyzed the effects of dual task on young and/or elderly participants. Four studies analyzing the effects of dual task on young and elderly participants were included in the meta-analysis.[17,20,80,94] Thirteen studies analyzing similar variables in terms of age and dual tasks were not included in the meta-analysis as they did not include descriptive statistics explicitly, but in figures, ie, bar diagrams.[16,67,68,72,75,76,79,82,85–89] Shumway-Cook and Woollacott[83] and Shumway-Cook et al[84] evaluated the effects of dual task on postural stability during balance perturbations in participants predisposed to falls, their healthy counterparts, and young participants, while the studies differed in terms of utilized dual tasks. Mak et al,[78] on the contrary, included a rather novel aspect of visual feedback during standing and utilized dual tasks in conjugation with this feedback approach. Hwang et al[77] also utilized one leg standing as compared to the counterpart studies, which utilized a basic two-legged standing under different conditions. Brauer et al[69,70] analyzed postural recovery post balance perturbation with dual tasks among participants predisposed to falls, their healthy counterparts, and young participants with similar dual tasks. Likewise, Brown et al[71] also utilized a similar approach and effective comparisons could have been drawn between studies to evaluate the effects of dual task on postural stability. Due to lack of descriptive statistics, and not heterogeneity, the studies could not be included in the analysis.

Outcomes

The results suggest clear evidence for a positive impact of dual-task training for enhancing postural stability among fall-prone elderly population groups and participants affected

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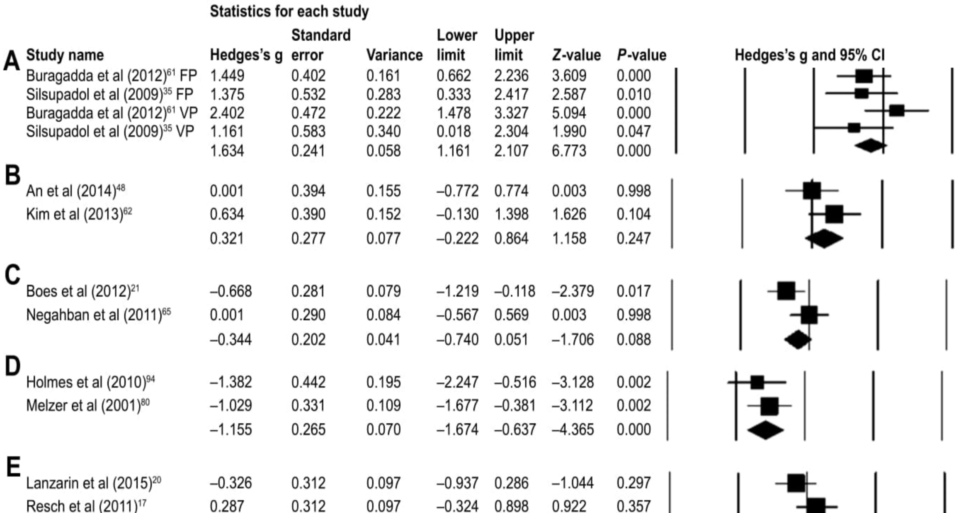
from stroke. A negative impact of dual tasks was observed in studies evaluating the effects of dual tasks on postural stability among fall-prone population groups affected by neurological disorders and/or with prior history of fall, as compared to their younger healthier counterparts.

Meta-analysis report

Dual-task training

Eight studies evaluated the effects of dual-task training on postural stability.[34–36,48,61–64] One RCT[34] and two CCTs evaluated the effects of dual-task training on postural stability in subacute and chronic stroke patients, respectively. Two RCTs[35,36] and three CCTs evaluated the effects of dual-task training on elderly and young participants. Significant enhancements in postural stability were reported in one good[35] and six fair-quality studies.[34,48,61–64] However, one good-quality study reported no significant enhancements in postural stability. A random-effect meta-analysis was conducted across two categories. First, two studies evaluated the effects of fixed and variable priority dual-task training on postural stability among elderly population groups.[35,61] A random letter generation task was utilized during the training phase which lasted for a 45-min session, three times a week for 4 weeks. Scores from Berg balance scale were utilized to assess the postural stability. Upon analysis, a large effect size was observed (Hedge's *g*: 1.63), and 95% CI (1.16–2.10) was reported in the positive domain, demonstrating a beneficial effect of variable task priority within dual-task training to enhance postural stability (Figure 3A). Heterogeneity tests reported negligible heterogeneity (I^2: 20.26%, $P<0.01$). Moreover, the studies were then reevaluated on the basis of fixed and variable priority dual-task training. In the condition of fixed priority dual-task training, upon analysis, a large effect size was observed (Hedge's *g*: 1.42) and 95% CI (0.79–2.05) in the positive domain. Similarly, in the condition of variable priority dual-task training, a large effect size was observed (Hedge's *g*: 1.91) and 95% CI (1.19–2.63) in the positive domain. Thereby, demonstrating a beneficial effect of variable priority over fixed priority dual-task training method.

Second, two studies analyzing the effects of dual-task training on postural stability among patients affected from chronic stroke were included in the meta-analysis.[48,62] The studies utilized a similar dual-task training duration phase of a 30-min session, three times a week for 8 weeks. Postural stability in the studies was assessed using functional reach test. Upon analysis, a large effect size was observed (Hedge's *g*: 0.32), and 95% CI (−0.22 to 0.86) cm was reported in the positive domain, demonstrating a beneficial effect of within dual-task training to enhance postural stability (Figure 3B). Heterogeneity tests reported negligible



	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
A	Buragadda et al (2012)[61] FP	1.449	0.402	0.161	0.662	2.236	3.609	0.000
	Silsupadol et al (2009)[35] FP	1.375	0.532	0.283	0.333	2.417	2.587	0.010
	Buragadda et al (2012)[61] VP	2.402	0.472	0.222	1.478	3.327	5.094	0.000
	Silsupadol et al (2009)[35] VP	1.161	0.583	0.340	0.018	2.304	1.990	0.047
		1.634	0.241	0.058	1.161	2.107	6.773	0.000
B	An et al (2014)[48]	0.001	0.394	0.155	−0.772	0.774	0.003	0.998
	Kim et al (2013)[62]	0.634	0.390	0.152	−0.130	1.398	1.626	0.104
		0.321	0.277	0.077	−0.222	0.864	1.158	0.247
C	Boes et al (2012)[21]	−0.668	0.281	0.079	−1.219	−0.118	−2.379	0.017
	Negahban et al (2011)[65]	0.001	0.290	0.084	−0.567	0.569	0.003	0.998
		−0.344	0.202	0.041	−0.740	0.051	−1.706	0.088
D	Holmes et al (2010)[94]	−1.382	0.442	0.195	−2.247	−0.516	−3.128	0.002
	Melzer et al (2001)[80]	−1.029	0.331	0.109	−1.677	−0.381	−3.112	0.002
		−1.155	0.265	0.070	−1.674	−0.637	−4.365	0.000
E	Lanzarin et al (2015)[20]	−0.326	0.312	0.097	−0.937	0.286	−1.044	0.297
	Resch et al (2011)[17]	0.287	0.312	0.097	−0.324	0.898	0.922	0.357
		−0.019	0.221	0.049	−0.451	0.413	−0.085	0.932

Figure 3 Forest plot illustrating individual studies evaluating the effects of (**A**) dual-task training with fixed (FP) and variable (VP) priority in elderly participants, (**B**) dual-task training in elderly participants affected from stroke, (**C**) dual-task in postural stability of participants affected from multiple sclerosis, (**D**) dual-task in postural stability of elderly participants, (**E**) dual-task in postural stability of young participants.

Notes: Adjusted effect sizes; Hedge's *g* (boxes), and 95% CI (whiskers) are presented, demonstrating repositioning errors for individual studies. Diamond represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups.

Abbreviation: CI, confidence interval.

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heterogeneity (I^2: 23.2%, P=0.24). The studies according to the PEDro methodological scale computed an average score of 4.8, indicating the average quality of the studies to be fair.

Neurological impairments

Eight studies evaluating the effects of dual-task performance on postural stability among participants affected by neurological disorders, such as cerebellar disorder, Parkinson's disease,[22,92–94] and multiple sclerosis,[21,65,66,91] were included in the review. Significant enhancements in postural stability were reported in one good[65] and one fair-quality study.[94] Additionally, five fair-quality studies reported a significant reduction in postural stability among individuals affected by Parkinson's disease,[22,93,94] multiple sclerosis,[66] and degenerative cerebellar disorder.[91] One good-quality study reported a reduction in postural stability (not significant) among participants affected by Parkinson's disease.[92] Five studies evaluated the comparative effects between healthy participants and participants affected by neurological disorders,[66,91,92,94] but one study evaluated the comparison between participants affected by mild and moderate multiple sclerosis.[21] Also, two studies evaluated the inclusion of stable and unstable surfaces for maintaining postural stability while performing a dual task.[65,91]

A random-effect meta-analysis was conducted across one category, for evaluation of the effects of dual task on multiple sclerosis.[21,65] Even though the two included studies conducted the tests using different dual tasks, the methodology and included participants were similar at baseline. The meta-analysis comprehensively demonstrated the differential effects of complexity of dual tasks on postural stability, ie, where on the one hand silent backward counting task improved the postural stability of the participants with multiple sclerosis, on the other hand incorporating word list generation task, incorporated by Boes et al,[21] adversely impacted postural stability. Upon analysis, a large effect size was observed (Hedge's g: –0.34) and 95% CI (–0.74 to 0.05) cm was reported marginally in the negative domain, demonstrating a differential effect of dual-task complexity on the postural stability of participants with multiple sclerosis (Figure 3C). Heterogeneity tests reported considerable heterogeneity (I^2: 63.6%, P=0.08). The increased heterogeneity could be attributed to the differential complexity of dual tasks within the studies, which according to Vuillerme and Vincent[97] might affect the outcome of the primary task. According to PEDro methodological scale, the studies overall scored an average of 4.8, indicating the quality of the studies to be fair.

Young and elderly

Twenty-six studies evaluated the effects of dual-task performance on postural stability among young, elderly, young/elderly, and participants with/without history of falls.[16,17,20,67–80,82–89] Eleven fair-quality studies evaluated the effects of dual tasks on young participants.[16,17,20,67,72,75,77,81,82,85,89] Four fair-quality studies reported significant enhancements in postural stability,[16,17,77,85] whereas seven fair-quality studies reported significant reduction in postural stability.[20,67,72,75,81,82,89]

Two fair-quality studies evaluated the effects of dual tasks on elderly participants.[70,74] Both the studies reported a significant reduction in postural stability post dual-task intervention.

Thirteen fair-quality studies compared the effects of dual tasks between young and elderly participants.[68,69,71,73,76,78–80,83,84,86–88] Four studies included a comparison between elderly participants with/without history of falls.[69,70,83,84] Three studies reported significant enhancements in postural stability among both young and elderly participants.[68,76,86] Eight studies reported significant reductions in postural stability of elderly participants as compared to younger participants where enhancements in postural stability were observed.[21,73,79,80,83,84,87,88] Two studies reported reduced postural stability (nonsignificant) among elderly participants; however, enhancements were observed in younger counterparts. Similarly, significantly reduced posturasl stability was reported for participants with prior history of fall as compared to their healthy counterparts.[69,70,83,84] A random-effect meta-analysis was conducted across two categories for evaluation of the effects of dual task on healthy young participants. The two studies analyzed the postural stability using sensory orientation test; however, differential dual tasks were incorporated in the review.[17,20] The methodology and included participants were similar at baseline. The meta-analysis comprehensively demonstrated the differential effects of complexity of dual tasks on postural stability, ie, where on the one hand auditory switch task improved the postural stability of the participants,[17] on the other hand, incorporating a complex mental arithmetic task adversely impacted postural stability among young participants. Upon analysis, a trivial effect size was observed (Hedge's g: –0.02) and 95% CI (–0.45 to 0.41)% was reported marginally in the negative domain, demonstrating a differential effect of dual-task complexity on the postural stability of young participants (Figure 3E). Heterogeneity tests reported considerable heterogeneity (I^2: 48.2%, P=0.93), which could possibly be related to the differential complexity of the dual

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tasks incorporated within the studies. A second random-effect meta-analysis was conducted to evaluate the effects of dual task on elderly participants. The two studies analyzed the postural stability using length of center of pressure path; however, different dual tasks were included in the studies. Despite the complexity, these cognitive tasks demonstrated detrimental effects of dual tasks on postural stability of elderly participants. The methodology and included participants were similar at baseline. Upon analysis, a large effect size was observed (Hedge's *g*: −1.15) and 95% CI (−1.67 to −0.63) cm was reported considerably in the negative domain, demonstrating a negative effect of dual-task complexity on the postural stability of elderly participants (Figure 3). Heterogeneity tests reported negligible heterogeneity (I^2: 0%, $P>0.01$). The studies according to the PEDro methodological scale computed an average score of 4.2, indicating the average quality of the studies to be fair.

Discussion

This systematic review aimed to extend our understanding of the effects of dual tasks and dual-task training on static and dynamic postural stability among healthy and fall-prone population groups. Beneficial effects of dual-task training on postural stability of participants especially with poor balance capabilities were observed in this review. A PEDro 1b level of evidence and random-effect meta-analysis demonstrated the beneficial effects of dual-task training for enhancing postural stability among fall-prone population groups.

The review observed beneficial effects of dual-task training in studies analyzing patients affected from subacute[34] and chronic stroke.[48,62] The studies reported patients affected from stroke to possess considerable impairments in their cognitive–motor domain. Because of this, altered weight distribution has been reported in stroke patients while maintaining static and dynamic postures.[98] However, An et al[48] and Kim et al[62] performed a dual-task training regime (30-min session, three times a week for 8 weeks) and reported beneficial effects on postural stability even for conditions with visual restriction and/or unstable base when presented with dual tasks. These enhancements were also evident in the meta-analysis where enhancements in functional reach test (Hedge's *g*: 0.32) and 95% CI (−0.22 to 0.86) cm were observed. The authors justified the beneficial effects by suggesting prevention of tipping effect.[48] This review, however, believes training could have possibly allowed skill acquisition for the cognitive and motor task while making the use of reactive forces, which in turn has been shown to reduce active muscular contraction.[99] This can possibly aid in reduction of muscular coactivation and muscle guarding-related decrements in postural stability.[6] A meta-analysis conducted by Wang et al[51] also reported similar beneficial effects among stroke patients; 95% CI (0.54–5.21).

Furthermore, Silsupadol et al[35] and Buragadda et al[61] in their respective studies demonstrated a differential aspect of dual-task training with variable task prioritization. Meta-analysis revealed a beneficial effect of 95% CI (1.19–2.63) in variable priority as compared to 95% CI (0.79–2.05) in the fixed priority condition. The authors in their respective studies also reported enhancements in cognitive task performance, rate of learning, and ability to maintain skill level during follow-up period. Silsupadol et al[35] interestingly affirmed the enhancements obtained because of dual-task training toward the task integration hypothesis, which states better development of task coordination skills following practicing with two tasks together. Likewise, Kramer et al[100] in their study reported similar benefits during variable priority training and suggested that participants under variable priority conditions can learn to coordinate between two tasks during training. The authors speculated that the processing demand needed to perform a task was less when the attention was divided between two tasks. Moreover, the authors also reported a training effect during a 3-month follow-up within the variable priority condition as compared to fixed priority condition.[35] According to Shigematsu et al,[101] the training phase with a motor component enhances neural functioning and reduces response latency by effectively recruiting postural muscles resulting in improved sensory information processing. The review also identified radiological evidence by Erickson et al,[102] which suggested enhanced cerebral hemodynamics in dorsolateral prefrontal cortex within the dual-task training group, and associated this effect with improved performance. In addition, certain centers of the brain associated with dual-task processing showed less activation posttraining, implying reduced processing demands posttraining.[102] Some studies have also implied this training maneuver to act as a cognitive therapy for patients with attentional deficits and cognitive impairments.[34,52] Furthermore, this review identified dual-task training regimes to also allow benefits in cognitive performance.[38,52] According to Hiyamizu et al[36] and Wollesen and Voelcker-Rehage,[38] enhancements in cognitive performance might lead toward smoothening of cognitive activities while maintaining static and dynamic postures, resulting in preventing falls. The authors of the present review also believe that the enhancements in stability and dual-task performance are highly associated with the findings of Wolpert et al[103] and Masters and Maxwell.[9] In the present study, the initial phase of learning is suggested to be

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more cognitively driven as compared to the later stages of learning, which in a dual-task training setting might get more fluent and independent. Our results are in line with previously conducted systematic reviews, where dual-task training has been reported to enhance postural stability and cognitive performance.[38,49,50,52] However, this review is the first to reveal beneficial effects of dual-task training in a meta-analysis and a level of evidence analysis.

This review observed detrimental effects of dual tasks on postural stability for the participants with higher predisposition to fall. For instance, complexity-associated reduction in postural stability was reported for patients affected with multiple sclerosis[21] and Parkinson's disease.[93] Researchers suggest incorporation of two underlying theories for this detrimental effect, ie, bottleneck and capacity model theories.[21,104] Boes et al[21] suggested that since the patients with neurological impairments such as multiple sclerosis, stroke, Parkinson's disease, and elderly participants have cognitive deficits, it is possible that the neurological capacity for these patients would be even less in terms of the aforementioned models. However, the findings of systematic reviews conducted by Learmonth et al[31] and Wajda and Sosnoff[30] concluded minimal effects of cognitive–motor interferences on postural stability for patients with multiple sclerosis and their healthy counterparts. The meta-analysis conducted by Learmonth et al[31] revealed a small effect size of −0.11.

Furthermore, explaining the factors causing additional balance discrepancies in patients with parkinsonism, Bohnen et al[105] and Andrade et al[22] discussed that the dopaminergic and cholinergic pathways play a significant role in stabilizing the control of posture. These pathways play an important role in affecting the prioritization of posture and dual tasks within the central sharing model. The review conducted by Dirnberger and Jahanshahi[106] supported these results and pointed out the considerable reduction in dopaminergic neuron in posterior putamen, anterior striatum, limbic nuclei, and neocortical extensions.[107,108] As mentioned earlier, the basal ganglia–cortical network is involved in managing the "conscious" aspects of postural stability.[6] Therefore, it might play an extensive role in causing considerable cognitive–motor interferences to reduce dual-task performance and postural stability and even promote posture "second" strategy.[109] Marchese et al[92] added that the dual task, ie, calculation, motor sequence of thumb opposition task, might have caused the Parkinson's patients to shift their attention, further leading to disturbed conscious control and reduced stability. Interestingly, one study analyzing patients with parkinsonism revealed beneficial effects of dual-task application. The authors from the study suggested that the patients constrained their posture for directing attention toward the dual task, which ironically also enhanced their posture. However, the authors of the review argue that factors of complexity within a dual task have played a role for enhancing stability, ie, reduced anterior posterior sway during nonspeech conditions.

Brauer et al[69,70] and Shumway-Cook et al[84] reported postural stability and its recovery to be poorer among participants with prior history of fall as compared to their healthy counterparts, while performing a dual task (verbal reaction to auditory tone task and sentence completion with visual perception tasks). Radiological evidence by Herath et al[110] and Szameitat et al[111] reported the involvement of cortical areas along inferior frontal sulcus, middle frontal gyrus, and the intraparietal sulcus while performing auditory and visual reaction dual tasks. Therefore, suggesting that superimposing a dual task over already weak reorganized cortical structures may impart more stress and adversely impact postural stability.[14] The findings of the present review are in line with recent review studies,[6,26] where poor postural stability was also observed in fall-prone population groups as compared to their healthy younger counterparts.

Interestingly, the review found differential effects of dual tasks in studies evaluating healthy young participants and participants with balance deficits. For instance, researchers such as Vuillerme et al,[89] Ramenzoni et al,[82] Pellecchia,[64] and Lanzarin et al[20] reported detrimental effects of dual tasks on young participants; on the other hand Donker et al,[16] Bergamin et al,[68] Huxhold et al,[76] Mak et al,[78] Resch et al,[17] and Hwang et al[77] reported beneficial effects even among fall-prone elderly participants. In addition, beneficial effects of the dual-task application were also observed in participants with multiple sclerosis[65] and Parkinson's disease.[94] Conventionally, according to published reports fall-prone population groups experience poor postural stability under the influence of higher information processing constraints. However, this review observed these differential results and suggests an inverse correlation between the complexity of the dual tasks and the postural stability. Researchers suggest that according to the Yerkes–Dodson law a U-shaped relation between cognitive demand and postural sway might reflect the level of arousal associated with dual cognitive task demand,[76] thereby suggesting an increase in postural sway with added complexity in a cognitive task.

Jacobi et al[91] analyzed the postural stability of ataxic and healthy controls using a verbal working memory task. The authors reported less center of pressure sway with reduced

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dual-task complexity for the ataxic group during a sensory orientation test. According to the authors, the involvement of cerebellum in both cognitive and motor tasks can result in increased interference,[112] thereby affecting dual-task and postural performance. Also, the role of cerebellum has been reported especially during the performance of dual tasks while maintaining executive control including working memory, language, and visuospatial information.[113] Radiological evidence also demonstrates increased BOLD (blood oxygen level dependent) response in the cerebellar vermis and anterior lobe while simultaneous performance of cognitive–motor tasks.[114] This review also observed articulation as a major factor for complexity in terms of a dual task, yielding differential effects upon postural stability. Bensoussan et al,[115] Marchese et al,[92] and Yardley et al,[116] for instance, reported detrimental effects of aloud verbal, arithmetic tasks on postural stability. On the contrary, Negahban et al[65] and Lanzarin et al[20] reported beneficial effects of nonverbal tasks on postural stability of fall-prone participants. Literature analysis revealed research studies identifying commonly used dual tasks such as verbal recital, n-back, and counting backward to be considered as more cognitively driven.[117] This review also observed the studies to ignore the verbal and hearing component incorporated in a dual-task paradigm. A functional magnetic resonance imaging analysis by Behroozmand et al[118] revealed the involvement of bilateral superior temporal gyrus, Heschl's gyrus, precentral gyrus, supplementary motor area, Rolandic operculum, postcentral gyrus, putamen insula, and right inferior frontal gyrus during speech production.[119] Moreover, the authors mentioned that speech production is also followed by a feedback error detection system in the sensory cortex that again activates the motor areas for speech adjustments, therefore suggesting the auditory feedback as an additional factor for increasing complexity in a dual-task setting.

Yardley et al[116] speculated the interaction between muscular control of speech-associated respiration and posture to cause perturbation in posture. The authors compared complex articulated, mental tasks while analyzing postural stability and reported beneficial effects on stability in the absence of articulation. This present review also suggests that the reinvolvement of higher motor centers during speech production in a dual task might possibly result in central interference, which might impact the person's dual task and stability performance. This review also adds to the existing knowledge that dual-task paradigms involving only a mental component, such as mental arithmetic task, might also include a motor component. As mentioned earlier, hearing also incorporates activation of cortical structures, precisely bilateral superior temporal gyrus, and Heschl's gyrus.[118] The phase of instructions might activate this cortical pathway and can add to the certain amount of complexity in the dual-task scenario, which although trivial might result in considerable adverse effects in fall-prone population groups. This review did not find any study that analyzed the effects of dual-task posture in the absence of auditory information, ie, via noise canceling headphones, white noise; therefore possibly explaining the reduction in stability for studies employing nonverbal dual tasks.[20,67]

In summary, a systematic review was conducted across five online academic search databases: Scopus, PEDro, MEDLINE, EMBASE, and SportDiscus. A total of 1,284 articles were incorporated in our initial search, which later on implementing our inclusion criteria were reduced to 42 (Figure 1). The meta-analysis conducted on studies suggested beneficial effects of dual-task training with variable priority for enhancing postural stability, especially among elderly participants. Moreover, an inverse relation was observed between the complexity of dual task and postural stability. This review also observed an articulation component within a dual task to be a component of added complexity, which further might enhance cognitive–motor interference in fall-prone population groups. This study also reveals detrimental effects of complex dual tasks among population groups with a higher predisposition to fall, as compared to their healthy counterparts.

Strengths

This present review is the first to analyze and compare the effects of dual-task training and dual task on postural stability. Respective authors of the included papers were contacted for additional descriptive data or information. The review conformed to PRISMA guidelines in all applicable areas. A meta-analysis and a PEDro level of evidence were included for the studies included in this present review. The data used to compute the meta-analysis were used from the descriptive statistics and not identified from figures to reduce the incidence of bias. This present review was also an effort to address the limitations pertained by previously conducted reviews. For instance, a few of the previous systematic reviews carried out the search across few academic databases. For instance, Ruffieux et al[26] conducted the search across two academic databases, Boisgontier et al[6] across three databases, and Agmon et al[49] across four academic databases. This present review identified five widely utilized and reputed academic databases and continuously updated the data over a duration of 9 months. Additionally, few keyword search terms were identified as a possible limitation factor in the previous systematic reviews. However, during our literature

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search the authors utilized a broad variety of MeSH keyword search terms (Supplementary material), which might have increased the possibilities of including a wide array of studies. The meta-analysis carried out in this present review is the first to evaluate the effects of dual-task training on elderly participants. However, it also aimed to replicate previous findings, while addressing the increased heterogeneity.

Limitations

Several limitations persisted in the systematic review, which are to be considered while interpreting the results. The average quality of the included studies according to PEDro methodological quality scale was found to be 4.7, indicating a fair quality of the studies. A high risk of bias prevailed because of the limited number of RCTs. The restriction of search strategy limited to English language, exclusion of conference proceedings and observational studies might have resulted in omission of relevant research. Inability to retrieve descriptive statistics from the respective studies and including fewer studies in the meta-analysis was also a major limitation of this study.

This present study did not impose restrictions on the type of included dual task, in order to analyze the differential effects of complexity of dual task. Therefore, a higher chance of biasing and differential outcomes can be expected. Likewise, the systematic difference between the population group base statistics related to age, weight, gender, and disease severity led to difficulty in comparing studies. A majority of the incorporated studies had a small sample size, which generates a high possibility of a type II error.[120] The conclusions derived in the review based on incorporation of dual-task training in rehabilitation protocol are based on limited research.

Future directions

Future studies should focus on combining easier, nonverbal dual tasks in training during rehabilitation. Neuroimaging studies can provide additional insights for mechanisms involved during execution of nonverbal dual tasks. The review also suggests training fall-prone population groups to prioritize balance, ie, posture "first" in complex fall-prone environments; for instance escalators, narrow alleyways.[121] Likewise, nonverbal tasks utilized during activity of daily living can be analyzed in dual-task training regimes. Together, real-life implications can be drawn from these studies.

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Disclosure

The authors report no conflicts of interest in this work.

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Chapter 8: Literature review: Main findings & Interpretations

Main findings & interpretations

This literature review was conducted to develop a state of knowledge concerning the influence of auditory stimulations, dual-tasks on motor recovery in both healthy and population groups with neurological disorders. The main findings and the limitations in the scientific literature are as follows:

Findings:

1. Auditory stimulations can facilitate motor recovery in both healthy and population groups with neurological disorders.
2. Auditory stimulations facilitate motor recovery effectively as compared to conventional rehabilitation approaches for instance, electrical stimulation, virtual reality, physiotherapy, hydrotherapy etc.
3. The findings from the dose-response meta-analysis contradict conventional approach of thought that states more training is beneficial for recovery. The findings however suggest that a small training duration on an average ranging from 25-45 minutes lasting for 3-5 times a week can yield maximum increments in motor performance.
4. Training with auditory feedback can reduce incidence of cognitive overload and prevent movement re-investment i.e. conscious control of movement, prevent movement failure i.e. falls.
5. Auditory stimulations can facilitate recovery by acting on several mechanisms. For instance, facilitating activations in neurological pathways, instigating plasticity, smoothening musculoskeletal activation and more.
6. Rehabilitation approaches incorporating auditory stimulations are extremely cost-effective and follow best-practice principles in rehabilitation. Therefore, their application is highly plausible especially in developing countries where morbidity and mortality associated with movement disorders is high.

Limitations:

1. Joint proprioception: In the conducted literature review that evaluated a total of 6,147 studies. No study reported the direct influence of auditory stimulations on joint proprioception. Although, several studies speculated the beneficial influence on joint proprioception, no clinical evaluation has been performed till date. This lack of knowledge inhibits the interpretation concerning how auditory and proprioceptive modalities might converge to facilitate motor control and performance.

2. Lack of sonification research: In the literature review only few studies were identified that analyzed the influence of real-time kinematic auditory feedback on motor recovery. One of the review studies reported substantial enhancements in arm recovery (Fugl Meyer assessment: Sonification 1.3 vs Rhythmic auditory cueing 0.6) in stroke patients. Therefore, expanding the research concerning the beneficial influence of real-time auditory feedback on motor control and learning is a topic that warrants immediate research.
3. A training dosage of rhythmic auditory cueing has been comprehensively evaluated in the published literature. However, no study till date has evaluated the amount of training essential with real-time auditory feedback i.e. sonification.

The main findings from the literature allowed in a better understanding of the mechanisms by which auditory stimulations allowed enhancements in motor performance. Thereby, helping in development of efficient experimental protocols. Moreover, the gaps identified in the current state of literature will provide a clearer perspective of what specific aspects strongly warrant clinical research.

Experiments

Chapter 9: Auditory proprioceptive integration: Effects of Real-Time Kinematic Auditory Feedback on Knee Proprioception

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Auditory Proprioceptive Integration: Effects of Real-Time Kinematic Auditory Feedback on Knee Proprioception

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The purpose of the study was to assess the influence of real-time auditory feedback on knee proprioception. Thirty healthy participants were randomly allocated to control ($n = 15$), and experimental group I (15). The participants performed an active knee-repositioning task using their dominant leg, with/without additional real-time auditory feedback where the frequency was mapped in a convergent manner to two different target angles (40 and 75°). Statistical analysis revealed significant enhancement in knee re-positioning accuracy for the constant and absolute error with real-time auditory feedback, within and across the groups. Besides this convergent condition, we established a second divergent condition. Here, a step-wise transposition of frequency was performed to explore whether a systematic tuning between auditory-proprioceptive repositioning exists. No significant effects were identified in this divergent auditory feedback condition. An additional experimental group II ($n = 20$) was further included. Here, we investigated the influence of a larger magnitude and directional change of step-wise transposition of the frequency. In a first step, results confirm the findings of experiment I. Moreover, significant effects on knee auditory-proprioception repositioning were evident when divergent auditory feedback was applied. During the step-wise transposition participants showed systematic modulation of knee movements in the opposite direction of transposition. We confirm that knee re-positioning accuracy can be enhanced with concurrent application of real-time auditory feedback and that knee re-positioning can modulated in a goal-directed manner with step-wise transposition of frequency. Clinical implications are discussed with respect to joint position sense in rehabilitation settings.

Keywords: perception, rehabilitation, sonification, coordination, joint position sense

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INTRODUCTION

Real-time kinematic auditory feedback can be effective in enhancing motor perception, control, and learning (Effenberg, 2005, 2014; Sigrist et al., 2015; Effenberg et al., 2016; Dyer J. et al., 2017). The perception of additional real-time acoustic feedback driven by dynamic or kinematic movement parameters obviously supports sensory/perceptual-motor representations (Effenberg, 2005; Schmitz et al., 2013) by enhancing cross-modal stimulation (Scholz et al., 2015; Ghez et al., 2017), multisensory integration (Schmitz et al., 2013; Effenberg et al., 2016), internal motor simulation (Schmitz and Effenberg, 2017), and neural plasticity (Altenmüller et al., 2009; Ghai et al., 2017c). Literature indicates strong associations between auditory and motor areas for enhancing the performance in music (Lahav et al., 2013), breathing (Murgia et al., 2016), writing (Effenberg et al., 2015; Danna and Velay, 2017), sports (Sigrist et al., 2013, 2015; Effenberg et al., 2016), and rehabilitation (Altenmüller et al., 2009; Murgia et al., 2015; Pau et al., 2016; Scholz et al., 2016; Ghai et al., 2017c; Mezzarobba et al., 2017). Strong auditory motor couplings have also been confirmed in neuroimaging studies, where enhanced activation in cortical and sub-cortical structures associated with biological motion perception were reported (Scheef et al., 2009; Schmitz et al., 2013). Several underlying theories have been suggested to ascertain the beneficial effects of concurrent auditory feedback on motor performance. For instance, the concurrent auditory feedback is thought to amplify the brain's ability to integrate multiple congruent perceptual streams, leading to formation of stable internal feed-forward models (Wolpert and Miall, 1996; Calvert et al., 2000; Shams and Seitz, 2008; Van Vugt, 2013). Moreover the real-time availability of feedback can serve as an external guidance for motor execution (Dyer J. F. et al., 2017) as well as an error feedback (Altenmüller et al., 2009; van Beers, 2009; Sigrist et al., 2015; van Vugt and Tillmann, 2015), and can enhance motor imagery (Sigrist et al., 2013), cognitive-emotional functioning (Eschrich et al., 2008; Sihvonen et al., 2017; see also Sigrist et al., 2013).

A strong influence of real-time auditory feedback on motor performance (Eriksson and Bresin, 2010; Schmitz et al., 2014; Scholz et al., 2015; Sigrist et al., 2015; Danna and Velay, 2017; Dyer J. F. et al., 2017), indicates a proportional influence of auditory domain over proprioception (Pantev et al., 2001; Scholz et al., 2015; Effenberg et al., 2016; Danna and Velay, 2017; Sihvonen et al., 2017), and it becomes effective as an integral component of motor control and coordination process (Proske, 2005; Ghai et al., 2017a). Scholz et al. (2015) mentioned that spatio-temporal associations generated by real-time kinematic auditory feedback during motor execution might allow substitution of proprioceptive deficits, possibly by closing the sensorimotor loop (Altenmüller et al., 2009; Särkämö et al., 2016; Scholz et al., 2016). Dyer J. et al. (2017) and van Vugt and Tillmann (2015) further added that the concurrent auditory feedback might supplement the low temporal-perceptual resolution of the proprioceptive domain (Tinazzi et al., 2002). Danna and Velay (2017) in their recent study proposed auditory-proprioceptive substitution for the enhancements the authors reported in handwriting performance for deafferented subjects receiving concurrent auditory feedback. These findings draw inferences from literature pertaining to cross-modal stimuli processing (Stein and Meredith, 1993; Calvert, 2001; Bavelier and Neville, 2002). For instance, sensory convergence from different sensory modalities have been reported to provoke cross-modal interactions (Macaluso et al., 2000; Macaluso and Driver, 2001). Furthermore, these claims are supported by neuroanatomical studies, reporting the presence of long range cortico-cortical connections in between sensory cortices (Falchier et al., 2001; Foxe, 2009; Keniston et al., 2010; Butler et al., 2012), and multisensory integration sites (Chabrol et al., 2015; for a detailed review see Calvert, 2001). This might suggest the possibility of a level of interdependency that the sensory modalities might share with each other to generate an integrated multimodal percept (Macaluso et al., 2000; Macaluso and Driver, 2001; Bavelier and Neville, 2002; Butler et al., 2012). In addition, several psychophysical studies have reported strong associations between the auditory and motor areas (Jokiniemi et al., 2008; Chen et al., 2009; Yau et al., 2009; Wilson et al., 2010b; Butler et al., 2012). These findings are further supplemented by the neuroimaging studies, reporting shorter pathways between the auditory and motor cortices, especially for multisensory integration (Lang et al., 1990; Zatorre et al., 2007; Foxe, 2009; Keniston et al., 2010; Butler et al., 2012; Chauvigné et al., 2014; Ishikawa et al., 2015). This might explain the strong influence of such audio-tactile cross-modal stimuli in terms of processing temporal (Fujisaki and Nishida, 2009), and certain impact on spatial information (Belardinelli et al., 2009; Jimenez and Jimenez, 2017; for a review see Lu et al., 2013). Nevertheless, despite the vast amount of literature indicating a strong influence of the audio-motor coupling for sensorimotor processing (Ghai et al., 2017c,d,e, 2018), a gap in literature persists concerning its applications in rehabilitation (Danna and Velay, 2017; Ghez et al., 2017), and/or sports (Ghai et al., 2017c).

As mentioned before, proprioception is an integral component of the coordination processes of the body (Gentilucci et al., 1994; Laskowski et al., 2000; Smith et al., 2012; Aman et al., 2014; Ghai et al., 2016, 2017a). Deficits in proprioceptive perception are directly linked with poor sensorimotor and somatosensory functioning (Aman et al., 2014; Ghai et al., 2016), characterized by a wide range of musculoskeletal and neuromuscular disorders (Sacco et al., 1987; Jensen et al., 2002; Ribeiro and Oliveira, 2007; Gay et al., 2010; Konczak et al., 2012; Ghai et al., 2017a). Its predominant role in rehabilitation has been emphasized in several studies (Lephart et al., 1997; Laskowski et al., 2000; Ribeiro and Oliveira, 2007; Rosenkranz et al., 2009; Gay et al., 2010; Aman et al., 2014). Therefore, exploring the possible influences of concurrent auditory feedback on proprioception might provide multifaceted benefits. First and foremost, the outcomes might provide a better understanding of intervention designs in rehabilitation, and sport settings with auditory feedback. Moreover, the evaluation of audio-proprioceptive coupling during an arbitrary action (knee-joint proprioception) might allow a better understanding of trans-modal activity of auditory and motor domains beyond music and language (Altenmüller et al., 2009). Finally, a better comprehensive understanding might be developed to support the psychophysical (Butler et al., 2012), neurophysiological (Ishikawa et al., 2015), studies analyzing the multisensory and cross modal integration between auditory and proprioceptive domains. Till this date, only a handful of researchers have attempted to answer the possible effects of real-time auditory feedback on proprioception (Van Vugt, 2013; Scholz et al., 2016; Danna and Velay, 2017; Dyer J. et al., 2017; Ghez et al., 2017). However, their interpretations on proprioceptive-auditory substitution are mostly speculative. For instance, none of the performed studies excluded vision during the performance of the motor task. As a result, possible influences from the visual modality during multisensory or cross modal integration processes can be expected (Plooy et al., 1998; Verschueren et al., 1998; Lönn et al., 2000). Research indicates the importance of isolating inputs from specific sensorimotor structures to provide a better understanding of direct influence over proprioception (Gay et al., 2010).

In a first attempt we tried to analyse the effects of real-time auditory feedback on clinical aspects of knee joint proprioception in a joint position sense test (Sherrington, 1907; Dover and Powers, 2003; Van Vugt, 2013). Based on interpretations drawn from state feedback control theory (Wolpert and Miall, 1996; Shadmehr and Krakauer, 2008), we expected real-time auditory feedback to cause enhancements in knee-joint proprioception or. Moreover, in a second step, we tried to analyze the effects of subliminal transposition of real-time auditory feedback's frequency on auditory-proprioceptive perceptions. The motivation of this part of study was derived from psychophysical studies revealing strong evidence of convergence between auditory and motor systems for computing frequency (Pantev et al., 2009; Wilson et al., 2009, 2010a), especially within well matched stimuli reflecting a similar event (Foxe, 2009). We expected that if auditory feedback could influence proprioception, understanding the role of frequency in this attained effect could allow a better understanding of the results. We therefore, evaluated influence of any divergent step-wise transposition of frequency with real-time auditory feedback would allow directed modulation of proprioceptive perceptions in terms of knee position.

In this article two experiments are mentioned. The second experiment is an extension of the first study, which was conducted after the analysis of results. The experiment II follows the same design and protocol but differs in terms of the magnitude and direction of step-wise transposition of the frequency of the feedback. se experiments differ based on magnitude and direction of step-wise transposition. We expect the outcomes from this study to provide novel practical implications in rehabilitation and sports settings.

METHODS

Experiment I

Experimental Design

This whole CCT was carried out between August 2016 and February 2017. Participants were randomly allocated to experimental or control group. In each group, participants carried out the active (knee-joint) repositioning task with their dominant legs. The experimental group concurrently received real-time and transposed (0.25°/repetition) auditory feedback while performing the active knee re-positioning tasks. The control group received white noise. The experiment consisted of five treatment blocks. Re-positioning tasks without any auditory feedback were performed on the odd numbered blocks. Auditory feedback (real-time, modulated, white noise) was provided in the even treatment blocks. The participants performed 15 repetitions per angle in a block i.e., 30 repetitions per block. The target angle for the repositioning task was 40 and 75°.

Participants

Thirty participants, randomly divided in control [8 males/7 females; mean ± SD (age): 23.5 ± 2.5 years], and experimental group I (7 male/8 female; 24.2 ± 3.7 years) volunteered to participate in the study. All participants self-reported as healthy with no history of significant hip, knee, or back injury. Written informed consent was obtained from each participant, and ethical approval was obtained from the Ethics Committee of the Leibniz University Hannover. All participants underwent a baseline test for auditory capabilities (HTTS Audiometry) and were asked to fill a self-reported questionnaire post the experiment. All participants received eight Euros for their participation.

Experimental Procedure

Participants were comfortably seated with their feet on the floor, their back resting against a wall, and their pelvis stabilized (Tiggelen et al., 2008; Ghai et al., 2016). During the sitting position, the knee joint was maintained at the right angle. This position of the knee joint was considered as 0° and further extension from this position onwards was referred as positive angles from this value (Supplementary File 1). Participants wore wireless headphones (Sennheiser, Wedemark, Germany), and were blindfolded to eliminate visual cues. The experimenter passively moved the dominant leg to a previously identified target position (40 or 75°) in an open kinetic chain and held at the target angle to allow the participant to memorize the position (Selfe et al., 2006; Ghai et al., 2016). The experimenter, a physiotherapist, checked and rechecked the angle while using a handheld goniometer, and motion capture reading to confirm the target angle. The leg was then returned to the initial position, and following a 5 s interval, the participant attempted to reposition the leg at the same joint angle. The participant was instructed to repeatedly re-position the leg to the instructed angle with an instruction "please re-position your leg to the performed angle hold the angle for 2 s and then return it to the starting position." The experimenter counted 15 repetitions and asked the participants to stop. This protocol was repeated for both the target angles (40 and 75°), across 5 treatment blocks. During the first, third, and fifth treatment blocks no auditory feedback was provided to the participants. However, during the second treatment block the same protocol was followed with real-time auditory feedback i.e., the experimenter initially took the dominant leg to the target angles with real-time auditory feedback. Thereafter, the participants performed the same target angles with real-time auditory feedback. During the fourth block, the experimenter initially positioned the dominant leg passively with real time auditory feedback, after which participants re-positioned their knee unaware of the modulation in frequency of auditory feedback (Supplementary File 2). Dynamic repositioning accuracy was computed to determine discrepancies while consecutively repositioning the knee joint. For instance, the repositioning performance of 40, 38, 43, 37°… the computation of repositioning error was performed by subtracting the performed angle with the previous angle i.e., 38°–40°, 43°–38°, 37°–43°…and so on. After the experiment was concluded, the participants were asked to fill a four-point questionnaire. The questionnaire enquired about the perceived duration of the experiment, the fatigue level, the excerptions perceived if any in the quality of the auditory feedback (for identifying whether participants were consciously able to detect changes in the frequency of the real-time auditory feedback), and subjective rating for compliance with auditory feedback on a 10-point Likert scale. The experimental protocol lasted approximately for 45 min.

Real-Time Auditory Feedback Mapping

Real-time auditory feedback was generated using Python (version 2.7) and Csound version 6.0. Sound synthesis was based on a band-limited oscillator bank with lowpass filtering. Knee joint angle and angular velocity are mapped onto pitch and amplitude of the auditory feedback, respectively. During sitting the right angle at the knee joint is regarded 0°, and any extension from this point onwards is referred in positive values from this angle. The changes in angles from 0 to 90° of full extension is configured from 120 to 300 Hz of frequency change, respectively. Here, amplitude is a function of square of knee angular velocity which is relevant to kinematic energy. For the amplitude function, exaggerated representation of the angular position was added because, as the frequency increases, human ear gets less sensitive in identifying the same pitch differences. The exaggeration in amplitude can therefore complement the lack of sensitivity, which properly stimulates the human ears. These mapping functions are also provided as a mathematical equation for clarity.

$$\begin{aligned} Pit &= 2 \times \theta_{knee.joint} + 120 \ (Hz). \\ Amp &= \alpha\omega^2_{knee.joint} + \beta\left(\cos\left(90^\circ - \theta_{knee.joint}\right) - k\right). \end{aligned}$$

In the equations, Pit is pitch (audio frequency), $\theta_{knee.joint}$ is the knee joint angle, Amplitude is Amp, $\omega_{knee.joint}$ is joint angular velocity. The equation also includes coefficients α, β as well as a constant value, k.

Modulation of real-time auditory feedback was subtle and provided in an under-transposition manner. Here, the mapping information between audio frequency and knee angle was manipulated during repetitions. For example, 15 repetitions in a step-down transposition by −0.25° (−0.5 Hz/rep) at the target angle. Frequency was changed per repetition, for instance from 180 to 193 Hz which would be is equivalent to a change of the knee angle from 40 to 36.5° in the constant original mapping (Supplementary Files 3, 6) for 15 repetitions. A sample for both the real-time auditory feedback (Supplementary File 5) and modulated auditory feedback (Supplementary File 6) have been provided.

Kinematic Analysis

Repositioning error (RE) was assessed in each trial using XSENS MVN Biomech (XSENS Technologies B.V, Netherlands), in a configuration mode limited to the lower body. High reliability and validity of this inertial sensor based motion analysis device has been previously reported (Cooper et al., 2009; Zhang et al., 2013). Seven pre-identified inertial measurement units (IMUs) were placed by a physiotherapist on sacrum, lateral side of femoral shaft, medial surface of tibia, and tarus using velcro straps (Supplementary File 1; Zhao et al., 2016). The angular repositioning data, expressed in sensor coordinate frame was wirelessly recorded with a sampling frequency of 60 Hz in a laptop (Lenovo INC, Hongkong) and saved in MVN file format. Thereafter, the saved file was converted to XML format (MVNX) and imported in a Microsoft Excel spreadsheet. This format incorporates information concerning sensor data, segment kinematics and joint angles. Marked data points (highlighted in MVN file during recording) were matched with MVN recording graphs and the data was manually extracted by two researchers for further calculations. Absolute and constant error were then computed for characterizing the repositioning error in both the magnitude and direction of error, by considering the target angle as the previous consecutive angle to the current performance by the participant.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Science (V. 23.0, SPSS Inc., Chicago, IL). In 2 separate analysis for absolute and constant errors. We analyzed Repositioning Error (the dependent measure), by conducting a Group (Experimental/control) × block (1–5) × Angles (40/75°) RM-ANOVA with repeated measures on the last two factors. Effect sizes of the independent variables were expressed using partial eta squared ($\eta_p{}^2$), with effect sizes <0.01 considered to be small, effect sizes between 0.01 and 0.06 considered to be medium and effect sizes >0.14 considered to be large (Sedlmeier and Renkewitz, 2008). *Post-hoc* comparisons were performed using stepwise Bonferroni holm corrections. The overall significance level was set to 5%.

Results

Absolute Error

Figure 1 illustrates the absolute repositioning accuracy in both groups. The experimental group I, with real-time auditory feedback performed significantly better than the control group without auditory feedback as confirmed by the significant main effect of group [$F_{(1, 28)} = 6.92$, $p = 0.014$, $\eta_p{}^2 = 0.20$]. Furthermore, repositioning accuracy depended on block [$F_{(4,112)} = 10.16$, $p < 0.001$, $\eta_p{}^2 = 0.27$]. Differences between block were mainly caused by the auditory feedback in the experimental group I as shown by the interaction block*group [$F_{(4,112)} = 8.34$, $p < 0.001$, $\eta_p{}^2 = 0.23$]. A *post-hoc* test confirmed significant differences between the first and second block in the experimental group I ($p < 0.001$), but not in the control group ($p > 0.999$). Furthermore, the second ($p < 0.001$), but not the first ($p > 0.999$) block differed significantly between groups. After the removal of feedback this effect diminished. Accordingly, both groups performed in block 3 not significantly different than in block 1 (experimental group I: $p > 0.999$; control group: $p > 0.999$). Differences between angles were not significant [angles: $F_{(1, 28)} = 3.39$, $p = 0.076$, $\eta_p{}^2 = 0.11$; angle*group; $F_{(1, 28)} = 3.65$, $p = 0.066$, $\eta_p{}^2 = 0.12$; angle*block: $F_{(4,112)} = 0.46$, $p = 0.714$, $\eta_p{}^2 = 0.02$; angle*block*group: $F_{(4,112)} = 0.49$, $p = 0.690$, $\eta_p{}^2 = 0.02$].

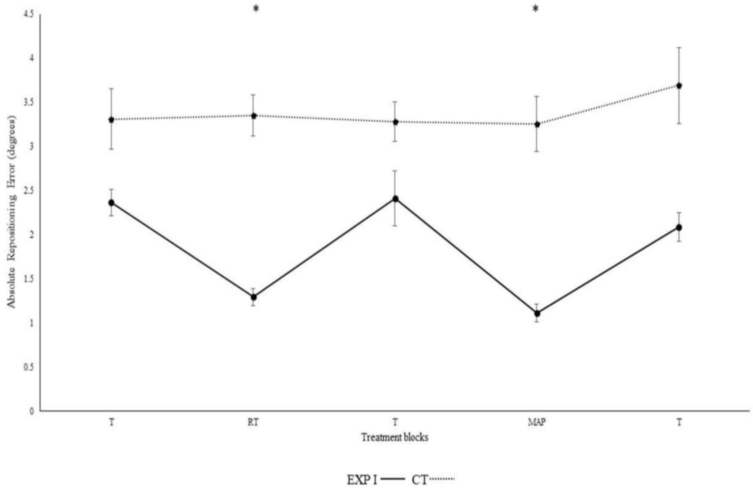

FIGURE 1 | Absolute mean and standard error of repositioning error (°) for the control, experimental group I (Dotted line represents control group. Darkened black line represents experimental group I, T: Proprioceptive test without auditory feedback, RT: Real-time auditory feedback, MAP: Acoustic mapping, CT: Control group, EXP: Experimental group). *Represents significant differences.

Constant Error

Figure 2 illustrates the constant repositioning error in both groups. The experimental group I with real-time auditory feedback performed significantly better than the control group without auditory feedback, as confirmed by the significant main effect of group [$F_{(1,\,28)} = 6.150$, $p = 0.019$, $\eta_p^2 = 0.18$]. Furthermore, a main effect was observed for block [$F_{(4,112)} = 4.320$, $p = 0.030$, $\eta_p^2 = 0.13$]. Differences between blocks were mainly caused by the auditory feedback in the experimental group I as shown by the interaction block*group [$F_{(4,112)} = 4.560$, $p = 0.002$, $\eta_p^2 = 0.140$]. A *post-hoc* test confirmed significant differences between the first and second block in the experimental group I ($p < 0.001$), but not in the control group ($p = 0.360$). Furthermore, the second ($p < 0.001$), but not the first ($p = 0.810$) block differed significantly between groups. After the removal of feedback this effect diminished. Accordingly, both groups performed in block 3 not significantly different than in block 1 (experimental group I: $p > 0.999$; control group: $p > 0.999$).

In the 4th block, modulation in frequency of real-time feedback were introduced. We observed significant differences between the 3rd and 4th block of experimental group I ($p = 0.001$), and as compared to the 4th block control group ($p < 0.001$). No such differences were observed between 3rd and 4th block in control group ($p = 0.660$). Likewise, in 5th block both groups performed not significantly different than in 1st and 3rd block (all p's > 0.05). Significant differences were also not evident when the 4th block was compared with the 2nd block ($p > 0.999$) i.e., modulated feedback with un-modulated feedback. Constant error was significantly larger for angle 40° as compared to 75° [$F_{(1,\,28)} = 21.80$, $p < 0.001$, $\eta_p^2 = 0.44$]. However, none of the interactions with the effects of the angles were significant, but not for angle*group; [$F_{(1,\,28)} = 0.40$, $p = 0.532$, $\eta_p^2 = 0.01$]; angle*block [$F_{(4,112)} = 0.36$, $p = 0.838$, $\eta_p^2 = 0.01$] angle*block*group [$F_{(4,112)} = 0.20$, $p = 0.941$, $\eta_p^2 = 0.01$].

Experiment II

Experimental Design

This whole trial was carried out between March 2017 and September 2017. Participants were allocated to experimental group II. Due to the identical experimental design as experiment I data from the same control group was utilized for comparison and the data from control group of first experiment was utilized. Here, the participants carried out the active (knee-joint) repositioning task with their dominant legs. The experimental group concurrently received real-time, modulated (±1.3°/repetition) auditory feedback while performing the re-positioning tasks. The control group received white noise. The experiment consisted of five treatment blocks. Re-positioning tasks without any auditory feedback were performed on the odd numbered blocks. Auditory feedback (real-time, modulated, white noise) was provided in the even treatment blocks. The participants performed 15 repetitions per angle in a block i.e., 30 repetitions per block. The target angle for the repositioning task was 40 and 75°.

Participants

Twenty healthy participants were included in experimental group II [10 females/10 males; mean ± SD (age): 26.8 ± 3.5 years]. All participants underwent a baseline test for auditory capabilities (HTTS Audiometry). All participants received eight Euros for their participation.

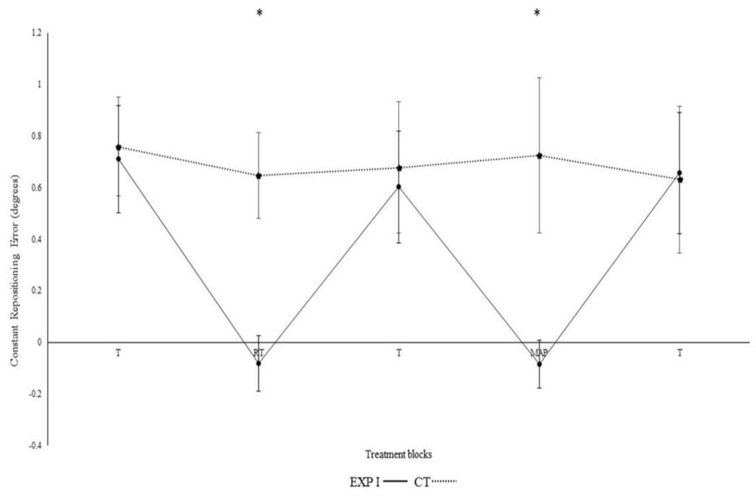

FIGURE 2 | Constant mean and standard error of repositioning error (°) for the control, experimental group I (Dotted line represents control group. Darkened black line represents experimental group I, T: Proprioceptive test without auditory feedback, RT: Real-time auditory feedback, MAP: Acoustic mapping, CT: Control group, EXP: Experimental group). *Represents significant differences.

Experimental Procedure

Same as experiment I.

Real-Time Auditory Feedback Mapping

Real-time auditory feedback was generated using Python (version 2.7) and Csound version 6.0. Sound synthesis was based on a band-limited oscillator bank with lowpass filtering. Knee joint angle and angular velocity are mapped onto pitch and amplitude of the auditory feedback, respectively. During sitting the right angle at the knee joint is regarded 0°, and any extension from this point onwards is referred in positive values from this angle. The changes in angles from 0 to 90° of full extension is configured from 120 to 300 Hz of frequency change, respectively. Here, amplitude is a function of square of knee angular velocity which is relevant to kinematic energy.

The modulation of real-time auditory feedback was subtle and provided in an over/under-transposition manner. Here as well, the frequency of the auditory feedback was manipulated per repetition, for 15 repetitions. However, the gradient of change was larger i.e., ±2.6 Hz (equivalent to ±1.3° change). Here during step down-up the change in frequency was equivalent as a change from 180 Hz (40°) to 167 Hz (34.8°) in the 5th repetition, and then to 182.6 Hz (41.7°) for the 10th repetition, and finally to 167 Hz (34.8°) for the 15th repetition. For instance, in step up-down manner 15 repetitions were accounted in three continuous steps: first five repetitions i.e., 1–5 transposition were performed in step-up manner i.e., 40, 41.3, 42.6, 43.9, 45.2°. Thereafter, for repetitions 6–10 continuously the direction of transposition was changed in step-down manner i.e., 43.9, 42.6, 41.3, 40, 38.7°. Lastly, for the final 11–15 repetitions the transposition was again changed to step-up manner i.e., 40, 41.3, 42.6, 43.9, 45.2°. This transposition change was randomized with step down-up approach during the study. For better clarity see Supplementary Files 4, 7.

The application of transposition was counterbalanced across four sub-groups i.e., sub-group I (40°: under-over-under, 75°: over-under-over), sub-group II (40°: over-under-over, 75°: over-under-over), sub-group III (40°: over-under-over, 75°: under-over-under), and sub-group IV (40°: under-over-under, 75°: under-over-under). Therefore, the number of participants was balanced across the conditions and increased to 20 i.e., 5 in each sub-group. A sample for both the real-time and modulated auditory feedback (Supplementary Files 6, 7) have been provided.

Kinematic Analysis

Same as experiment I.

Statistical Analysis

Like experiment I, in 2 separate analysis absolute and constant errors were compared with control group. Here, the control group from experiment I was utilized. We analyzed Repositioning Error (the dependent measure), by conducting a Group (Experimental/control) × blocks (1-5) × Angles (40/75°) RM-ANOVA with repeated measures on the last two factors. Additionally, data were decomposed for the 4th block, where the frequency was modulated, across four different sub-groups. Here, the data were normalized on an individual level to the real-time non-modulated auditory feedback by subtraction. The four sub-groups differed in performance of episodes of transposition i.e., sub-group I (40°: under-over-under, 75°: over-under-over), sub-group II (40°: over-under-over, 75°: over-under-over), sub-group III (40°: over-under-over, 75°: under-over-under), and sub-group IV (40°: under-over-under, 75°: under-over-under). Here, each episode represented the mean of five subsequent movements.

For the analysis the values for the over-transposition were inverted. Here, analysis of variance was performed on normalized repositioning errors as dependent variable and between subject factor sub-groups (I, II, III, IV) and within subject factor episodes (1–3) and angles (40/75°). Here, each episode represented the mean of five subsequent movements. *Post-hoc* comparisons were performed using step wise Bonferroni holm corrections.

Results

Absolute Error

Figure 3 illustrates the absolute repositioning error in both groups. Significant differences were observed in between blocks $[F_{(4,\,132)} = 38.3,\ p < 0.001,\ \eta_p^2 = 0.54]$ and interaction was evident for block*group $[F_{(4,132)} = 4.4,\ p < 0.01,\ \eta_p^2 = 0.12]$. A *post-hoc* test confirmed significant differences between the first and second block in the experimental group I ($p < 0.001$), but not in the control group ($p = 0.940$). Furthermore, the second ($p < 0.001$), but not the first ($p = 0.30$) block differed significantly between groups. After the removal of feedback this effect diminished. Accordingly, both groups performed in block 3 not significantly different than in block 1 (experimental group I: $p > 0.999$; control group: $p > 0.999$). None of the other results were significant group $[F_{(1,\,33)} = 2.0,\ p = 0.15,\ \eta_p^2 = 0.06]$, angles $[F_{(1,\,33)} > 0.01,\ p = 0.970,\ \eta_p^2 < 0.001]$, angle*group $[F_{(1,\,33)} = 0.01, p = 0.920, \eta_p^2 < 0.001]$, angle*block $[F_{(4,132)} = 0.3,\ p = 0.780,\ \eta_p^2 = 0.01]$, angle*block*group $[F_{(4,132)} = 0.77, p = 0.490, \eta_p^2 = 0.02]$.

Constant Error

Figure 4 illustrates the constant repositioning accuracy in both groups. The repositioning accuracy depended on block $[F_{(4,132)} = 14.2,\ p < 0.001,\ \eta_p^2 = 0.3]$. Differences between conditions were mainly caused by the auditory feedback in the experimental group I as shown by the interaction block*group $[F_{(4,112)} = 4.56, p = 0.002, \eta_p^2 = 0.14]$. A *post-hoc* test confirmed significant differences between the first and second block in the experimental group I ($p = 0.003$), but not in the control group ($p = 0.730$). Furthermore, the second ($p = 0.001$), but not the first ($p > 0.999$) block differed significantly between groups. After the removal of feedback this effect diminished. Accordingly, both groups performed in block 3 not significantly different than in block 1 (experimental group I: $p > 0.999$; control group: $p > 0.999$). In the fourth block, subliminal modulation in frequency of real-time feedback were introduced. We observed no significant differences in the 4th block of experimental group II ($p = 0.220$), control group ($p = 0.770$) as compared to the 3rd block. This difference was however, significant when compared to the control group ($p = 0.010$). Likewise, both groups performance in 5th block did not significantly different than in block 1, and 3 (experimental group II: $p > 0.999$; control group: $p > 0.999$). Significant differences were not evident when modulated feedback in 4th block was compared with un-modulated feedback in the 2nd block ($p > 0.999$). Differences were significant in between the angles $[F_{(1,\,33)} = 19.6,\ p < 0.01,\ \eta_p^2 = 0.37]$ i.e., constant errors were larger for 40° as compared to 75° and for angle*group; $[F_{(1,\,33)} = 14.5,\ p = 0.001,\ \eta_p^2 = 0.31]$, but not for group $[F_{(1,\,33)} < 0.01,\ p = 0.990,\ \eta_p^2 < 0.01]$, angle*block $[F_{(4,132)} = 0.6,\ p = 0.650,\ \eta_p^2 = 0.02]$, angle*block*group $[F_{(4,132)} = 0.89,\ p = 0.470,\ \eta_p^2 = 0.03]$.

Transposition Condition

For specifying the effect of transposition, we decomposed the data from the 4th block. We computed constant errors

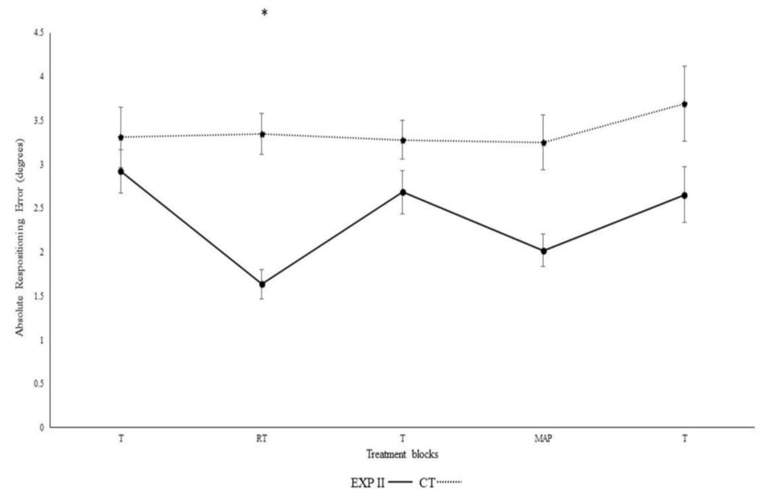

FIGURE 3 | Absolute mean and standard error of repositioning error (°) for the control and experimental group II (Dotted line represents control group. Darkened black line represents experimental group II, T: Proprioceptive test without auditory feedback, RT: Real-time auditory feedback, MAP: Acoustic mapping, CT: Control group, EXP: Experimental group). *Represents significant differences.

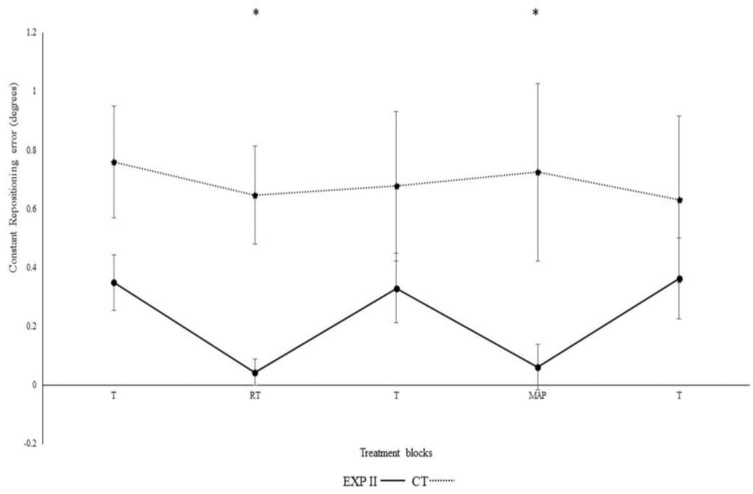

FIGURE 4 | Constant mean and standard error of repositioning error (°) for the control, and experimental group II. (Dotted line represents control group. Darkened black line represents experimental group I, gray line represents experimental group II, T: Proprioceptive test without auditory feedback, RT: Real-time auditory feedback MAP: Acoustic mapping step-down 0.25/rep for exp I, 1.3/rep for exp II, CT: Control group, EXP: Experimental group). *Represents significant differences.

separately for every five repetitions with transposition in the same directions. Each episode began with either over-under-over or under-over-under transposition. **Figure 5** shows the constant errors separately for participants with different episodes. Here, four sub-groups were distinguished with five participants each i.e., sub-group I performed for (40°: under-over-under, 75°: over-under-over), sub-group II (40°: over-under-over, 75°: over-under-over), sub-group III (40°: over-under-over, 75°: under-over-under), and sub-group IV (40°: under-over-under, 75°: under-over-under). **Figure 5** indicates that the re-positioning performance tended to compensate in the opposite direction in which the auditory feedback was manipulatively directed i.e., the participants knee flexion when the feedback was over transposed and vice versa for the under transposition. For the analysis, the over transposition repositioning errors were multiplied with −1.

The data were normalized for the analysis according to individual real-time auditory feedback performance of each participants. Further, step-up transposition findings were multiplied with −1 to allow the direction of transposition to be similar for all episodes (1–3). The statistical analysis revealed that episodes had no significant effect [Episode: $F_{(3.16)} = 1.51$, $p = 0.414$, $\eta_p{}^2 = 0.16$; angle*episode: $F_{(3.16)} = 0.72$, $p = 0.556$, $\eta_p{}^2 = 0.12$; block*episode: $F_{(6.32)} = 1.43$, $p = 0.233$, $\eta_p{}^2 = 0.22$; angle*episode*group: $F_{(6.32)} = 1.04$, $p = 0.420$, $\eta_p{}^2 = 0.16$] indicating that over- and under-transpositions did not differ in their impact. However, the transpositions were more effective in the second compared to the first episode ($p = 0.002$) as confirmed by post-hoc comparisons to the main effect of episode [$F_{(2,\,32)} = 7.39$, $p = 0.002$, $\eta_p{}^2 = 0.32$]. Differences between the first and the third ($p = 0.267$) or the second and the third episode ($p = 0.090$) were not significant.

To scrutinize whether the altered mapping between auditory feedback and angle changed the repositioning error we performed *t*-tests against zero separately for episodes (1–3). The results confirmed significant differences to zero in episode 2 ($p < 0.001$) and episode 3 ($p = 0.029$) but not block 1 ($p = 0.208$).

DISCUSSION

Results from the current experiment demonstrate beneficial effects of real-time auditory feedback on knee re-positioning accuracy. Significant enhancement in re-positioning accuracy was observed for both absolute ($p < 0.001$) and constant error ($p < 0.01$) and both within and across the experimental I and II (For clarity see **Figures 1–4**), with real-time auditory feedback. These findings agree with previous literature indicating strong associations between the auditory and motor domains (Foxe, 2009; Butler et al., 2012; Schmitz et al., 2013; Ishikawa et al., 2015), and support the possibility of the auditory-proprioceptive substitution hypothesis raised by Altenmüller et al. (2009), Danna and Velay (2017), and Scholz et al. (2015). In this experiment, the enhancement in re-positioning accuracy with real-time auditory feedback could possibly be associated with the "guidance hypothesis" (Schmidt, 1991; Park et al., 2000). The auditory feedback could have made it easier for the participant to identify the target angles, reduce errors, and re-produce the instructed target angles more precisely. This enhancement in re-producibility of target angles could also be due to high spatio-temporal precision of combined audio-motor domains (Hancock et al., 2013; van Vugt and Tillmann, 2015; Dyer J. et al., 2017), which also might have lowered the somatosensory

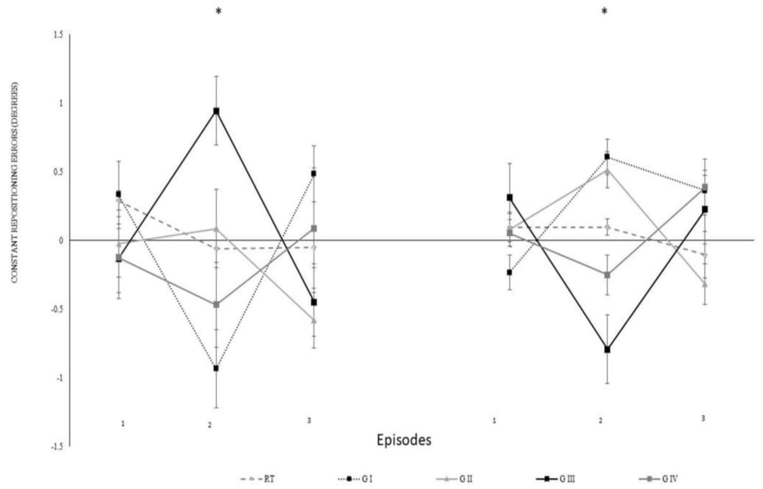

FIGURE 5 | Constant mean and standard error of repositioning error (°) for the experimental II, 2nd and 4th block, also for episodes (1–3). Difference in proprioceptive perceptions in between decomposed mapping conditions have been described for 5 sub-groups i.e., RT: real-time auditory feedback, sub-group I (G I: 40°: under-over-under, 75°: over-under-over), sub-group II (G II: 40°: over-under-over, 75°: over-under-over), sub-group III (G III:40°: over-under-over, 75°: under-over-under), and sub-group IV (G IV: 40°: under-over-under, 75°: under-over-under), and across 3 treatment blocks. The values on left represent 40°, and right 75° (RT: Real-time kinematic auditory feedback). *Represents significant differences.

mismatch negativity (Butler et al., 2012). These changes were also affirmed by Fujioka et al. (2012a). The authors reported modulations in the functional reorganization of spatio-temporal patterns of neuromagnetic β activity (between auditory and sensorimotor modalities; Fujioka et al., 2012a,b). Moreover, the enhanced activation in multisensory integration sites (such as neocortex, superior colliculi, striatum, and cerebellum) and action observation system (Superior temporal sulcus, BA 44, 45) might have aided in enhancing the saliency of executed movement patterns (Schmitz et al., 2013; Stein et al., 2014; Chabrol et al., 2015).

These enhancements in re-positioning accuracy however, were not as stable. Once the auditory feedback was removed in the third treatment block, the re-positioning errors returned to their initial levels. This lack of retention in re-positioning accuracy might be linked with over dependency of the participants with the concurrent feedback (Schmidt, 1991). Park et al. (2000) reported that the concurrent feedback can make the learners dependent on the feedback for maintaining their performances, possibly by bypassing the important internal correction and/or error detecting mechanisms (Schmidt, 1991). Moreover, the concurrent feedback might also limit a performer's initial movement error's (Winstein and Schmidt, 1990), which are thought to represent internal variability of the motor system and are considered as essential for the learning process (see dynamic system theory; Clark and Phillips, 1993). Similarly, the rapid change in knee re-positioning accuracy with substitution of auditory feedback could be affirmed with changes in attentional resources. Recently, Ghai et al. (2016) demonstrated that proprioception is adversely impacted under the influence of higher information processing constrains. However, Hopkins et al. (2017) suggested that cross modal cueing can avoid information overload in the native sensory modality by directing task-irrelevant information toward the underused sensory modality (Hameed et al., 2009). Here as well, the introduction of auditory feedback could have possibly allowed enhancements in re-positioning accuracy by transferring excess information in the sister domain (Lohnes and Earhart, 2011; Ghai et al., 2017b).

Furthermore, we analyzed modulations in knee repositioning performance with modulations in frequency of the auditory feedback. We confirmed with a self-reported questionnaire that participants were not able to consciously perceive any differences introduced in the frequency of the auditory feedback in both group I and II. However, our results demonstrate that these modulations were dependent on the magnitude of modulation introduced in the frequency. In experiment group I, the step-wise modulations were produced in a step-down transposition by 0.5 Hz/repetition (0.25° or 0.2%/rep). Although a trend toward step-wise modulation was observed for some individual participants, possibly due to their different inherent auditory perceptual capabilities (Kagerer et al., 2014), these differences could not be proven statistically ($p > 0.05$), when compared with real-time auditory feedback condition. Thereafter, upon deliberate examination in multiple pilot trials, a step-wise modulation by 2.6 Hz/repetition (1.3° or 1.1%/rep) was identified and included. The step-wise modulation was performed in three steps, across both the directions i.e., under, over, under transposition across 15 repetitions and vice versa. The direction was changed after five repetitions to avoid conscious perceptions i.e., five repetitions accounted for 6.5° change in one direction, and 19.5° overall change 15 repetitions. On the contrary, in experiment I only 3.5° change was evitable across 15 repetitions. During the initial analysis, no significant differences in knee repositioning accuracy were observed, possibly due to the negation of directional errors in perceptions across the blocks by step-up/down transposition. Therefore, upon factorial re-analysis of decomposed data for directional changes for knee repositioning, we observed significant effect of modulated auditory feedback as compared to real-time auditory feedback. The participants tried to compensate their knee re-positioning by tending to either extend or flex their knee's more with step-down and step-up transposition in frequency (**Figure 5**), respectively. In our analysis we observed a significant effect of transposition as compared to real-time auditory feedback and demonstrated a combined effect of the transposition to manipulate knee repositioning. As demonstrated in **Figure 6**, the participants could have taken time to adjust their re-positioning according to the dynamically transposed auditory feedback, or the significance in the next two episodes might be due to practice effect. Previously, published literature has demonstrated the effectiveness of audio-motor coupling due to subliminal changes in rhythmic auditory feedback (Repp, 2000, 2001; Tecchio et al., 2000; Kagerer et al., 2014). These findings also build up on psychophysical studies demonstrating the cross-sensory impacts of frequency modulation between auditory and motor domains (Foxe, 2009; Butler et al., 2012). We demonstrate that subliminal modulation of frequency can lead to goal-directed changes in knee repositioning. To the best of our knowledge, this study for the first time demonstrates modulation in knee repositioning due to subliminal changes in frequency of real-time auditory feedback. Previously, published literature has only demonstrated this association of audio-motor coupling with subliminal changes in inter stimulus interval for rhythmic auditory feedback (Repp, 2000, 2001; Tecchio et al., 2000; Kagerer et al., 2014).

Finally, building upon the strong correlation suggested for proprioceptive, re-positioning tasks (Vidoni and Boyd, 2009; Van Vugt, 2013), and similar open kinetic chain training regimes in rehabilitation (Tagesson et al., 2008; Fukuda et al., 2013; see review Glass et al., 2010), we believe enhancements observed in this experiment can have a range of practical implications in both rehabilitation and sports settings. Fukuda et al. (2013), for instance reported considerable enhancement in quadriceps, hamstrings strength recovery in patients with ACL reconstruction while performing similar non-weight bearing open kinetic chain movements at the knee joint. Moreover, changes in movement patterns associated with subliminal changes in frequency can also have practical implications. For instance, enhancement in breathing (Murgia et al., 2016), music learning (Hol, 2011; Lahav et al., 2013), arm reaching (Maulucci and Eckhouse, 2001; Schmitz et al., 2014; Scholz et al., 2016), gait (Maulucci and Eckhouse, 2011; Zhang et al., 2013; Mezzarobba et al., 2017), sports (Eriksson and Bresin, 2010; Sigrist et al., 2013), performance with real-time auditory feedback has been demonstrated in a few studies. Here, subliminal modulation in frequency during training can be introduced to enhance variability in movement patterns, which further can lead to a dynamic learning pattern (Stein et al., 2014). Moreover, introduction of subliminal changes can be used to prompt the patient or sports person to exceed their performance parameters without consciously perceiving them i.e., possibly reducing movement re-investment (see Masters and Maxwell, 2008). Future studies can evaluate these aspects of modulation in training paradigms in both sports and rehabilitation settings. Finally, the subjective rating of the compliance of auditory

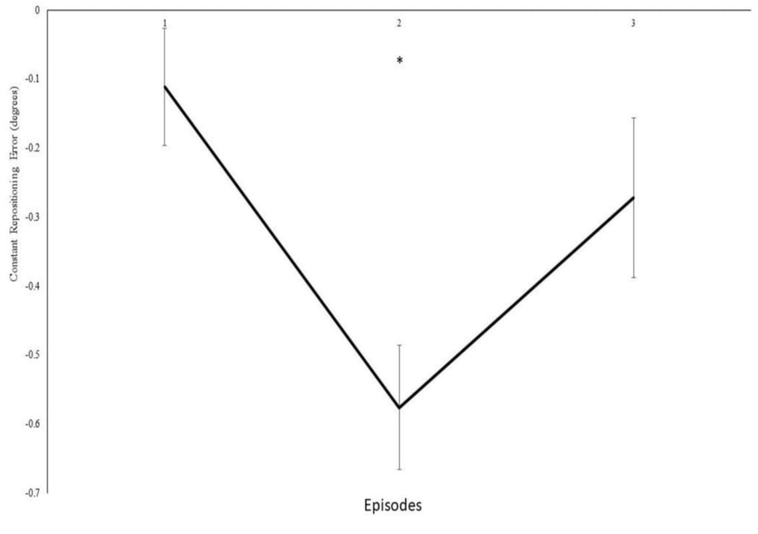

FIGURE 6 | Constant mean and standard error of the repositioning error (°) for the experimental II, 4th block, the values of transposition are normalized, and step-up transpositions have been multiplied with −1 to allow the direction of transposition to be similar for all three blocks. Mean values across the 2 angles for episodes (1–3). *Represents significant differences.

feedback in the experiment revealed higher rating for the auditory feedback (6.1 ± 1.0) as compared to the control condition (3.5 ± 1.5). A higher compliance with auditory feedback in past has been associated with enhanced motivation, attention and arousal (Menon and Levitin, 2005; Cha et al., 2014). Thereby, possibly supporting the applications of such type of concurrent auditory feedback in rehabilitation settings.

AUTHOR CONTRIBUTIONS

AE, GS, and SG developed the research question; SG, AE, and GS developed the research paradigm; SG conducted the experiment, collected the data, and wrote main parts of the paper; GS performed the statistical analysis supported by AE; SG contributed to the results section; T-HH was responsible for technical implementing and customization of the sonification system; AE supervised the project. All authors critically revised the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2018.00142/full#supplementary-material

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Chapter 10: Training proprioception with sound: Effects of real-time auditory feedback on intermodal learning

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Training proprioception with sound: effects of real-time auditory feedback on intermodal learning

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Our study analyzed the effects of real-time auditory feedback on intermodal learning during a bilateral knee repositioning task. Thirty healthy participants were randomly allocated to control and experimental groups. Participants performed an active knee joint repositioning task for the four target angles (20°, 40°, 60°, and 80°) bilaterally, with or without additional real-time auditory feedback. Here, the frequency of auditory feedback was mapped to the knee's angle range (0–90°). Retention measurements were performed on the same four angles, without auditory feedback, after 15 min and 24 hours. A generalized knee proprioception test was performed after the 24-h retention measurement on three untrained knee angles (15°, 35°, and 55°). Statistical analysis revealed a significant enhancement of knee proprioception, shown as a lower knee repositioning error with auditory feedback. This enhancement of proprioception also persisted in tests performed between the 5th and 6th auditory–motor training blocks (without auditory feedback). Enhancement in proprioception also remained stable during retention measurements (after 15 min and 24 h). Similarly, enhancement in the generalized proprioception on untrained knee angles was evident in the experimental group. This study extends our previous findings and demonstrates the beneficial effects of real-time auditory feedback to facilitate intermodal learning by enhancing knee proprioception in a persisting and generalized manner.

Keywords: perception; rehabilitation; sonification; coordination; joint position sense; motor learning

Introduction

Acquisition of a motor skill depends on the availability of task-relevant perceptual information that can mediate motor control and performance.[1,2] According to Wolpert *et al.*,[3] the process of skill acquisition involves the establishment of associations between motor and sensory variables, such as internal models, which represent features of movement execution. Here, amplifying the representation of the perceptual information by the means of augmented sensory feedback, such as real-time auditory feedback, can allow enhancements in performance.[4] The availability of additional perceptual information might allow a performer to selectively adjust their attention toward the task-relevant perceptual modality for effectively completing the task.[5–7] Moreover, such a feedback can enrich the development of perceptomotor representations by amplifying the brain's ability to integrate multiple congruent perceptual streams, therefore aiding in the formation of stable internal feed-forward models.[3,8]

Research conclusively suggests that mapping a performer's action with real-time auditory feedback can enhance both the perceptuomotor representations in the brain and motor performance.[8–12] Strong influence of real-time auditory feedback on motor performance was thought to be due to its influence over the proprioceptive modality.[13–16] Hasegawa *et al.*,[16] for instance, reported that training with auditory augmented biofeedback might facilitate the integration of auditory and proprioceptive systems. The authors suggested that the auditory system could promote a challenging, resource-dependent learning environment that might increase the reliance on proprioceptive

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information. Recent research by Ghai *et al.*[19] also demonstrated that real-time auditory feedback could influence knee–proprioceptive perceptions. The authors reported that concurrent application of auditory feedback can enhance knee joint repositioning accuracy. However, these effects were merely transient, as once the feedback was removed the proprioceptive errors returned to the levels observed before training. This goes in line with previous research reporting performance decrements with the withdrawal of augmented feedback (see guidance hypothesis in Ref. 17). According to the main reason for such performance, decrements could be an overdependence of a learner on an augmented feedback at the expense of relying on their intrinsic sources to support their performance when the feedback is removed as the retention test.[18] Conventionally, a motor skill cannot be considered "learned" until retention and/or skill transfer has been demonstrated. Therefore, a lack of retainable and transferrable effects can raise serious concerns regarding the viability and robustness of an intervention.

In the study by Ghai *et al.*,[19] two main limitations could have accounted for the lack of retainable effects. First, the use of a constant or blocked training regimen. In the experiment, participants were instructed to consecutively reposition their dominant knee 15 times at two different target angles, each. Here, a lack of variability (15 continuous repetitions for 40° and then 75°) could have been the main reason for performance decrements during the retention measurements. According to Cross *et al.*,[20] incorporating a variable training regimen can induce mechanisms of contextual interference, which might force a learner to effortfully reconstruct internal models in their working memory.[21,22] Therefore, promoting a persistent, robust representation of the skill set in the memory systems, which could then be retained and/or transferred to another skill set.[23,24]

Second, the short training duration (5–7 min) with auditory feedback by Ghai *et al.*[19] could also have served as an important factor in the lack of retainable effects.[25] Previous research analyzing the effects of auditory feedback on motor performance with shorter training durations such as Dyer *et al.*[26] has also demonstrated performance decrements during a 24-h retention (RET 24 h) measurements.[6] Here, the main reasons for the lack of performance retention could be interpreted from neuroimaging research by Bangert and Altenmüller,[27] and Ross *et al.*[28] These studies outline a temporal course necessary for establishing stable intermodal auditory–sensorimotor coactivation. Bangert and Altenmüller,[27] for instance, analyzed cortical activation patterns during an audio-motor training session (20 min). Based on EEG measurements, the authors reported auditory–sensorimotor coactivity emerging after 20 min of training. Similarly, Ross *et al.*[28] reported functional neuroplastic changes (higher positive peak (P2) activity and β-band oscillation) with a prolonged auditory–motor training session (30 min). Several of the systematic reviews and meta-analyses have also suggested a similar temporal course for auditory–motor training regimens to allow enhancements in motor performance.[29–34]

In the present research, we aim to address the limitations of the experimental design used, and also to elucidate the influence of auditory feedback on motor learning. An expanded intermodal auditory-proprioceptive training protocol has been developed to investigate the efficacy of real-time auditory information on proprioceptive motor learning. First, we extend the length of training duration with auditory feedback by incorporating more target angles (four versus two), a higher number of auditory–motor knee repositioning trials (288 versus 30), and with a bilateral distribution. Second, we induce variability in the training protocol by inducing randomized performance on four target angles, as compared with a consecutive performance by Ghai *et al.*[19] We also aim to deduce a temporal course for the development of auditory–motor coupling by incorporating pure proprioceptive measurements (without auditory feedback) between audio-motor training blocks. Finally, we also test the robustness of the intervention by analyzing both delayed retention on trained angles and generalized proprioceptive performance on untrained angles after completion of the experiment.

In the present study, we propose two main hypotheses: (1) based on extended auditory–motor training duration, a persistent enhancement of knee-proprioceptive accuracy (enhanced knee-proprioceptive performance) should be maintained on the trained angles in the absence of auditory feedback (immediately after 15 min and 24 h), and (2) the enhancements of knee-proprioception accuracy will be demonstrated on untrained repositioning angles of the same knee. Our study examines these two aspects of real-time auditory feedback on intermodal learning.

Methods

Experimental design

Participants were randomly placed in equal numbers to the control ($n = 15$) and the experimental ($n = 15$) groups. In each group, participants carried out active knee-joint repositioning tasks, bilaterally for four different angles of 20°, 40°, 60°, and 80°, designated as the four target angles. The experimental group received movement induced real-time auditory feedback, whereas the control group received ocean wave noise to control for possible effects of an unspecific acoustic stimulus. The design (Fig. 1) consisted of nine treatment blocks, which were preceded and followed by passive knee proprioceptive tests (PPTs). Repositioning tasks without any auditory feedback were performed on the first, third, fifth, and seventh blocks. These blocks analyzed proprioceptive performance on the four target angles. Thereafter, the 8th and 9th blocks analyzed proprioceptive performance on the same four angles in delayed retention measurements after 15 min and 24 h of the final test. Auditory feedback was provided in the second, fourth, and sixth blocks. After the final retention measurement at the ninth block (after 24 h), generalized proprioceptive accuracy was analyzed on three untrained angles of 15°, 35°, and 55°.

Participants

Thirty participants, recruited from the Department of Sports Science at the Leibniz University Hannover, were randomly allocated to the control (seven males and eight females; age (mean ± SD): 25.3 ± 3.2 years), and the experimental group (six males and nine females; age (mean ± SD): 23.2 ± 3.0 years) volunteered to participate in the study. All participants were self-reported as healthy with no history of significant hip, knee, or back injuries. Ethical approval was obtained from the Ethics Committee of the Leibniz University Hannover, and participants gave a written informed consent for participating in the study. All participants underwent a baseline auditory test (HTTS Audiometry) to check for normal hearing ability. All participants were paid €16 for their participation.

Procedure

Participants were comfortably seated with their feet in the air, their backs resting against a wall, and their pelvis stabilized.[19,35] During the sitting position, the knee joint was maintained at the right angle (Supplementary Fig. S1, online only). This position of the knee joint was considered as 0° and further extension from this position onward was referred to as a positive change in the angular values. Participants wore wireless headphones (Sennheiser®, Wedemark, Germany), and were blindfolded to eliminate visual information. Initially, a familiarization session was performed to accustom participants with the four target angles they had to perform during the experiment. Here, the experimenter passively moved the dominant leg to previously identified target angles in an open kinetic chain and held it at each angle for 2 s to allow the participant to memorize the position.[36] This process was repeated on the nondominant leg. The experimenter asked participants to memorize each target position as angle 1 (20°), angle 2 (40°), angle 3 (60°), and angle 4 (80°), on both legs. Participants received no information concerning the actual values of the angles they were performing.

After the familiarization session, a passive knee repositioning test was performed for the four target angles, bilaterally. Here, the experimenter passively positioned the leg at one of the four angles and held it for 5 seconds. Thereafter, the experimenter returned the leg at the initial 0° position. Next, participants were instructed to actively reposition their leg at the specific angle. This was repeated for the four target angles, bilaterally (see initial PPT (pretest) in Fig. 1).

Further, in the first block of the experimental setup (see PPT-1 in Fig. 1), participants were verbally instructed by the experimenter to perform the same four target angles (angles 1–4), with no auditory feedback, and without any prior passive knee repositioning instruction. The verbal instructions for the performance of angles were randomized as right leg/angle 1, right leg/angle 4, right leg/angle 3, and so on. A total of 32 repetitions were performed by the right leg. This process was repeated by the left leg. A total of 64 repetitions were performed in this block, which took about 8–10 minutes. Furthermore, before the commencement of the second block, participants were introduced to the auditory feedback (the control group was introduced to an

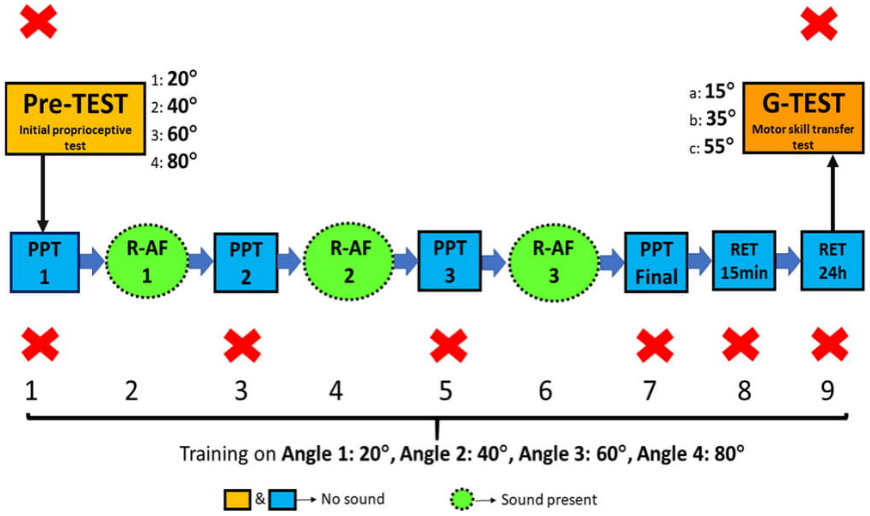

Figure 1. Experimental design. Green blocks represent training phase with real-time auditory feedback (R-AF1, R-AF2, and R-AF3), blue blocks represent repositioning blocks without auditory feedback (PPT-1, PPT-2, PPT-3, and PPT-final) and subsequent retention test blocks (RET 15 min and RET 24 h) without auditory feedback. The control group received ocean wave noise during the green training blocks. pretest, initial proprioceptive test; PPT, verbal repositioning test without auditory feedback; RET 15 min, a 15-min retention test; RET 24 h, a 24-h retention test; G-test, generalized PPT.

ocean wave noise). Here, the experimenter first passively repositioned the legs at four angles, bilaterally, and with auditory feedback. This was performed to ensure that participants could associate the four target angles with their respective sounds (Supporting Video S1, online only). After that, participants were verbally instructed to reposition their knee joints by themselves, in the presence of auditory feedback (see real-time auditory feedback (R-AF) 1; Fig. 1). Here as well, the verbal instructions for the performance of angles were randomized as right leg/angle 4, right leg/angle 3, and right leg/angle 1, and so on. This process was again repeated on the left leg. A total of 96 repetitions were performed in this block (48 right + 48 left). The duration of the training blocks (R-AFs) lasted for 15–20 minutes. Here, both the experimental and control groups trained with an identical duration.

After this, the third block analyzed proprioceptive accuracy without any auditory feedback (see PPT-2 in Fig. 1). Like the first block, participants were verbally instructed by the experimenter to actively reposition their knee joints at the four target angles in a randomized order. The procedure, total number of repetitions, and duration were identical to the first block. The fourth block was an auditory–motor training block (see R-AF2 in Fig. 1). Here, auditory feedback was present. Like the second block, the experimenter initially repositioned the participant's knee passively with auditory feedback. Thereafter, participants were verbally instructed, in a randomized order to reposition their knee joints. The procedure, total number of repetitions, and duration were identical to the second block.

The fifth block analyzed proprioceptive accuracy without any auditory feedback (see PPT-3 in Fig. 1). Like the first and third blocks, participants were verbally instructed, in a randomized order, to actively reposition their knee joints at the four target angles. The procedure, total number of repetitions, and duration were identical to the first and third blocks. Thereafter, the sixth block was a training block (see R-AF3 in Fig. 1). Here, auditory feedback was present. Like the second and fourth blocks, the experimenter initially repositioned the participant's knee passively with auditory feedback. Thereafter, participants were verbally instructed, in a randomized order to actively reposition their knee joints. The procedure, total number of repetitions, and duration were identical to the second and fourth blocks. The seventh block analyzed the proprioceptive accuracy in a final step without any auditory feedback (see PPT final in Fig. 1). Like the first, third, and fifth blocks, participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles. The procedure, total number of repetitions, and duration were identical to the first, third, and fifth blocks.

Thereafter, the eighth block analyzed the retention of performance after 15 min of completion of the seventh block (PPT final), without any auditory feedback (see a 15-min retention (RET 15 min) in Fig. 1). Like the first, third, fifth, and seventh blocks, participants were verbally instructed, in a randomized order, to actively reposition their knee joints at the four target angles. The procedure, total number of repetitions, and duration were identical to the first, third, fifth, and seventh blocks. The ninth block analyzed the retention of performance after 24 h of completion of the seventh block, without any auditory feedback (see RET 24 h in Fig. 1). Like the first, third, fifth, seventh, and eighth blocks, participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles. The procedure, total number of repetitions, and duration were identical to the first, third, fifth, seventh, and eighth blocks.

Finally, after the completion of the 24-h retention measurement, transferability of skill was analyzed in a generalized PPT (G-test). Here, the participants' performance on three completely untrained angles (15°, 35°, and 55°) was tested (see G-test in Fig. 1). Like the pretest, the experimenter first passively repositioned the knee at one of the target angles and held the position for 5 seconds. Thereafter, participants were instructed to actively reposition their leg at the specific angle. This process was repeated for all the three target angles (15°, 35°, and 55°), bilaterally. Figure 1 illustrates the entire experimental procedure. Moreover, a detailed breakdown of the blocks in terms of a total number of repetitions performed, the presence of auditory feedback and target angles performed has been illustrated in Supplementary Box S1 (online only). The experimental protocol lasted approximately for 100–120 minutes.

Auditory feedback used in this experiment was identical to that used by Ghai *et al.*[19] The changes in angles from 0° to 90° of full knee-extension were mapped to a frequency spectrum ranging from 120 to 300 Hz. A sample of auditory feedback has been provided in Supplementary Video S1 (online only). The mapping functions as a mathematical equation have been mentioned by Ghai *et al.*[19]

Kinematic analysis

Xsens® MVN Biomech (Xsens Technologies B.V., the Netherlands) in a lower body configuration mode was used to assess knee joint angles. Seven wireless inertial measurement units were positioned by the experimenter on participants using Velcro straps. The inertial measurement units were positioned on the sacrum, the lateral side of the femoral shaft, the medial surface of the tibia, and the talus. With the wireless data transmission, kinematic motion was recorded in a three-dimensional Cartesian coordinate system at a 60-Hz sampling frequency. The knee joint angle data are analyzed by an Xsens® MVN Studio 4.3 software (Xsens Technologies B.V.) that recorded the movement and the kinematic data in MVN file format. Thereafter, the repositioning data for each trial were matched with the MVN data recordings and were extracted manually by two researchers. The absolute error was calculated to quantify the magnitude of the repositioning error.[35] Studies have reported high reliability and validity of the Xsens® motion capture system for joint angular data measurement.[37,38] The total number of trials performed in this experiment was 742 (Supplementary Box 1, online only). No trial was excluded from the final analysis.

Statistical analysis

Statistical analyses were performed using Statistica (V. 12. StatSoft, Hamburg, Germany). According to the first research question, we wanted to investigate the changes of proprioceptive accuracy over time induced by auditory feedback training and whether changes persist in the retention tests after 15 min and 24 hours. Therefore, we submitted repositioning errors (the dependent measure) to a two-way ANOVA with the between-subject factor group (experimental/control) and the within-subject factor block (PPT-1, R-AF1, PPT-2, R-AF2, PPT-3, R-AF3, PPT final, RET 15 min, and RET 24 h). A post-hoc Bonferroni test allowed us to perform pairwise group comparisons for each block to scrutinize whether group differences emerge over time. Furthermore, it became possible to perform within-group comparisons between all proprioceptive blocks without auditory feedback (PPT-1, PPT-2, PPT-3, PPT final, RET 15 min, and RET 24 h) to test whether retention measures (RET 15 min and RET 24 h) differ from PPT1 and PPT final. The second research question was analyzed by a two-way ANOVA with the between-subject factor group and the within-subject factor test (pretest and G-test). Effect sizes of the independent variables were expressed using partial eta squared ($\eta_p{}^2$), with effect sizes < 0.01 considered being small, effect sizes of 0.06 considered being medium, and effect sizes >0.14 considered being large. The Bonferroni correction was performed for post-hoc analyses. The overall significance level was set to 5%.

Results

Effect of audio–motor training on proprioceptive accuracy

Knee repositioning errors of both groups are shown in Figure 2 (for descriptive statistics, see Supplementary Tables S1 and S2, online only). Both groups started at the same level but diverged from the second block on (R-AF1). This was due to the performance increase of the experimental group, which became evident when participants were provided with auditory feedback for the first time (R-AF1). Accordingly, an ANOVA yielded significance for the main effects as well as their interaction (group: $F(1,28) = 84.02$, $P < 0.001$, $\eta_p{}^2 = 0.75$; block: $F(8,224) = 3.24$, $P < 0.001$, $\eta_p{}^2 = 0.17$; block × group: $F(8,224) = 7.75$, $P < 0.001$, $\eta_p{}^2 = 0.22$). The Bonferroni-adjusted post-hoc comparisons revealed significantly better performance in blocks R-AF1, R-AF2, and R-AF3 for those participants who were provided with auditory feedback and not the control stimulus (all $P < 0.001$).

With respect to proprioceptive accuracy, groups did not differ significantly at the first two PPTs (PPT-1: $P > 0.999$; PPT-2: $P > 0.915$), but at all other PPTs (PPT-3, PPT final, RET 15 min, and RET 24 h). Furthermore, participants in the experimental group maintained their proprioceptive accuracy from PPT-3 onward. In more detail, PPT-3, PPT final, RET 15 min, and RET 24 h did not differ significantly from each other, but they all differed significantly from PPT-1 (all $P < 0.001$) and PPT-2 (all at least $P < 0.05$). In the control group, no differences were significant (all $P > 0.05$).

Generalization effect

Repositioning errors of the pretest and the generalization test (G-test) are illustrated in Figure 3. Prior to feedback exposure, both groups had the same level with respect to repositioning accuracy, which diverged post exposure. Accordingly, an ANOVA confirmed a significant group effect ($F(1,28) = 17.33$, $P < 0.001$, $\eta_p{}^2 = 0.38$) as well as a significant group × test interaction ($F(1,28) = 24.42$, $P < 0.001$, $\eta_p{}^2 = 0.47$). A post-hoc test of this interaction showed that between-group differences were not significant in the pretest ($P > 0.999$), but in the G-test ($P < 0.001$). Furthermore, generalized enhancement in knee proprioception was significant in the experimental ($P = 0.002$), but not in the control group ($P = 0.051$).

Discussion

This experiment for the first time analyzed the effects of real-time auditory feedback on knee proprioceptive learning. Here, active knee repositioning trials were performed for the four target angles (20°, 40°, 60°, and 80°), bilaterally, and with or without additional real-time auditory feedback. The main findings of our study are:

1. Real-time auditory feedback significantly enhanced knee proprioception (lower repositioning errors).
2. Significant enhancements in knee proprioception were observed in the experimental group after 30–40 min of training, evident from the PPT-3 and were also evident in the final PPT.
3. Significant enhancements in knee-proprioception accuracy were also evident in the experimental group during delayed retention measurements after 15 min and 24 hours.
4. Significant enhancements in knee proprioception were also demonstrated in the experimental group during a knee G-test on completely untrained angles (15°, 35°, and 55°).

In agreement with our previous study, beneficial effects of real-time auditory feedback on proprioception were observed in the training blocks (R-AF in Figs. 1 and 2).[19] The mechanisms underlying such benefit are likely to be multifactorial. For instance, auditory feedback could have provided external guidance for repositioning,[12] enhanced error feedback,[6] enhanced multisensory integration,[39] strengthened perceptuomotor representations,[40] allowed selective attentional allocation,[41,42] and more[43,44] (for a detailed discussion, see Ref. 19).

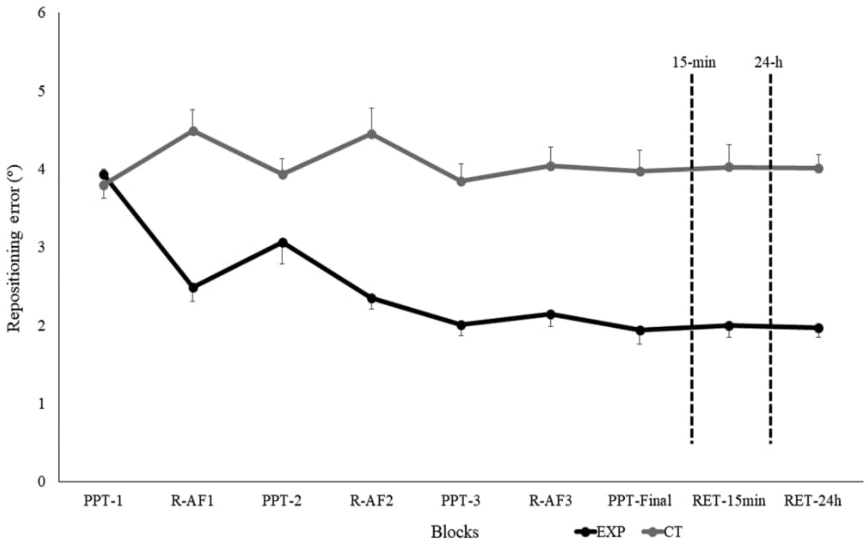

Figure 2. Absolute mean and standard error of repositioning error (°) for the mean of four angles in control, experimental group. Darkened black line represents experimental group. Darkened gray line represents control group. PPT, verbal repositioning test; R-AF, training block with a real-time auditory feedback; RET 15 min, a 15-min retention; RET 24 h, a 24-h retention test.

In this study, our focus was to address the limitations of Ghai *et al.*,[19] by demonstrating knee-proprioceptive enhancements during retention and G-tests. We analyzed whether modifications in terms of variability in training and prolonged training duration could influence knee-proprioceptive learning. First, we adapted our auditory–motor training intervention in terms of duration by increasing the number of angles (four), and the number of auditory–motor training repetitions (288), performed bilaterally. In agreement with our hypothesis, enhancement in knee-proprioceptive accuracy was observed with the prolongation of auditory–motor training. We report significant enhancements in proprioception accuracy observed from the PPT-3 (Fig. 1). These enhancements in proprioception accuracy were evitable after two blocks of auditory–motor training (R-AF1 and R-AF2), which lasted for approximately 30–40 min (Fig. 2). This conclusion is drawn on the basis that a single R-AF1 auditory–motor training block (15–20 min) allowed only transient enhancements in knee-proprioception accuracy (similar to our previous study[19]). Nevertheless, after the second blocks of auditory–motor training (R-AF1 and R-AF2), the enhancements in proprioception were stable and were also evident in the final proprioceptive and retention tests (PPT final, RET 15 min, and RET 24 h). However, this was not the case for the control group, which received task-irrelevant ocean wave noise. Here, the proprioceptive performance remained largely unchanged during the entire course of training. Inference for this different time-dependent development of proprioceptive accuracy between the experimental and the control groups could be affirmed to the findings of Auksztulewicz *et al.*[45] The authors reported that task-relevant sensory information could allow the modulation of behavior in terms of enhanced spatial–temporal predictability and discrimination. On the contrary, task-irrelevant feedback adversely affected this predictive mechanism, possibly because of the wasteful processing by cognitive resources.[45] Therefore, explaining the differential time-dependent changes in proprioceptive perceptions between the experimental and the control groups.

Likewise, the findings concerning time-dependent enhancement in proprioceptive accuracy in the experimental group are also in line with the results of neuroimaging studies outlining a temporal course for the establishment of auditory–sensorimotor coactivation.[27,28] Furthermore, with respect to our retention measurements (after 15 min and 24 h), findings of Tremblay *et al.*[46]

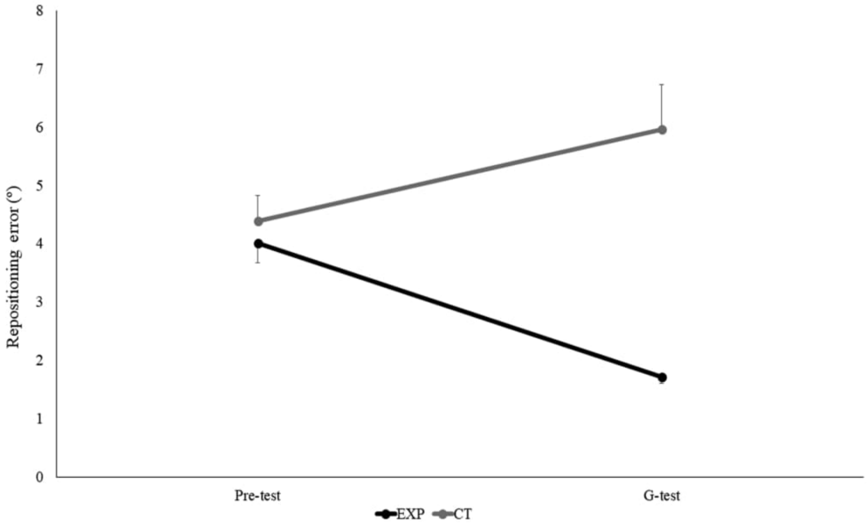

Figure 3. Absolute mean and standard error of repositioning error (°) for the mean of four angles (20°, 40°, 60°, and 80°) in pretest condition, and three untrained (15°, 35°, and 55°) angles in G-test condition for both experimental and control groups.

are referred to. Tremblay *et al.*[46] suggested that repeated exposure of an auditory stimulus during audio-motor training might effectively prime the auditory system, thereby allowing retention of skill even after a long period of time.[46] Similarly, in their study, Hasegawa *et al.*[16] revealed that training with auditory biofeedback led to robust, retainable enhancements in spatial and temporal components of postural stability.

Additionally, in the present experiment, we demonstrate the robustness of auditory–motor coupling in a G-test. Here, participants in the experimental group demonstrated a "generalized" enhancement in knee proprioception on completely untrained angles after 24 h of the experiment. Here, relevant to the findings of Bangert and Altenmüller,[27] we presume that auditory–motor training could have facilitated the development of an interfaced mapping (intermodal coupling between the auditory and proprioceptive systems). In simpler terms, participants performed knee extensions from the initial starting position of 0° to the four target angles. We believe participants could have developed an implicit, interfaced audio–proprioceptive map for the entire range of motion performed from 0° to 80°. This could also mean that participants not only learned to reproduce the pitch precisely but learned a more precise use of proprioceptive information from the knee joint. This eventually could have allowed enhanced performance on both the trained and untrained angles.

Furthermore, modifications in terms of variability (randomized performance of target angles and a leg) were also introduced to our previous training paradigm.[19] This inclusion of variability could have also played an important role in maintaining proprioceptive performance during retention and G-tests.[24,47,48] Several reasons can be asserted for this enhancement in motor performance based on the theory of contextual interference. According to Battig,[22] a variable training paradigm could have allowed a learner to encode different strategies such as using multiple routes to acquire a new skill. This could then have promoted a more elaborate memory representation as compared with single elaborate strategies such as constant training.[22] Furthermore, this strategy could allow an enhanced retention and skill transfer by promoting retrieval of a learned skill set through multiple retrieval routes established during variable training. Moreover, a variable training regimen might also promote effortful execution on behalf of a learner, eventually developing a stronger representation of performed motor skill set. This then might promote the development of efficient action plan reconstruction which can allow enhancements in performance during both retention and motor skill transfer tests.[49] Neuroimaging studies also confirm that the indulgence of variability during training can promote a broader network of sensorimotor, premotor–parietal networks, and subcortical areas as compared with constant training.[20,50] Likewise, the longitudinal analysis demonstrated stable or increased activation in areas associated with motor preparation, sequencing, and response selection in the group training variably.[20] In our previous study, we assumed that a constant training on the two target angles (40° and 75°) could have been one of the main reasons for the lack of retainable effects in the consecutive retention block. Nevertheless, in the present study, retainable and generalized enhancements in the proprioceptive performance might also have been due to the indulgence of variability in auditory–motor training regimen.

As an additional and important aspect, we postulate that an intermodal integration of auditory and proprioceptive information could have further enhanced the spatial contingency,[51] as was demonstrated in the current repositioning task. According to Effenberg *et al.*,[8] convergent sensory feedback, which shares a high level of spatiotemporal proximity, can get implicitly fused to promote intermodal learning (in this case auditory and proprioceptive).[10] Here, an additional inference can be drawn from literature emphasizing the importance of intermodal knowledge for obtaining spatial knowledge of the body in space.[52,53] Likewise, evidence from neuroimaging studies also supports the notion that a high level of stimulus–response consistency (meaningful organization of perceptual and motion events) can promote sensorimotor coactivations[27] and motor priming.[54] Therefore, we propose that in the current study, the convergence of the perceptual modalities (auditory–proprioceptive) due to the comprehensive audio-motor execution could have allowed a feature overlap between perception and action,[10,55,56] and/or supported the development of important amodal relations.[53] This then could have provided a platform for the development of consistent sensorimotor representations perceived in a unified manner, therefore enhancing intermodal learning.[51,53] In terms of neuroplastic changes that might have taken place with our auditory–motor training paradigm, we interpret our results from the findings of Classen *et al.*[57] Based on the findings of these authors, we presume that the mechanisms of short-term potentiation were involved in our present study.[57] A major limitation persisted in our study in terms of the generalization proprioception test. Here, we compared initial performance of the four target angles with three untrained angles (G-test: 15°, 35°, and 55°). This indirect comparison might limit our interpretations as to the generalized proprioceptive influence of auditory–motor training on terminal knee angles of $>55°$.

In conclusion, we report significant enhancement of knee-proprioception accuracy with real-time auditory feedback. Moreover, we report that modification of an auditory–motor training paradigm, in terms of longer training duration, and variable training regimen can allow retainable (after 15 min and 24 h) and generalized (skill transfer on untrained angles) enhancements in proprioceptive accuracy. In terms of practical applications, we strongly refer to research outlining the beneficial aspects of joint position sense (similar to the present joint repositioning task) in musculoskeletal disorders.[58,59] Research suggests that the sense of joint position possibly mediates thixotropic changes in muscle spindles and slow-adapting mechanoreceptors.[60–62] Evidence from knee studies also confirms the predominant role of mechanoreceptors in the ligamentous structures of the knee joint (especially cruciate ligaments).[61,62] Therefore, enhancements observed in the perception of knee joint position sense in the current study could be applicable both as a prophylaxis[58,63] and a rehabilitation strategy for many knee disorders, such as a meniscal tear, cruciate ligament injuries, knee arthroplasty, and patellofemoral pain syndrome.[58,64–67]

Finally, a plausible explanation for our findings can be the auditory system's high-resolution capability of pitch differences and temporal features. Higher auditory resolution could have trained the comparably lower resolution proprioceptive system in both domains via intermodal referencing. Such enhancements that are based on intermodal processing between modalities of different perceptual characteristics could be addressed, in this context, as core mechanisms of intermodal learning. Here, the feedback can simultaneously assist in shaping the perceptuomotor representations without the need for attention and higher cognitive resources.[8,68]

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Supporting information

Additional supporting information may be found in the online version of this article.

Figure S1. Illustration of the experimental setup and IMU sensor placements (for representational purpose only).

Video S1. Sample MVN file depicting four repetitions first for the right and then for the left knee for angles 1, 2, 3, and 4 repetitions performed with real-time auditory feedback (the position of the trunk is not a true position because the upper body was not tracked; the real position is demonstrated in Supplementary Fig. S1, online only).

Box S1. The breakdown of experimental blocks in terms of the angles trained in the block, the presence of sound, that is, on/off and total number of trials performed.

Table S1. Descriptive statistics for absolute error (mean ± standard error of mean) in the experimental and control groups.

Table S2. Individual absolute mean repositioning error for the experimental (EXP) and control groups (CT).

Author contributions

A.O.E. and S.G. together with G.S. developed the research question. S.G., A.O.E., and G.S. developed the research paradigm. S.G. conducted the experiment, collected the data, and wrote the main parts of the paper. G.S. performed the statistical analysis supported by A.O.E. and S.G., and contributed to the results section. T.H. was responsible for technical implementation and customization of the sonification system. A.O.E. supervised the project. All authors critically revised the paper.

Competing interests

The authors declare no competing interests.

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Chapter 11: Auditory guidance of imagined movements: Effects of real-time auditory feedback (sonification) guided mental imagery on knee proprioception

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Abstract

Motor imagery training has been realized in sports and motor rehabilitation successfully. With decreased ability of physical training due to limitations of cognition or physiology mental training is of increasing relevance. A new kind of auditory self-guided motor imagery training (ASG-MIT) is introduced and applied here, using individual acoustical models created by one's own movement kinematics in the physical training session in advance to ASG-MIT. Results demonstrate enhanced efficiency of ASG-MIT on a knee angle repositioning-task compared to conventional motor imagery and control groups. ASG-MIT seems to lead towards more specific allocations of sensory-motor representations resulting in more precise internal simulations during imagery. ASG-MIT is applicable on performance optimization in sports as well as in motor rehabilitation in future: On Polyneuropathy or stroke induced hemiparesis etc. Especially on Parkinson patients therapeutic use of established ASG-MIT in combination with real-time movement sonification on movement therapy is a promising approach. (WHO Trial:DRKS00014244)

Introduction

Proprioception is integral during motor planning, control and learning (Collins, 2009). Literature reports that deficits in proprioception are strongly correlated with higher predisposition to injuries and movement disorders (Fridén, Roberts, Ageberg, Waldén, & Zätterström, 2001; Lephart, Kocher, Fu, Borsa, & Harner, 1992). Deficits in proprioceptive afferents might affect the development of perceptuomotor representations and exacerbate motor deficits (Meyer, Karttunen, Thijs, Feys, & Verheyden, 2014; Sober & Sabes, 2003). Research indicates that augmented auditory knowledge of performance enhances the performance in a dynamic balance task (Hasegawa, Takeda, Sakuma, Mani, Maejima, & Asaka, 2017). Nevertheless, recent studies have reported that this deficit can be supplemented by a native sensory modality which might share high level of spatiotemporal congruency with the proprioceptive modality during skill acquisition (Dyer, Stapleton, & Rodger, 2017; Effenberg & Schmitz, 2018; Sigrist, Rauter, Marchal-Crespo, Riener, & Wolf, 2015). More recently Ghai, Schmitz, Hwang, and Effenberg (2018a), too reported beneficial effects of real-time auditory feedback on knee-proprioceptive accuracy. The authors suggested that high spatiotemporal congruency between the auditory and proprioceptive inputs might induce a cross-modal exchange of inputs and thereby enhancing knee-proprioception subsequently. Schmitz, Mohammadi, Hammer, Heldmann, Samii, Münte et al. (2013) in an fMRI study reported that mere observation of a congruent audio-visual stimuli amplified the activation in the human action observation system including the cortical and sub-cortical structures of the motor loop.

Likewise, research by Ghai, Schmitz, Hwang, and Effenberg (2018b) reported that these beneficial effects of auditory feedback on proprioception are not limited to a cross-modal exchange of information. On the contrary, the auditory feedback can also be utilized in a training regimen being based on the principles of multisensory integration. (Ghai, Schmitz, et al., 2018b; Viswanathan, Fritz, & Grafton, 2012), demonstrated that knee-proprioceptive learning can be facilitated in a sustainable manner with self-generated real-time auditory feedback. The authors demonstrated that this modification in the auditory motor training regimen allowed enhancements in proprioceptive accuracy after 30-40 minutes of auditory motor training. In the current research we aim to extend the findings of this research by elucidating the joint influence of self-auditory guided motor imagery (ASG-MIT) on knee proprioception. Mental imagery is an established training strategy that plays a critical role in enhancing motor performance by working on the motor planning phase of a movement (Shenton, Schwoebel, & Coslett, 2004; Willems, Hagoort, & Casasanto, 2010). Literature reports that imagined and executed movement share a high level of spatio-temporal congruence (Heremans, Helsen, De Poel, Alaerts, Meyns, & Feys, 2009), are bound by the same motor laws , and lead to similar autonomic changes in the body (Pinto, Ramos, Lemos, Vargas, & Imbiriba, 2017). Previous studies have confirmed that disruptions in sensory afferent information can disrupt motor imagery (McCormick, Zalucki, Hudson, & Lorimer Moseley, 2007). Therefore, it can be expected that externally supplementing the sensory information might also support the motor imagery of the simulated movement.

Previously, demonstrated that external sensory cueing can facilitate the vividness, spatio-temporal resolution of the motor imagery. The participants in this study performed/imagined cyclic wrist movements in the presence/absence of auditory cues. The authors reported that movement related auditory cues facilitated motor imagery as demonstrated for higher scores in vividness and temporal congruence with the application of external auditory cueing. Similarly, beneficial effects of auditory cued motor imagery have been reported to facilitate gait recovery in patients with neurological disorders (Ghai & Ghai, 2018; Seebacher, Kuisma, Glynn, & Berger, 2016). Based on the findings of (Ghai, Schmitz, et al., 2018b), we expected that modifying the experimental paradigm by inducing mental imagery with concurrent auditory guidance might even enhance the perceptuomotor representations of the movement i.e. during mental imagery. Here, the intricate auditory-motor interfaced mapping after the auditory-motor training could further allow additional enhancements in feedforward and feedback information that in turn can facilitate proprioception. Therefore, we deduced three hypotheses for the current experiment.

Efficiency of multimodal training

1) According to our previous findings , we expect auditory-motor training to enhance knee-proprioception persistently.

Efficiency of multimodal training

2) ASG-MIT enhances knee-proprioception compared to conventional mental imagery or no mental imagery persistently.

Specific vs. Generalization

3) Effects of auditory-motor training and auditory guided mental imagery are not limited to the trained angles but are given for the whole trained range of motion.

Methods

Experimental Design

Forty-two participants were randomly placed in equal numbers to control group (CT, n=14), experimental group performing conventional mental imagery without auditory guidance (EXP MP, n=14) and experimental group performing mental imagery with auditory guidance (EXP ASG-MIT, n=14). All the groups initially trained identically with auditory feedback. Thereafter, the interventions in the groups differed. For instance, CT group performed no mental imagery at all, instead they were asked to solve mathematical equations in a non-verbal manner. The EXP MP group performed mental imagery without any guided auditory feedback i.e. they heard ocean waves as "shame acoustics" during the mental imagery phase. The EXP ASG-MIT group performed mental imagery with self-recorded auditory feedback. In each group, participants executed a verbally instructed, active (knee-joint) repositioning task, bilaterally for four different angles 20°, 40°, 60° and 80°. The experiment consisted of nine treatment blocks, which were preceded by a knee repositioning test (pre-test). Re-positioning tasks on four angles i.e. 20°, 40°, 60°, and 80° without any auditory feedback were performed on 1st, 3rd, 5th, 7th, 8th and 9th block. Here, the 8th and 9th block represented retention measurements post 15 minutes and 24 hours respectively. Auditory feedback was provided in the 2nd, 4th, 6th and 8th block. Post retention measurement, proprioceptive accuracy was tested in a generalized knee proprioception test i.e. G-test for four untrained target angles i.e. 10°, 30°, 50° and 70. This study was registered at the German Clinical Trian Registry and WHO International Clinical Trials Registry Platform (DRKS ID: DRKS00014244).

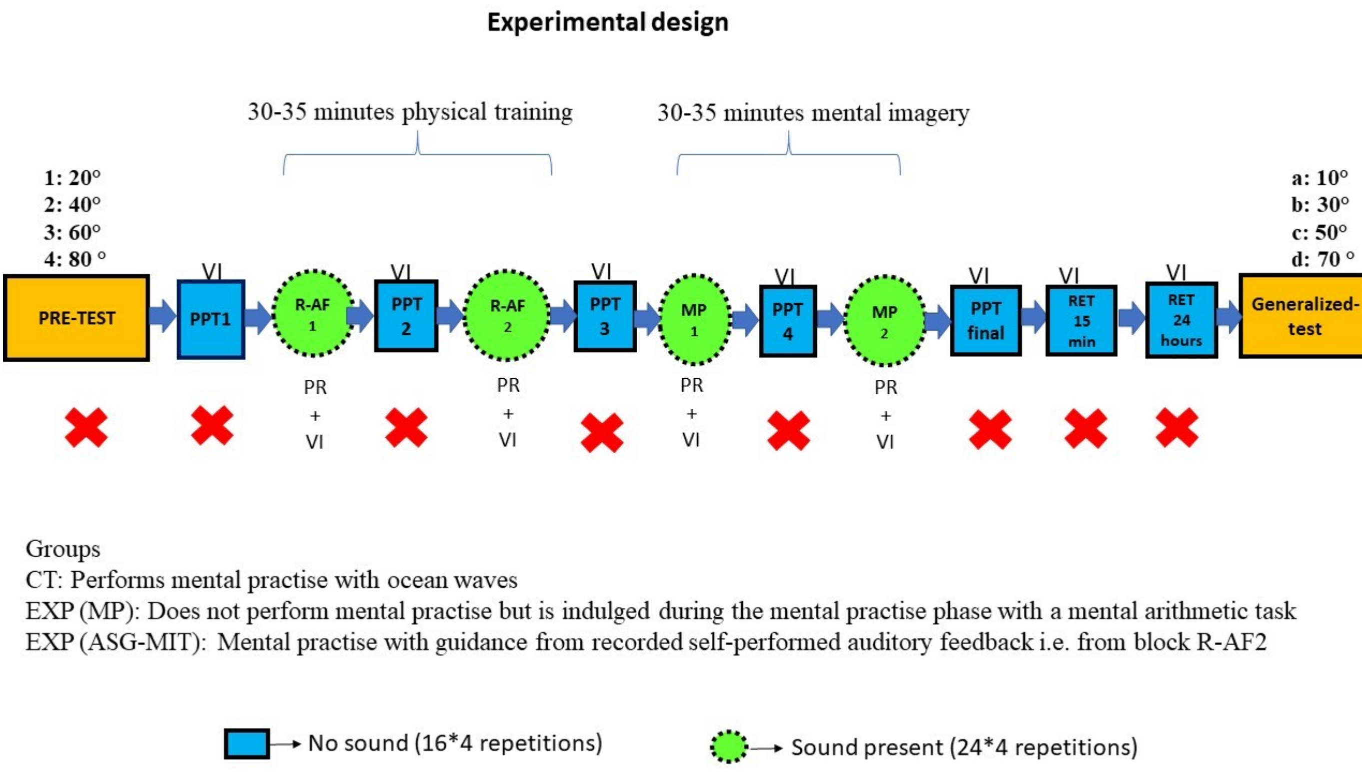

Figure 1 Experimental schematics for each block performed by three groups. Green blocks represent active training phase with real-time auditory feedback (R-AF1, R-AF2), and mental imagery (MP1, MP2) blue blocks represent initial and further re-positioning blocks (PPT-1, PPT-2… PPT-Final) and retention measurements (RET 15min, RET 24 hrs) without auditory feedback. (Pre-test: Initial proprioceptive test, PPT 1: verbal re-positioning test without auditory feedback, R-AF: Training block with real-time auditory feedback, MP: Mental imagery blocks, RET 15min: 15 min retention, RET 24hrs: 24 hours retention test, G-test: Generalized knee-proprioception test, VI: Verbal instructions, PR: Passive repositioning)

Participants

Forty-two students from Leibniz Universität Hannover volunteered to participate in this study. The participants were randomly divided into three groups. The participants were initially subjected to the Movement Imagery Questionnaire-3. This scale is a 12-item questionnaire that quantifies a participant's ability to imagine four different activities internally, externally and kinesthetically (Williams, Cumming, Ntoumanis, Nordin-Bates, Ramsey, & Hall, 2012) (see Figure 2). Here, the groups CT (6 females/8 males; mean ± SD (age): 25.6 ± 1.8 years, MIQ3: First person perspective (FPP): 5.8 ± 0.9, External perspective (EP): 5.4 ± 0.4, Kinesthetic imagery (KI): 5.4 ± 1.3), EXP MP (8 females/4 males; 26.3 ± 1.9 years, FPP: 5.3 ± 0.6, EP: 5.3 ± 0.8, KI: 5.1 ± 0.5) and EXP ASG-MIT (7 females/5 males; 25.3 ± 2.3 years, FPP: 5.5 ± 1.2, EP: 5.8 ± 0.8, KI: 5.0 ± 0.9) were all self-reported healthy participants with no history of significant hip, knee or back injury. After the conclusion of the experiment participants were asked to report their attention levels on a 10-point Likert scale during mental imagery blocks. Written informed consent was obtained from each participant, and ethical approval was obtained from the Ethics Committee of the Leibniz University Hannover. All the participants underwent a baseline auditory test (HTTS Audiometry). The participants received 20 Euros as compensation for their participation.

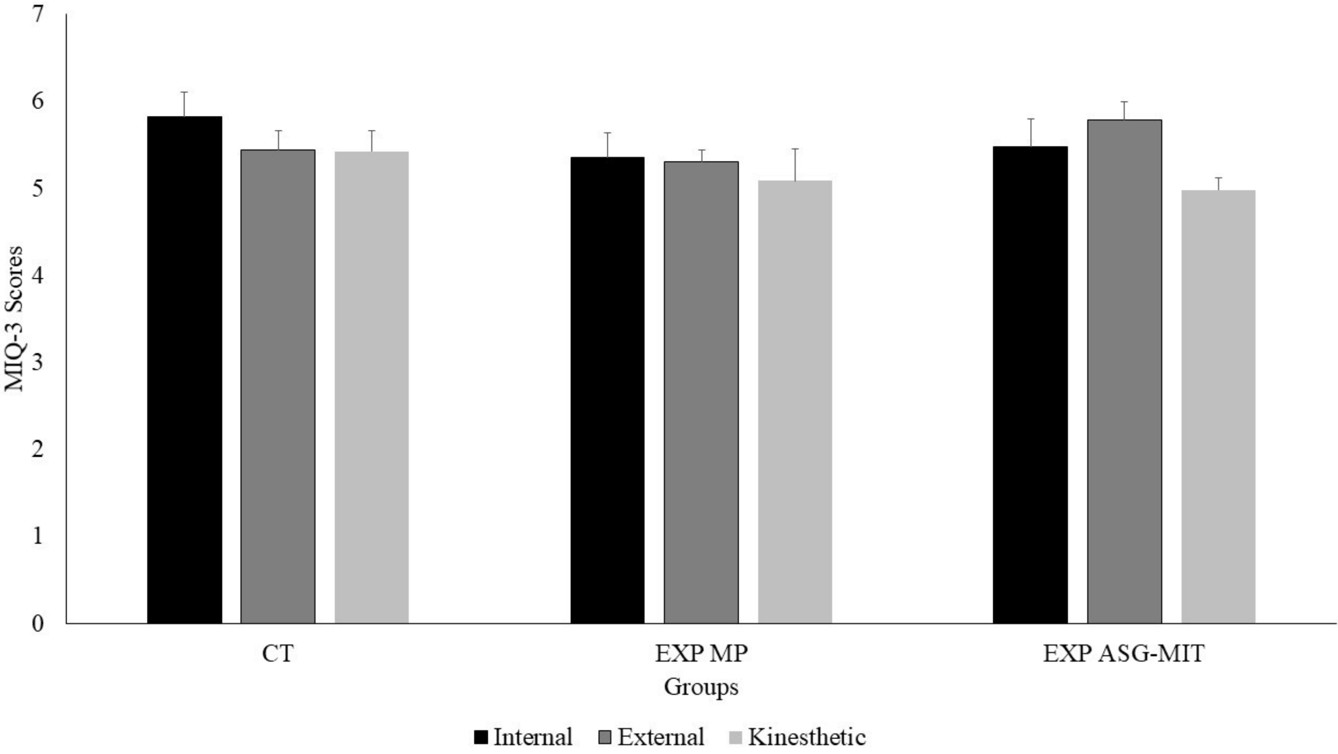

Figure 2 Illustration of mean and standard error for MIQ-3 questionnaire scores across the three groups (Scores mentioned for: Internal: First person perspective, External: Third person perspective, Kinaesthetic: Feeling the movement, CT: no mental imagery performed, EXP MP: Conventional mental imagery without auditory guidance, EXP ASG-MIT: mental imagery with auditory guidance)

Procedure

During the initial phase of the experimental procedure i.e. Block 1-5, real-time auditory feedback and kinematic analysis components were identical to (Ghai, Schmitz, et al., 2018b).

Participants were comfortably seated with their feet in the air, their back resting against a wall, and their pelvis stabilized (Ghai, Schmitz, et al., 2018a). During the sitting position, the knee joint was maintained at the right angle (Supplementary Figure 1). This position of the knee joint was considered as 0° and further extension from this position onwards was referred as positive change in the angular values. Participants wore wireless headphones (MM450, Sennheiser, Wedemark, Germany), and were blindfolded to eliminate visual perception. Initially, a familiarization session was performed to accustom the participants with the four target angles (20°, 40°, 60° and 80°) they had to perform during the experiment. Here, the experimenter passively moved the dominant leg to previously identified target angles in an open kinetic chain and held at each target angle for two seconds to allow the participant to memorize the position. This process was repeated again on the non-dominant leg. The experimenter asked the participants to memorize each target position as angle 1: 20°, angle 2: 40°, angle 3: 60° and angle 4: 80°, on both legs. Participants received no feedback of result concerning their performance.

After the familiarization session, a passive knee-re-positioning test was performed for all the four angles 1, 2, 3 and 4 (20°, 40°, 60° and 80°), bilaterally. Here, the experimenter passively positioned the leg at one of the four angles and held it for five seconds. The experimenter confirmed the target angle by visualizing the joint angle values represented on a screen. Thereafter, the experimenter returned the leg at the initial 0° position. Thereafter, the participants were instructed to actively re-position their leg at the specific instructed angle, five times consecutively. This was repeated for all the four target angles, bilaterally (see Pre-test, Figure 1).

Further, in the 1st block of the experimental set-up (see PPT 1, Figure 1) participants were verbally instructed by the experimenter to perform the same four target angles (angle 1: 20°, angle 2: 40°, angle 3: 60°, angle 4: 80°), without any auditory feedback, and without any prior passive knee re-positioning instruction. The verbal instructions for the performance of angles were randomized i.e. right leg angle 1, right leg angle 4, right leg angle 3 and so on. A total of 32 repetitions were performed by the right leg. This process was again repeated on the left leg. A total of 64 repetitions were performed in this block of about 8-10 minutes duration. Furthermore, before the commencement of the 2nd block, participants were introduced to the auditory feedback. The group EXP MP was introduced to ocean wave noise. For both groups the experimenter first passively repositioned the legs at the four angles, bilaterally with the auditory feedback. This was performed to ensure that the participants could associate the target angles i.e. angle 1: 20°, angle 2: 40°, angle 3: 60° and angle 4: 80° with their respective sounds (Supplementary File 2). After that, the participants were verbally instructed to reposition their knee joints by themselves, in the presence of auditory feedback (see R-AF 1, Figure 1). Here as well, the verbal instructions for the performance of angles were randomized i.e. right leg angle 4, right leg angle 3, right leg angle 1 and so on. This process was again repeated on the left leg. A total of 96 repetitions were performed in this block (48 right + 48 left). The duration of the training blocks with real-time auditory feedback lasted for 15-20 minutes.

After this, the 3rd block analyzed proprioceptive accuracy without any auditory feedback (See PPT 2, Figure 1). Like the 1st block the participants were verbally instructed by the experimenter to actively reposition their knee joints at the four target angles (20°, 40°, 60° and 80°) in a randomized order. The procedure, number of repetitions, and duration were identical to the 1st block. The 4th block was an auditory-motor training block (See R-AF 2, Figure 1). Here, auditory feedback was present. Like the 2nd block the experimenter initially repositioned the participant's knee passively with the auditory feedback. Thereafter, the participants were verbally instructed, in a randomized order to reposition their knee joints. The procedure, number of repetitions, and duration was identical to the 2nd block. The 5th block analyzed proprioceptive accuracy without any auditory feedback (See PPT 3, Figure 1). Like the 1st and 3rd block the participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four angles (20°, 40°, 60° and 80°). The procedure, number of repetitions, and duration were identical to the 1st and 3rd block.

Thereafter, the 6th block was an ASG-MIT block (See MP1, Figure 1). As mental training was to be performed in this block, no initial passive re-positioning was initiated by the therapist. The experimental group EXP ASG-MIT was randomly instructed to feel the knee joint at the instructed angles for the same number of repetitions as in block 2 and 4. Moreover, experimental group EXP ASG-MIT heard the recorded auditory feedback of the own performance from 4th block. The experimental group EXP MP heard ocean waves in addition to the verbal instructions to feel the re-positioning of the own knee. The control group CT was asked to perform visual arithmetic equations, for example 641+547. The participants in CT group were asked to calculate non-verbally, and with their eyes open. They were then asked to report the correct answer to the experimenter. The experimenter instructed the angles to be performed in a similar way to that of the 4th auditory-motor training block. The number of repetitions, and duration were identical to the 2nd and 4th block. The 7th block analyzed the proprioceptive accuracy without any auditory feedback (See PPT 4, Figure 1). Like the 1st, 3rd and 4th block the participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles (20°, 40°, 60° and 80°). The procedure, number of repetitions, and duration were identical to the 1st, 3rd and 5th block. Thereafter, the 8th block again was an ASG-MIT block (See MP2, Figure 1). The entire procedure was identical to the 6th block. The duration as well was similar to the 2nd, 4th and 6th block for all three groups. After this, a final proprioceptive test (PPT-Final) analyzed the proprioceptive accuracy without any auditory feedback. Like the 1st, 3rd, 5th and 7th block the participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles (20°, 40°, 60° and 80°). The procedure, number of repetitions, and duration were identical to the 1st, 3rd, 5th and 7th block.

Thereafter, the 9th block analyzed the retention of performance after 15 minutes of completion of the 8th block (PPT Final), without any auditory feedback (See RET 15min, Figure 1). Like the 1st, 3rd 5th, 7th and 8th block the participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles (20°, 40°, 60° and 80°). The procedure, number of repetitions, and duration were identical to the 1st, 3rd, 5th, 7th and 8th block. The 10th block analyzed the retention of performance 24 hours after the completion of the 7th block, without any auditory feedback (see RET 24hrs, Figure 1). Like the 1st, 3rd, 5th, 7th, 8th and 9th block the participants were verbally instructed, in a randomized order to actively reposition their knee joints at the four target angles (20°, 40°, 60° and 80°). The procedure, number of repetitions, and duration were identical to the 1st, 3rd, 5th, 7th, 8th and 9th block.

Finally, after the completion of the 24-hour retention measurement, generalized knee proprioception was analyzed. Here, the participants performance on three completely untrained angles (10°, 30°, 50° and 70°) was tested (see G-test, Figure 1). Like the pre-test, the experimenter first passively repositioned the knee at one of the target angles and held the position for five seconds. Thereafter, the participants were instructed to actively re-position their leg at the specific angle. This process was repeated for all the three target angles (10°, 30°, 50° and 70°) bilaterally. Figure 1 illustrates the entire experimental procedure. The experimental protocol lasted approximately for 140-150 minutes.

The auditory feedback used in this experiment was identical to that used by Ghai, Schmitz, et al. (2018a). Using Csound 6.0 with Python 2.7, sound is synthesized by a band-limited oscillator and lowpass filters. Pitch and amplitude are mapped onto the angular displacement and velocity of the knee joint. The angular position changes between 0° and 90° (full knee-extension) was mapped to audio frequency range between 120 Hz and 300 Hz. The amplitude is a function of an angular velocity squared and a cosine with angular displacement. A sample of auditory feedback is provided as Supplementary File 2. The mapping functions as a mathematical equation have been mentioned by Ghai, Schmitz, et al. (2018a).

Kinematic analysis

XSENS MVN Biomech (XSENS Technologies B.V, Netherlands) was used in this present study to assess knee joint angles. In a lower body configuration mode, seven wireless inertial measurement units (IMU) were positioned by the experimenter on the participants using Velcro straps. The IMUs were positioned on sacrum, lateral side of femoral shaft, medial surface of tibia and tarus. With the wireless data transmission, kinematic motion was recorded in a 3-dimensional representation at a 60 Hz sampling frequency. The knee joint angle data are analyzed by a software (MVN Studio), which records the kinematic data with MVN file format. Thereafter, the re-positioning data for each trial were matched with MVN recording files and were extracted manually by two researchers. Absolute and constant errors were calculated to quantify the magnitude and direction of the re-positioning error (Ghai, Driller, & Masters, 2018). Studies have reported high reliability and validity of XSENS motion capture system for the measurement of joint angles (Zhang, Novak, Brouwer, & Li, 2013).

Statistical Analysis

The sample size was calculated with G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007), based on the data from (Ghai, Schmitz, et al., 2018b). This study had applied nearly the same experimental protocol as the present study. Considering a medium effect size (f=0.25), a correlation among repeated measures of 0.12, a nonsphericity correction according to the Huynh-Feldt procedure with ε=0.88, seven repeated measures (PPT-PPT24), a power of 80% and a significance level of 5%, a total sample size of 42 is suggested. Statistical analyses were performed using Statistica (V. 12. StatSoft, Hamburg, Germany). Firstly, the initial MIQ-3 questionnaire performance was evaluated between groups with a one-way ANOVA. Thereafter, the changes of proprioceptive accuracy over time induced by auditory feedback training i.e. from Block 1-5 were evaluated. Therefore, the re-positioning errors (the dependent measure) were analysed by a two-way ANOVA with the between-subject factor group (EXP ASG-MIT/EXP MP/CT) and the within-subject factor block (PPT 1, R-AF 1, PPT 2, R-AF 2, PPT 3). Thereafter, effects of mental imagery were analyzed by normalizing the data by subtracting on the individual mean of block PPT3. Here, a 2-way ANOVA with the between-subject factor group (EXP ASG-MIT/EXP MP/CT) and the within-subject factor block (PPT4, PPT Final, RET 15 min, RET 24 hrs) was realized. Thereafter, the generalized transfer of knee-proprioceptive performance was analyzed by a two-way ANOVA with the between-subject factor group and the within-subject factor test (pre-test, G-Test). The sphericity assumption was tested with Mauchley's test. If significant, the Greenhouse-Geisser correction was applied. Post-hoc-comparisons were performed with Tukey's post hoc test. The rating of self-reported attentional performance during mental imagery was compared between groups EXP and CT (MP) by Mann-Whitney-U-Test.

Results

Vividness of mental imagery as assessed by MIQ-3 questionnaire (Figure 2) did not differ a priori between groups ($F(2,39)=0.76$, $p=0.470$, $\eta_p^2=0.04$). The results of the initial passive repositioning task are illustrated in Figure 3. The groups did not differ significantly from each other as confirmed by a one-way ANOVA, indicating that all groups started from the same level ($F(2,39)=0.14$, $p=0.861$, $\eta_p^2=0.01$).

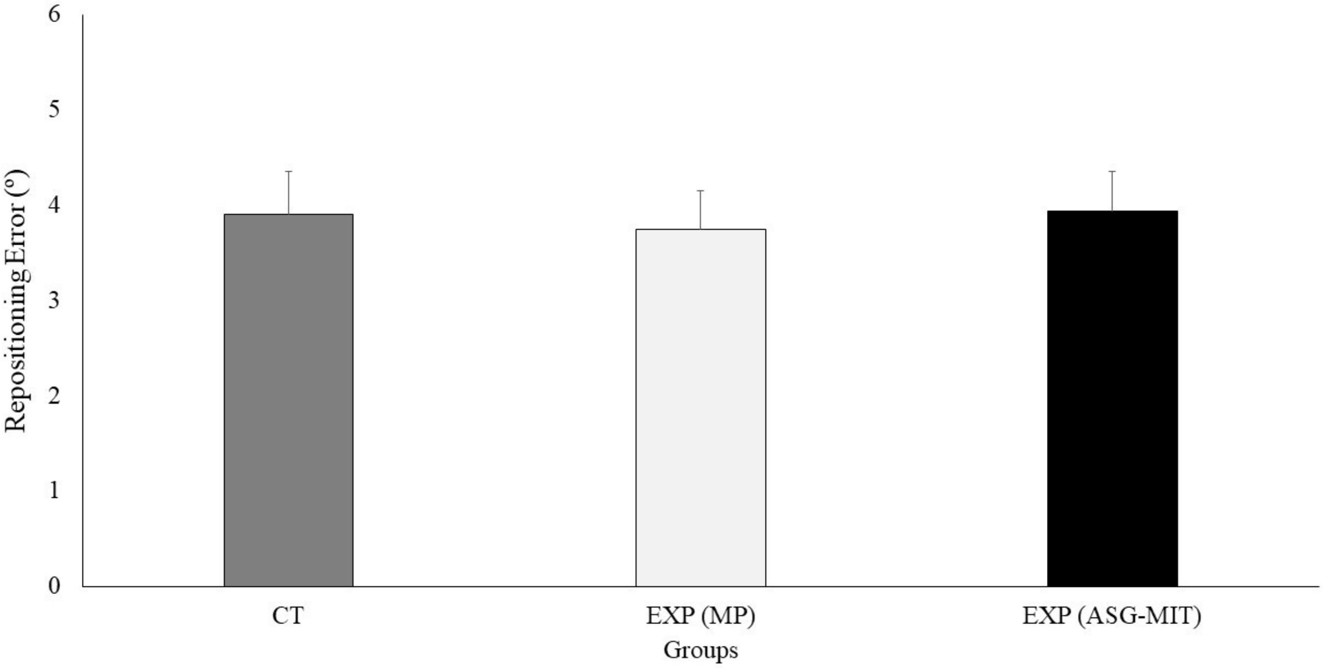

Figure 3 Illustration of mean and standard error for groups performance in initial Pre-test (CT: no mental imagery performed, EXP MP: Conventional mental imagery without auditory guidance, EXP ASG-MIT: mental imagery with auditory guidance)

Subsequent training with real-time auditory feedback enhanced the repositioning performance significantly (Figure 4). All three groups started at the same proprioceptive level and their performances during the following five training blocks was not different. An ANOVA yielded significance for the main effects for (block: F(4,156)=63.03, $p<0.001$, $\eta_p^2=0.61$) but not for group: F(2,39)=1.20, $p=0.309$, $\eta_p^2=0.05$; block*group: F(8,156)=0.58, $p=0.718$, $\eta_p^2=0.02$). Tukey HSD post-hoc comparisons revealed significant better proprioceptive performance in blocks R-AF1, R-AF2 and PPT-3 as compared to PPT-1 and PPT-2 for all the three groups (all $p<0.001$). Differences between PPT-1 and PPT-2 were not significant ($p= 0.242$).

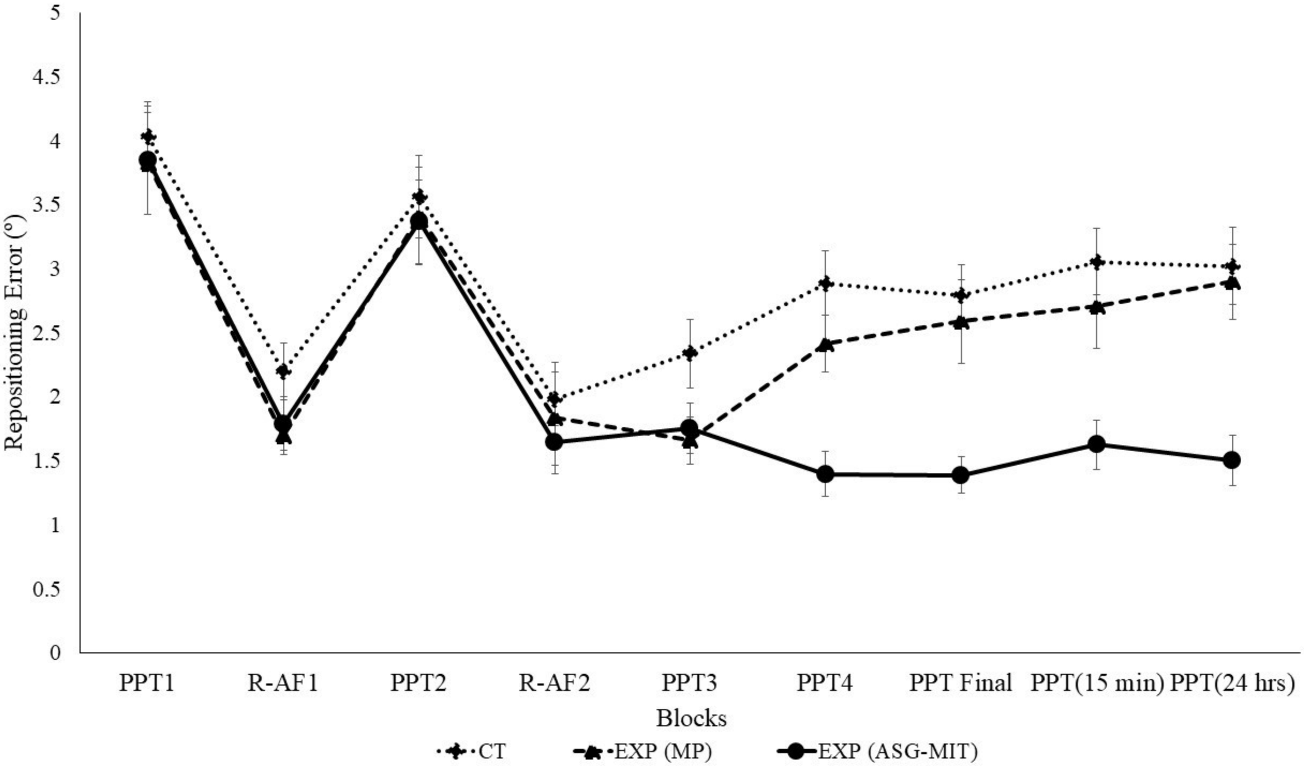

Figure 4 Illustration of mean and standard error for the course of auditory motor training and mental imagery across the three groups across blocks 1-9 (CT: no mental imagery performed, EXP MP: Conventional mental imagery without auditory guidance, EXP ASG-MIT: mental imagery with auditory guidance)

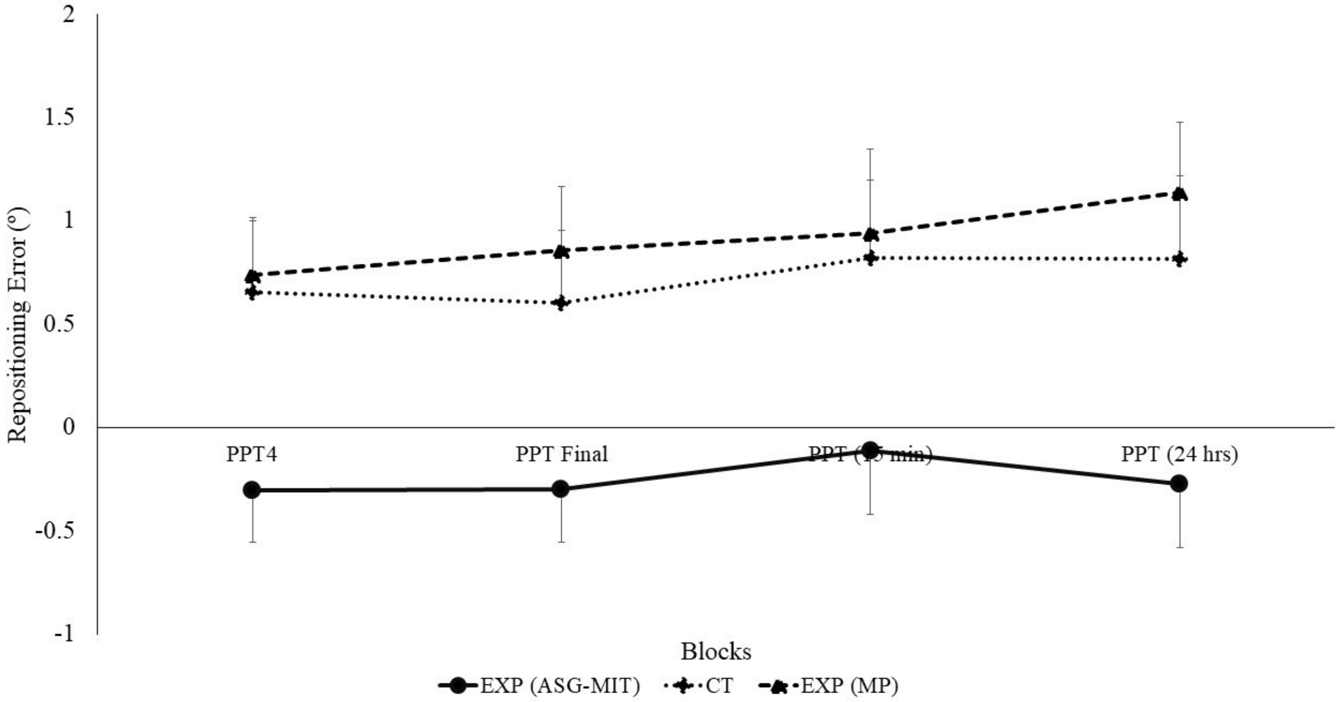

Figure 5 Illustration of normalized data for the mean and standard error for the course of mental imagery blocks i.e. blocks 6-9 across the three groups (CT: no mental imagery performed, EXP MP: Conventional mental imagery without auditory guidance, EXP ASG-MIT: mental imagery with auditory guidance)

To analyze the effect of mental training, performance of blocks 6 to 9 was compared across groups (normalized values mentioned in Figure 5). Thereafter, the groups performed mental training differently i.e. EXP ASG-MIT trained with auditory guidance, EXP MP trained without any auditory feedback, and CT did not perform training at all. The group performances from block PPT-4 diverged. Here, an ANOVA confirmed a main effect for the group (F(2,39)=2.39, p=0.001, $\eta_p^2=0.27$), whereas block (F(3,117)=1.68, p=0.173, $\eta_p^2=0.04$) and the interaction block*group (F(6,117)=0.41, p=0.868, $\eta_p^2=0.02$) were not significant. Tukey HSD post-hoc comparisons revealed significantly better performance in group EXP ASG-MIT as compared to EXP MP, and CT ($p<0.05$).

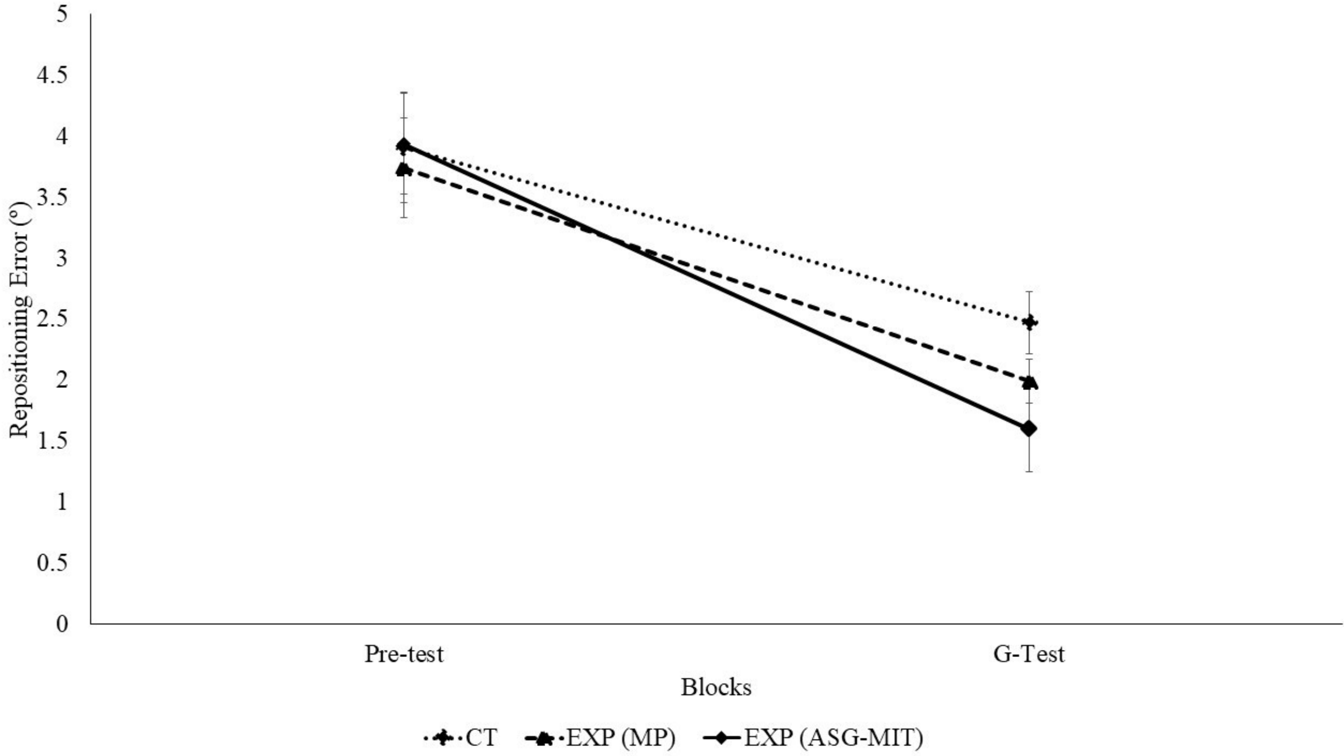

Figure 6 Illustration of mean and standard error of mean for three groups during generalized knee-proprioceptive test for pre-test (20°, 40°, 60° and 80°) and G-test (10º, 30º, 50º and 70º)

Repositioning errors of the pre-test and the generalization test (G-test) are illustrated in Figure 6. An ANOVA confirmed a main effect for test (F(1,39)=74.78, $p<0.001$, $\eta p^2=0.66$). Differences between groups were not significant (group: F(1,39)=1.88, $p=0.165$, $\eta p^2=0.09$; test*group: F(2,39)=1.73, $p=0.190$, $\eta p^2=0.08$). Therefore, generalized enhancement in knee proprioception was significant in all the groups i.e. EXP ASG-MIT, EXP MP, CT, but did not differ across groups.

The ANOVA on the self-reported attention scores on Likert scale also demonstrated a significant effect. Subjects of groups EXP MP (5.5±1.1) and EXP ASG-MIT (6.6±1.1) rated their performance during mental imagery a posteriori significantly different from each other (Box & whisker plot, Figure 7). The participants from group EXP reported significantly higher attention rates than the participants of group CTMP (Z=2.27, $p=0.018$).

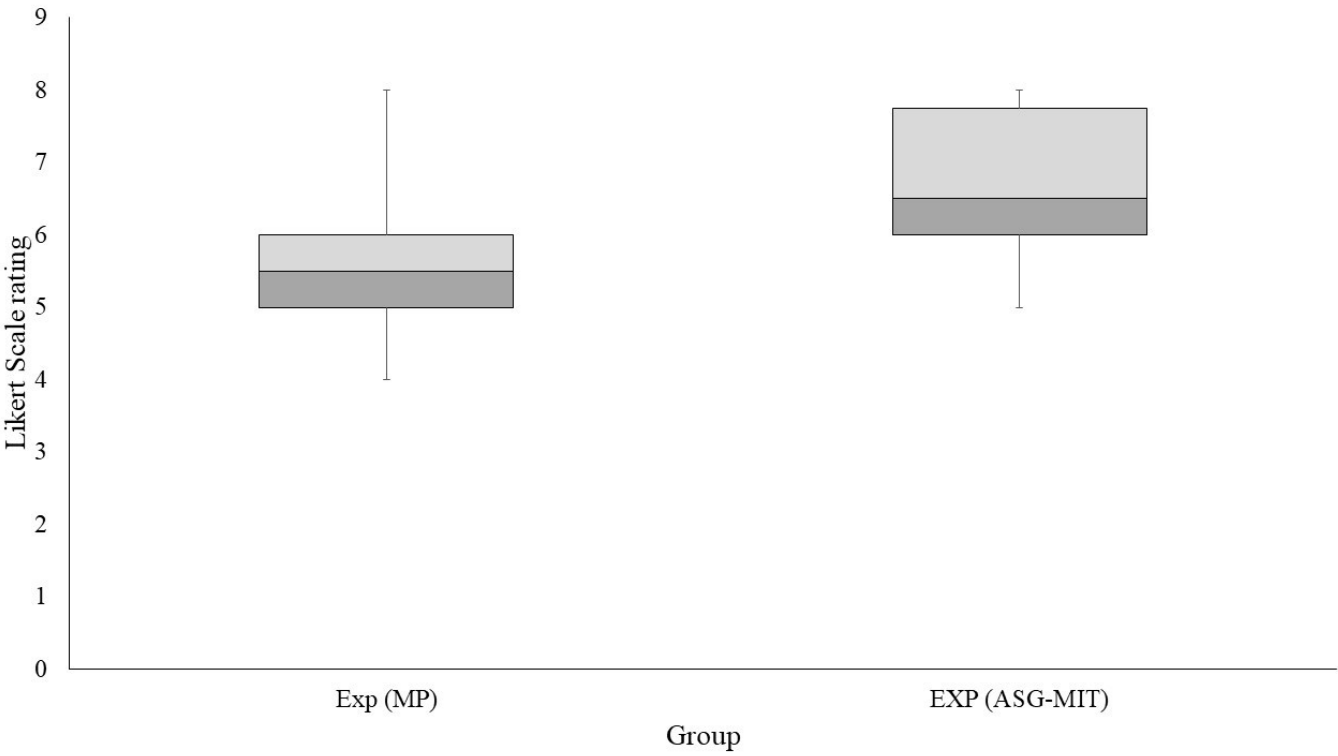

Figure 7 Illustration of Box and whisker plots for the self-reported attention levels in both mental training groups (EXP MP: Conventional mental imagery without auditory guidance, EXP ASG-MIT: mental imagery with auditory guidance)

Discussion

The main findings of this study confirm our main hypotheses.

a) Auditory-motor training significantly enhanced knee proprioception.

b) ASG-MIT significantly enhanced knee proprioception.

c) Auditory-motor training resulted in generalized enhancement in knee proprioception on untrained angles.

In agreement with our previous findings, enhancement in knee proprioception were observed in the presence of continuous real-time auditory feedback i.e. R-AF 1, R-AF 2. Here, several mechanisms could have allowed these benefits in proprioceptively controlled actions. For instance, the auditory feedback could have provided external guidance to effectively reposition the knee joint, enhanced congruent multisensory integration, amplified sensorimotor representations, and more (for a detailed discussion see (Ghai, Schmitz, et al., 2018a)). Moreover, in agreement with our second research enhancements in knee proprioception were also evident without auditory feedback i.e. after 30-40 minutes of training PPT-3. Here as well, the enhancements in knee proprioception could be attributed to two main aspects i.e. prolonged auditory motor training and variability in the training (Ghai, Schmitz, et al., 2018b).

The novelty of the present study lies in terms of the beneficial effects of auditory guided mental imagery as compared to conventional mental imagery. Previous studies have demonstrated that combining physical training with mental imagery can be beneficial in enhancing performance related outcomes as compared to only physical or mental training alone (Brouziyne & Molinaro, 2005; Butler & Page, 2006; Overdorf, Page, Schweighardt, & McGrath, 2004). Therefore, in the present experiment we modified our previous auditory motor training regime by incorporating auditory-guided mental imagery. Here, performance in mental imagery blocks clearly demonstrate, as to how self-generated auditory feedback guidance during mental imagery resulted in enhanced knee proprioception as\compared to its counterparts. These enhancements in knee proprioceptive accuracy could be affirmed to multiple reasons. Firstly, the proprioceptive performance could have been facilitated due to the auditory guidance by self-triggered movements (Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). In the present experiment, the auditory feedback that was used to guide a participant’s mental imagery was a recording of participants’ own movement sonification in the 4th block i.e. R-AF2. According to Jenkins et al. (2000), higher activations have been reported in dorsolateral pre-frontal cortex (area 9, 10 & 46), parietal cortex (area 40), left primary sensorimotor cortex, anterior cingulate cortex, rostral and caudal supplementary motor area during perception of self-generated movements as compared to externally triggered stimuli. The authors stated these higher activations correlate with enhancements in movement timings/selection, motor learning, and attention. Secondly, enhancements in the guided mental imagery group can be derived from MIIMS (Motor imagery integrative model) model (Guillot & Collet, 2008; Schuster, Hilfiker, Amft, Scheidhauer, Andrews, Butler et al., 2011). This model suggest that performing the mental imagery in an ecologically identical environment could enhance the quality of imagery and performance outcomes. Similarly, in the present experiment, auditory guidance could have enhanced the performance by aiding the mental representation of the knee movement in a more action relevant or ecological manner.

Additionally, an aspect to consider here is the spatial and temporal aspect of motor imagery. Studies have reported that the imagined movements share a high level of proximity in terms of timing, accuracy and spatial positioning to that of the real movements (Guillot, Moschberger, & Collet, 2013; Papaxanthis, Paizis, White, Pozzo, & Stucchi, 2012). Heremans et al. (2009) stipulated the same reasons for the enhancements observed in motor performance in their study. Here, the authors externally cued (auditory/visual) mental imagery and reported significant enhancements in spatial and temporal accuracy of the eye movements (Heremans et al., 2009; Heremans, Nieuwboer, Spildooren, De Bondt, D'hooge, Helsen et al., 2012). The authors suggested that external auditory cueing could have facilitated activation in preserved neural pathways i.e. cerebellar-thalamic-cortical circuitry as in patients with Parkinson's disease to enhance performance. Likewise, Hovington and Brouwer (2010) also utilized sensory cues to guide motor imagery and reported considerable enhancements in corticomotor excitability. Interestingly, the authors reported enhancements in corticomotor excitability, which was not global but rather specified to specific target muscles of the imagined movements. In the present study, a continuous self-generated feedback was utilized as compared to discrete stimuli utilized in previous research. Such type of an auditory feedback has been reported to extend the benefits of discrete rhythmic auditory cueing stimuli Effenberg, Fehse, Schmitz, Krueger, and Mechling (2016). The authors suggest that the continuous flow of additional auditory sensory information allows a participant to better perceive their movement amplitudes and positioning, thereby resulting in a more efficient development of motor commands governing both feedback and feed-forward models (Effenberg et al., 2016). Moreover, by allowing additional influence over the action observation system the real-time auditory stimuli might also enrich the internal stimulation of the executed movement (Effenberg et al., 2016; Schmitz et al., 2013). Although in the present research we did not compare the guidance effects of external auditory cueing and real-time auditory feedback, we recommend future research to elucidate these aspects.

Furthermore, we would like to draw the reader's attention towards the proprioceptive enhancements observed in retention measurements (post 15-min and 24-hour) for the trained four angles across the three groups. On comparison with our previous study where retention was analyzed after physical auditory motor training important implications could be drawn. Here, retention measurements are subjectively better in the auditory guided mental imagery group for both the 15 minutes (M° ±S.D°: current vs previous study 1.66±1.04 vs 1.99±1.20) and 24 hours (1.50±0.99 vs 1.96±1.02) retention measurements. We presume that in the current instance, the auditory feedback guiding during the mental imagery could have additionally facilitated the motor components without physical execution. The auditory feedback could have facilitated intermodal learning by avoiding the onset of fatigue, which is inversely proportional to proprioceptive accuracy (Van Tiggelen, Coorevits, & Witvrouw, 2008).

As an additional aspect we also included a self-reported assessment of the level of attention (10-pont Likert scale) during the mental imagination condition. Typically, mental imagery is associated with high instances of mind wandering and inattention (Morrison, Goolsarran, Rogers, & Jha, 2014). The main aim of including this factor in the study was to observe if auditory guidance could have influence the attentive levels of participants. We observed a strong correlation of the attentional levels in the auditory guided mental training group as compared to the conventional mental training group suggesting that the participants were much efficiently able to focus on specific movements during mental imagination. These findings seem quite plausible from a point of view that the auditory feedback guiding the mental imagery was a performer's own recording. Here, additional inference can also be drawn from the neuroimaging study by Ronsse, Puttemans, Coxon, Goble, Wagemans, Wenderoth et al. (2011). The authors demonstrated that training with auditory feedback resulted in an enhanced prefrontal cortex activation i.e. "increased attention to action". This in our opinion might have served as a major aspect for enhanced proprioceptive performance in auditory guided mental imagery group.

Lastly, contrary to our initial hypotheses, we observed no significant differences between the groups during the generalized proprioceptive tests. Here, we presume that since all three groups initially performed auditory-motor training, they possibly could have developed an interfaced mapping between the auditory and proprioceptive systems. Therefore, in the generalized proprioceptive test, they could have utilized the components of this interfaced auditory motor mapping (Bangert, Peschel, Schlaug, Rotte, Drescher, Hinrichs et al., 2006).

Finally, we presume that in this particular experiment the auditory system's high-resolution capability of pitch differences and temporal features could have supplemented the comparably lower resolution proprioceptive system in both domains via intermodal referencing. Taken together, the results of the present experiment provide foundational evidence for developing rehabilitation protocols in neurological disorders where physiological fatigue affects the prognosis of a patient (Schmitz, Kroeger, & Effenberg, 2014).

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Declarations of interests

None.

Author contributions

A.O.E., S.G and G.S developed the research question. S.G., A.O.E and G.S. developed the research paradigm. S.G. conducted the experiment, collected the data and wrote main parts of the paper. G.S. performed the statistical analysis supported by A.O.E. and S.G. and contributed to the results section. T.H. was responsible for technical implementing and customization of the sonification system. A.O.E. supervised the project. All authors critically revised the paper.

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Futurized perspective: Implementation of auditory feedback in neurological rehabilitation

Chapter 12: “Low road” to rehabilitation: a perspective on subliminal sensory neuroprosthetics

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PERSPECTIVES

"Low road" to rehabilitation: a perspective on subliminal sensory neuroprosthetics

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Abstract: Fear can propagate parallelly through both cortical and subcortical pathways. It can instigate memory consolidation habitually and might allow internal simulation of movements independent of the cortical structures. This perspective suggests delivery of subliminal, aversive and kinematic audiovisual stimuli via neuroprosthetics in patients with neocortical dysfunctions. We suggest possible scenarios by which these stimuli might bypass damaged neocortical structures and possibly assisting in motor relearning. Anticipated neurophysiological mechanisms and methodological scenarios have been discussed in this perspective. This approach introduces novel perspectives into neuropsychology as to how subcortical pathways might be used to induce motor relearning.

Keywords: motor learning, fear perception, internal simulation, sonification, cortical dysfunctions

Background

The structural organization of a human brain is like a mushroom growing inside out, suggesting the ancient prevalence of innermost subcortical structures such as brain stem, amygdala to superficial neocortical structure such as prefrontal cortex. Evolution has bestowed different functional roles on these neural centers based on their development; for instance, the innermost structures usually mediate basic survival functions, such as breathing and fear (threat) processing, whereas the outermost structures manage sophisticated abilities such as decision-making and self-control and more.[1] Being a basic survival function, fear is mainly mediated within the innermost, subcortical structures of the brain.[1–3] However, due to the evolutionary course, neocortical structures have also formed parallel connections for processing fear, possibly to allow a more cognitive and context-driven processing of the stimuli.[3–5] LeDoux[4] labeled such parallel processing of fear by subcortical pathways as "low road processing" and cortical pathways as "high road processing". However, these pathways operate on distinct terms. On one hand, the "low road" pathways process stimuli in a "quick and dirty" manner while utilizing subcortical pathways, and independent of consciousness.[6,7] This pathway prioritizes physical safety and acts as a fail-safe mechanism while ignoring any social or environmental context whatsoever. On the other hand, the "high road" pathways allow a rather slower resource-dependent cognitive processing of stimuli via higher cortical structures and prioritize contextual information associated with social, psychological and environmental factors. For instance, longer propagation latency has been reported when fear processing takes place through higher cortical structures, possibly suggesting costs for higher level processing,[8] whereas processing with "low road pathways" has been reported to be considerably shorter, ie, as low as 30–120 ms.[9]

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Neuroanatomical studies reveal that processing of stimuli through "low road" allows the propagation of fear stimuli in amygdala by the way of superior colliculi and pulvinar nuclei of thalamus,[4,10] a short pathway, whereas in the high road pathway, for visual information, the stimuli would pass from the retinal ganglion cells to lateral geniculate nucleus, visual cortex (V1, V2 and V4) and inferior temporal cortex, and then end up in amygdala. Under the conditions of threat, mediation of stimuli first to the "low road" pathway is gated by amygdala,[8] for both visual[11,12] and auditory streams.[13,14] It might be because of its higher sensitivity to process low spatial frequency information,[15,16] thereby initiating action even to a "close enough" stimulus.[6] For instance, Carter and Frith[5] proposed that parallel processing by high and low roads[17] allows mediating balance between cortex and the amygdala by allowing both contextualized and fail-safe responses to a threat, respectively.

Several cortical and subcortical structures take part in processing fear-related stimuli. For instance, hypothalamus, amygdala, superior colliculi, lateral geniculate nuclei, thalamus (pulvinar nuclei), locus coeruleus and periaqueductal gray are the main subcortical structures involved in mediating fear,[10,18] whereas (medial-lateral) prefrontal, orbitofrontal, visual, parietal cortices, anterior cingulate cortex and hippocampus and bilateral anterior insulate cortex are the main cortical structures.[8,18] Moreover, the functioning of "low road" subcortical pathways is suggested to be independent of higher cortical processing. For instance, diffusion tensor imaging has demonstrated projections between superior colliculi and amygdala via the pulvinar.[19] Furthermore, Morris et al[20] in their neuroimaging study reported perception of aversive visual stimuli in a patient with effective blind sight (extensive lesion in occipital cortex).[21,22]

Additionally, "low road" pathways possess specialized interconnections with the motor control centers of the brain, independent of cortical control, primarily to initiate fight or flight response to a threat. Grezes et al[23] using diffusion tensor magnetic resonance imaging and probabilistic tractography demonstrated interconnectivity of amygdala to descending corticospinal tracts, lateral and medial precentral, motor cingulate, primary motor cortices and postcentral gyrus. Gokdemir et al[24] further reported fear potentiation of both corticospinal and reticulospinal pathways in humans, post auditory and visual fear conditioning. Moreover, a strong role of these primitive subcortical pathways has also been reported for the perception of biological motion.[25,26] Furl et al[27] in an fMRI analysis revealed enhanced fear sensitivity in dorsal and ventral temporal motion-sensitive areas corresponding to superior temporal sulcus, hMT+/V5, inferior frontal gyrus, fusiform cortex (fusiform face area) and the action observation system.[28] The authors further added that amygdala might also control encoding and prediction of aversive incidence based on the elements of stimuli. Moreover, Bastiaansen et al[29] added that such interconnections of amygdala with these motor centers might be helpful in triggering for mirroring of emotions.

Likewise, this subcortical pathway (especially amygdala[2]) mediates a unique learning and memory mechanism. This mechanism has been reported to play a key role in predicting threat-based events before recognition of sensory stimuli.[2,30] Here, amygdala has also been reported to facilitate learning in a rapid,[31] habitual[1,31–34] and resilient manner.[35] Possibly, by modulating the activity and connectivity of prefrontal cortex,[36,37] Schwabe et al[38] suggested that threat-induced stress can selectively gate memory consolidation in favor of thalamus-dependent habitual learning[2,39] as compared to hippocampus.[33,35] Shiromani et al[31] too affirmed that the altered strength of synaptic signaling in amygdala is the major reason for habitual consolidation of memory. The authors stated that relatively weak conditioned stimuli (activating postsynaptic *N*-methyl D-aspartate receptors) gets strengthened by co-occurrence of unconditioned stimuli (triggering calcium influx), thereby eliciting robust responses in lateral nucleus. Moreover, the independence of this specialized memory system from cortical pathways and resilience in terms of long-term retention have also been reported (thalamo-amygdala pathways[7]). For instance, Maren and Quirk[2] reported lateral amygdala-associated memory plasticity during auditory fear conditioning, even in the presence of large lesions in auditory cortex.[40] Nevertheless, despite extensive research confirming the unique ability of the "low road" pathway to govern motor action, perception and memory consolidation independent of cortical structures, its possible role in enhancing prognosis in cases of neocortical dysfunctions has never been discussed in the literature.

As mentioned earlier, neocortex, the outermost and latest evolutionary development of brain, accounts for ~76% of the brain volume.[41] Any superficial damage to these structures in cases of trauma and cerebrovascular accidents might cause a wide array of cognitive[42–44] and sensory–motor dysfunctions.[45] Such damages together inflict debilitating symptoms on both cognitive and motor domains, thereby adversely impacting the prognosis of such patients. For instance, damage to prefrontal cortex (dysexecutive syndrome[46]) might considerably impair conscious perception;[47] self-control; task purportedly measuring fluency; concept formation; set shifting; inhibition; attention organization; abstract reasoning; novel problem-solving ability; stimuli inferencing decision-making

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ability; ability to encode task relevant information in working memory;[48,49] ability to select, monitor, manipulate and access current task information[44] and others. [50] Shumway-Cook and Woollacott[51] suggested that such deficits in attention, working memory allocation and short-term memory might considerably prolong the prognosis in a rehabilitation protocol, where explicit instructions are mainly emphasized.[52,53] In this study, we attempt to explain how the specialized abilities of these "low road" pathways could be exploited to enhance motor relearning for aiding in rehabilitation independent of such higher cortical functioning.

Accessing the "low" roads: the novel strategy

In this article, we attempt to suggest possible strategies that could be used to access the subcortical "low road" routes of the brain to facilitate or stimulate the damaged or dormant structures of the brain and aid in rehabilitation. We suggest utilizing task-specific multimodal neuroprosthetics to deliver aversive sensory stimuli subliminally to enhance motor perception and facilitate the process of motor relearning.[54] Real-time kinematic auditory feedback (sonification) and kinematic visual feedback generated in some of the widely researched rehabilitation approaches which allow comprehensive and efficient multisensory integration.[55,56] Kinematic auditory feedback is a relatively new interdisciplinary approach which has been utilized and demonstrated to enhance motor perception, motor control and learning in rehabilitation.[57,58] This methodology takes advantage of the strong relationship between auditory perception and motor control,[59–62] and has been reported to trigger neural centers associated with biological motion perception.[63,64] Also, sonification might provide valuable assistance toward enhancing movement perception of motor patterns associated with/without expertise, further aiding in enhancing representation and internal simulation of a motor task in the action observation system.[65,66]

Likewise, virtual reality is effective in rehabilitation.[67] The environment designed in virtual reality can be customized very similar to real-life settings[68] and can possess benefits in terms of transmitting kinematic visual stimuli for augmenting the brain functions by enhancing motor perception,[69] especially related to biological motion perception.[70] Moreover, the sensorimotor lability of both kinematic auditory and visual stimuli can be used to induce a compelling sense of immersion even when sensory inputs are incongruent and below the conscious threshold.[69] Therefore, coupling the use of methodologies can possibly provide opportunities to deliver multimodal multisensory information in terms of kinematic auditory and visual information concomitantly.[58,64,65,71] These methodologies have demonstrated to enhance perception,[64] efficient human behavior,[68,72] motor learning,[64] relearning[64] and performance,[73] thereby allowing benefits in the due course of rehabilitation. Radiological evidence by Schmitz et al[64] demonstrated robust activation of a specialized mirror–neuron system and human action observation system, precisely the activation of cortical: superior temporal sulcus, Brodmann's area 45, 6, and subcortical areas comprising striato-thalamo-frontal motor loop, ie, caudate nucleus, putamen and thalamus. The authors further speculated that such an activation of the action observation system while listening to motor activities might lead to an internal stimulation of perceived movement. Therefore, suggesting an association for increase in mental, auditory imagery.[55]

Utilizing such multisensory modalities for transmitting aversive subliminal stimuli might allow multifaceted benefits in perceptual domain, for instance, providing kinematic stimuli associated with fearful postures. Supposedly, a wild environment could be generated where a distant predator or imminent danger leads the person to choose a flight response and run away from the situation. Here, the patient could either be subjected to a first person or a third person view i.e., patient perceiving the threat on themselves or on a virtual avatar, respectively. This difference could be selected based on the level of cognitive and meta-cognitive dysfunctions. Further, coupling the audiovisual kinematic information for fearful postures and locomotion might instigate similar changes in the patient's action observation system and enhance internal simulation associated with locomotion for a "flight" response. For instance, Johansson[74] suggested that higher cortical centers are not the main components for perceiving basal biological motion, and therefore, this approach might be efficient in the condition of no-cortical dysfunction. Moreover, the stimuli might also be used to instigate reflexive behavior. For instance, Tamietto and De Gelder[75] suggested a strong relationship between the motor domain and amygdala while processing fearful stimuli to elicit reflexive behavior. In this study, we again suggest to possibly exploit this strong network and utilize multisensory integration modalities to address the deficits in motor execution. For instance, virtual reality can be used to generate a specific environment where a predator, such as a snake, tries to attack an extremity, eliciting a reflexive withdrawal reflex. Sonification in such a strategy can be used to superimpose on the executed reflexive action, for instance, aversive auditory feedback can be superimposed on the elbow imitating a flexor withdrawal reflex. Although due to motor restrictions these movements might not be physically executable, simulating

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these motor movements might allow preemptive facilitation (feed-forward manner) essential for execution.[76]

Such internal representations should elicit internal representations of motor tasks and thereafter aid in kinesthetic motor imagery for the perceived movement pattern. Moreover, facilitation of neural pathways might also be elicited as a rehabilitation perspective neural pathway for motor execution and imagery, and actively executed motions share a similar neural circuitry.[77] Ietswaart et al[78] suggested that enhanced brain plasticity because of mental practice can play a very important role in recovery following brain damage. Precisely, imagining or practicing movements could stimulate restitution and redistribution of brain activity, which can enhance the recovery of motor functions (refer "Hebbian theory"[79]). This when superimposed with conventional passive and active movements by a physiotherapist might provide additional benefits for relearning and performance.[80–82] Although highly speculative the fearful stimuli provided with biological motion might also instigate memory consolidation of movement patterns in a habitual manner, which in rehabilitation and performance settings have been demonstrated to be extremely beneficial.[83–87]

Moreover, to avoid the detrimental perceptual repercussions in behavior, the stimuli can be delivered subliminally. Perception of fear stimuli has been reportedly maintained even when a stimulus is masked,[88] with dichoptic stimulation,[89] when stimulus is presented at thresholds[90] and in the peripheral vision.[91,92] Additionally, visual activation of invisible stimuli can also be strong, when the invisibility is induced by neglect[93] or inattention.[94] Dehaene et al[95] suggested a state of contrast between subliminal and preconscious processing, which possibly could be an appropriate tool or the application of audiovisual stimuli, ie, masking of stimuli combined with inattentiveness. The author implied that within the conscious perception, a subject would be able to recognize and identify the presented stimuli.[8] On the contrary, the preconscious state of perception implies that the subject has a relatively strong neural response to the presentation, but either is not yet consciously aware or will miss it due to the absence of attention.[95] Finally, we hypothesize this methodological approach to attain perceptual and learning benefits by two mechanisms: first, by eliciting reflexive mechanisms in patients and activating dormant or damaged cortical pathways. Furthermore, this approach can be allocated with activities of daily living, where certain activities can be coupled with aversive sensory inputs. Together they are hypothesized to enhance biological motion perception, higher neural center activation, mental practice, cortical restructuring and regeneration and when coupled with physical therapy, they can lead to additional motor activity in terms of rehabilitative benefits. This perspective for the first time proposes the utilization of "low" road pathways for facilitating higher neocortical structures in case of damage. This approach could also have applications for patients in minimal conscious states where prognosis is exceptionally poor.[96] These patients exhibit characteristics similar to higher order cortical dysfunctions.[97,98] Additionally, the patients under minimal conscious states as per the categorization by Giacino et al[99] and Vincent[98] exhibit reproducible visual fixation, emotional and motor behavior. Producing reflexive motor actions via multisensory integration of aversive stimuli can allow the development of increased awareness and elicit neural reorganization. Finally, the main aim of this perspective is to elicit a scientific discussion on the topic, and we strongly urge future studies to analyze this gap in the literature.

As a future prospect, we would like to propose utilization of aversive olfactory stimuli as a possible medium in multisensory integration for enhancing fear perception. Studies have reported the effects olfactory stimuli possess on motor control of human body.[100–102] Sakamoto et al[102] speculated that olfaction possibly could have enhanced stability and motor performance by activating the insular cortex. Similarly, a multisensory integration pattern has been demonstrated in studies evaluating audio-olfactory domain[103] and visuo-auditory domain.[104] Nonetheless, the most important aspect why we are interested in incorporating olfaction in multisensory integration is its association with the limbic system. Baars and Gage[1] suggested that the afferent signals to amygdala arrive via four main pathways. However, the information drawn from olfactory stimuli is perpetuated directly at amygdala from the olfactory cortex without preprocessing at the thalamus, thereby suggesting a profound ability of odor as compared to other sensory stimuli on emotional consolidation of memories. Likewise, the findings of De Groot et al[105] are also important where olfactory fear stimuli were described to be as potent as audiovisual fear signals in inducing fear. This could considerably add toward the development of a comprehensive environment to elicit a fear response. Not only this but recent research by Jacobs et al[106] have also confirmed the presence of spatial coding information with high precision with olfaction in humans. These findings considerably add toward the prospective use of olfaction with movement perception and virtual reality where the spatial information about the motor movements derived from sensory inputs is a key component.[107] Nonetheless, the concept of utilization of olfaction as a possible medium of multisensory integration in movement perception is rather new and has been never discussed in

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published literature earlier. Recent advancements in virtual reality domain by coupling olfactory inputs by Ubisoft can possibly ascertain future application. Gaming modalities such as Nosulus rift can precisely incorporate aversive scents and couple them in a simulated environment providing enhanced perception benefits. This has been previously described by Richard et al.[108] Additionally, we would also suggest utilization of modern neuroprosthetics such as smart skins to enhance afferent inputs from skin receptors to aid in multisensory integration, and relearning.[109]

Summary

In this article, we propose a possible methodological approach which utilizes the "low" road fear pathways in rehabilitation of neurological disorders characterized by cortical damage primarily leading to executive dysfunctions. Based on the previous findings, this article bridges the published empirical findings and suggests that perception of fear can occur without consciousness. The article also proposes a methodological approach by using multisensory integration modalities, such as real-time kinematic auditory feedback, virtual reality to transfer aversive stimuli via audiovisual input, without conscious awareness to enhance biological motion perception, associated with activities of daily living to enhance mental imagery, practice, preparedness and possibly neural regeneration. Moreover, we also discuss possibly eliciting reflexive motor actions incurred by an aversive stimulus to enhance motor relearning. This coupled with physical rehabilitation can allow more benefits in terms of prognosis. This methodological perspective is aimed to address the poor prognosis faced by patients suffering from neocortical dysfunctions.

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Author contributions

Shashank Ghai conceptualized the perspective and wrote the article. Ishan Ghai and Alfred O Effenberg provided useful discussions and reviewed the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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PERSPECTIVE
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Role of Sonification and Rhythmic Auditory Cueing for Enhancing Gait Associated Deficits Induced by Neurotoxic Cancer Therapies: A Perspective on Auditory Neuroprosthetics

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Patients undergoing chemotherapy, radiotherapy, and immunotherapy experience neurotoxic changes in the central and peripheral nervous system. These neurotoxic changes adversely affect functioning in the sensory, motor, and cognitive domains. Thereby, considerably affecting autonomic activities like gait and posture. Recent evidence from a range of systematic reviews and meta-analyses have suggested the beneficial influence of music-based external auditory stimulations i.e., rhythmic auditory cueing and real-time auditory feedback (sonification) on gait and postural stability in population groups will balance disorders. This perspective explores the conjunct implications of auditory stimulations during cancer treatment to simultaneously reduce gait and posture related deficits. Underlying neurophysiological mechanisms by which auditory stimulations might influence motor performance have been discussed. Prompt recognition of this sensorimotor training strategy in future studies can have a widespread impact on patient care in all areas of oncology.

Keywords: cueing, chemotherapy, stability, rehabilitation, performance, balance, perception

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INTRODUCTION

Pharmacological treatment of cancer is varying dramatically with benefits for better patient outcomes and ease, but also with new toxicity profiles (1–3). Neurotoxicity is an unavoidable complication of life-saving cancer treatments, such as chemotherapy, radiotherapy, and immunotherapy (4, 5). Typically, treatment with immunotherapeutic agents involves activation of the body's own immune system for targeting malignant cells (6) (**Table 1**). During the treatment cross-adverse reactions with existing neural cells result in heightened neurotoxicity (7–9). Topp et al. (10) for instance, reported that approximately >50% of patients receiving Blinatumomab for acute B-lymphoblastic leukemia exhibited movement disorders, encephalopathic changes, cerebellar dysfunctions, and seizures. Similarly, chemotherapy acts by instigating damage to the structural composition of the DNA, and by also disrupting DNA repair and microtubule functioning. During its functioning the chemotherapeutic agents impart non-specific damage on the cells of the nervous system, thereby resulting in neurotoxicity (9) (**Table 1**). The most commonly

TABLE 1 | Pharmacological interventions for cancer treatment and associated neurotoxic effects.

Treatments	Drugs	Neurotoxic effects
Immunotherapy	Bispecific antibodies (Blinatumomab), Monoclonal antibodies (Trastuzumab, Brentuximab, Rituximab, Ramucirumab, Bevacizumab), Cellular treatments (Chimeric antigen receptor-T cells), Checkpoint inhibitors (Nivolumab Pembrolizumab, Ipilimumab), Tyrosine kinase inhibitors (Imatinib, Dasatinib, Ponatinib, Erlotinib, Pazopanib, Aflibercept, Idelalisib, Sorafenib, Sunitinib), Interferon alfa, Recombinant Interleukin 2	Peripheral nervous system: Gullian Barre syndrome, Myasthenia gravis, sensorimotor peripheral neuropathy, multifocal plexopathy/neuropathy, autonomic neuropathy, phrenic nerve palsy, cranial nerve palsy (optic, hypoglossal, facial nerve) Central nervous system: Aseptic meningitis, encephalitis, transverse myelitis, neurosarcoidosis, posterior reversible leukoencephalopathy syndrome, Vogt Harada Koyanagi syndrome, neurosarcoidosis, demyelination, vasculitis encephalopathy, generalized seizures, convulsions
Chemotherapy	Taxanes (Paclitaxel, Docetaxel), Epothilones (Ixabepilone), Platinum derived compounds (Cisplatin, Carboplatin, Oxaliplatin), Immunomodulatory drugs (Lenalidomide, Bortezomib, Thalidomide), Inhibitor of topoisomerase (Etoposide), Vinka alkaloids (Vincristine, Vindesine, Vinblastine, Vinorelbine), Metalloids (Arsenic), Alkylating agents (Procarbazine, Ifosfamide), Antimetabolites (5-Fluorouracil, Capecitabine, Gemcitabine, Fludarabine, Cytarabine), Farnesyltransferase inhibitors (Tipifarnib), Antiprotozoal and anthelmintic (Suramin)	Peripheral nervous system: Lhermitte's sign, (painful) sensory peripheral neuropathy, muscle cramps, post infusion parenthesias, sensorimotor peripheral neuropathy, mononeuroptherapy, cranial nerve palsy, autonomic neuropathy, myalgia, proximal motor weakness, lumbosacral radiculopathy, painful axonal peripheral neuropathy, ataxia, orthostatic hypotension, intrinsic hand muscle weakness, brachial plexopathy Central nervous system: Encephalopathy, headache, stroke, seizures, cortical blindness, ataxia, athetosis, parkinsonism, radiculomyeloencephalopathy, cerebellar dysfunctions, leukoencephalopathy, inflammatory leukoencephalopathy, stupor, somnolence, aseptic meningitis, myelopathy, ocular toxicity, blurred vision
Radiotherapy	-	Peripheral nervous system: Lumbosacral plexopathy and polyradiculopathy, brachial plexopathy, Lhermitte's sign, radiation myelopathy, dysthesia, motor neuron syndrome, muscle atrophy, fasciculations, areflexia Central nervous system: Encephalopathy, Bulbar palsy, cranial nerve injury, optic neuropathy, cochlear damage, radiation-induced central nervous system tumors (glioma, meningioma, vestibular schwannoma), diffused cerebral injury, stenosis/occlusion of extracranial or intracranial cerebral arteries, stroke-like migraine attack after radiation therapy (SMART syndrome), radiation necrosis

used class of chemotherapy drugs include Vinca alkaloids. This class of drugs has been reported to disrupt microtubule functioning, promote degeneration and axonal atrophy in dosages more than 2 mg/m^3 (11). Furthermore, radiotherapy inhibits cell division and promotes neurotoxicity by inducing vascular damage, hormonal disruption, alteration in cytokine expression, neural stem cell deletion, neural fibrosis (12, 13) (**Table 1**) [for a detailed review see (14)]. Several factors can influence the extent of neurotoxicity induced by radiation therapy i.e., volume of brain irradiated, fraction (>200cGy), cumulative radiation dosage (<5,000cGy), simultaneous administration of chemotherapy, administration of therapy in age groups <7 years old or more than 60 years old and pre-existence of stroke (15). Despite precarious planning to irradiate specific parts and minimize neuropathy, radiation-induced neurotoxicity is still prevalent in several parts of the neural axis (12).

There are several pathophysiological mechanisms by which neurotoxicity can be induced. For instance, therapeutic interventions can impart direct damage to the neuron, glia, and modify the cerebral microvasculature (8, 16–18). Moreover, pathological analysis has also suggested that onset of neural necrosis, axonal degeneration due to microtubular and secondary myelin disruptions (19), can result in central and peripheral nervous system neurotoxicity. Although, several sensory, motor, and cognitive deficits have been discussed in the published literature that can result due to neurotoxicity. In this present perspective our objectives are:

a) Outline the impact of cancer treatment-induced neurotoxicity on gait and posture.

b) Discuss the applicability of music-based external auditory stimulations for facilitating gait and postural recovery in cancer patients.

MOTOR DEFICITS (GAIT AND POSTURE)

Research has conclusively demonstrated that joint dysfunctions in sensory, motor and cognitive domains due to neurotoxicity can affect activities of daily living, such as gait (5, 20, 21), posture (22), and promote falls. Epidemiological evidence suggests that the majority of the diagnosed patients are geriatrics i.e., 60–70 years old (23, 24). Spoelstra et al. (25), for instance, reported that geriatric patients with a history of cancer were more likely to fall (33%) as compared to patients with no history of cancer (29%). This higher risk of fall can be due to joint additional neurological deficits imposed by drug-induced neurotoxicity and an age-associated neurological decline (2, 25). Studies analyzing the spatiotemporal gait parameters have also reported larger decrements in gait performance for cancer patients (2, 20, 26). Marshall et al. (2), reported a significantly reduced gait velocity, step length, and an increased duration in timed up and go test in patients with cancer as compared to their healthy counterparts (5, 27). Similarly, kinematic discrepancies during gait performance are also documented. Wright et al. (28) analyzed gait performance (3-D motion analysis, EMG) following treatment for acute lymphoblastic leukemia. The authors reported a significant reduction in peak hip extension, knee flexion during the loading phase, plantarflexion during pre-swing, dorsiflexion during initial heel contact, lower ankle moments, and power outputs. The authors also reported that the patients exhibited excessive co-activations and an atypical "out of phase" motor unit firing of gastrocnemius during the late swing and premature firing of tibialis anterior during terminal stance.

Monfort et al. (22) too in a longitudinal analysis reported a significant decrease in balance (center of pressure perturbations in medioateral direction) in breast cancer patients receiving taxane-based chemotherapy. The authors further correlated this decrease in balance with patient-reported outcomes i.e., EORTC QLQ-CIPN20 subscales (European Organization for Research and treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy) i.e., increased pain, fatigue, and disruption in physical functioning reported with the treatment progression.

COGNITIVE DEFICITS

In addition to the motor deficits, patients receiving cancer treatment also exhibit heightened cognitive deficits [see chemobrain or chemofog (29)]. These deficits can persist years after the treatment and can considerably affect a patient's quality of life (30). A wide range of cognitive disorders are manifested by patients i.e., disruptions in executive functions, multitasking, concentration, attentional allocation, even memory recall, visuospatial function, and more (29–31). The pathophysiological changes which account for such deficits include white matter abnormality, regional brain volume differences in superior and middle frontal gyri, parahippocampal gyrus, cingulate gyrus, and precuneus (32, 33). Silverman et al. (34), in a PET study, reported that breast cancer patients who received chemotherapy 5–10 years prior had differences in inferior frontal gyrus, contralateral posterior cerebellum, and left inferior frontal gyrus. The authors also implied the onset of cognitive overload by reporting a larger activation pattern of frontal cortical structures i.e., pre-frontal cortex during a memory task (34). This decline in cognitive performance due to adverse neurotoxic effects of oncologic therapy in our opinion might be amplified when coupled with an age-associated decline in cognition. This, then, might promote a major decline in cognitive performance, further affecting autonomic functions such as posture, gait (35). For instance, this reduced cognitive functioning might limit a patient's ability to effectively allocate attentional resources for instance in high-stress environments and instigate falls (36, 37).

SENSORY DEFICITS

A wide range of sensory deficits are accounted in patients due to neurotoxic effects on the nervous system (8). Evidence of optic neuropathy have been extensively documented due to radiotherapy, intra-arterial administration of drugs such as Carmustine, Oxaliplatin, Tamoxifen, and more (38, 39). Likewise, deficits in vestibular (40), and proprioceptive signaling (41), are also well reported. Vincent et al. (41) for instance, reported that administration of Oxaliplatin drug promoted the onset of movement disorders. The authors suggested that possibly neurotoxic changes impaired specific ionic current channels (NaPIC) on the sensory terminals of muscle proprioceptors further leading to a modified sensory encoding which could have affected motor functioning (41). Additionally, axonal degeneration of sensory neurons, which promotes receptor denervation, have also been associated with sensorimotor aberrations that affect motor execution (41–43). Bibi (44), for instance, reported that cancer therapy-induced neurotoxic changes can also promote pervasive deterioration in the autonomic mechanisms for sensory gating and sensory memory mechanisms. This contextual decline in the available state of sensory information might affect the state of a system to integrate sensorimotor information and develop internal models (45–47). Here, a mismatch incongruency of sensorimotor information or a decrease in the quality of perceptual information could promote sensorimotor deficits, further affecting motor planning, execution during gait, and postural performance (48, 49).

CONVENTIONAL REHABILITATION INTERVENTIONS

A few rehabilitation strategies have been discussed in the published literature that can enhance gait and balance dysfunctions in patients with cancer. These strategies include physiotherapy, physical exercises, virtual reality and more (21, 50, 51) (see **Table 2**). Moreover, to the best of our knowledge, only one recent systematic review has analyzed the influence of exercise rehabilitation interventions for managing deficits in gait and postural stability in cancer patients undergoing chemotherapy (21). Despite having a high prevalence for inducing fall-related morbidity and mortality (63), such a limited amount of research is a matter of concern for medical practitioners dealing with cancer patients. Therefore, the development of additional rehabilitation interventions that can be applied as an adjunct to conventional pharmacological interventions is strongly warranted.

PROSPECTIVE ROLE OF MUSIC-BASED THERAPIES: EXTERNAL AUDITORY STIMULATIONS

Music therapy has been extensively studied in cancer management [for detailed reviews see (64–66)]. This therapy has been reported to decrease pain, stress, anxiety associated

TABLE 2 | Conventional rehabilitation approaches for managing gait and postural deficits associated with neurotoxicity.

Disorders	Interventions
Gait	Physiotherapy (52)
	Physical exercise (53, 54)
	Virtual reality (obstacle crossing) (51)
	Sensorimotor balance training (55)
	Transcutaneous electrical stimulation (56)
	Joint stabilizers (56, 57)
Postural stability (static and dynamic)	Physiotherapy (58)
	Aerobic endurance training (55)
	Strength training (resistive TheraBand) (55, 59)
	Impact training (60)
	Home-based exercise programs (61)
	Virtual reality (obstacle crossing) (51)
	Closed kinematic chain exercises (62)
	Core stability ball exercises (62)
	Dynamic balance training (ankle point to point reach task) (51)
	Sensorimotor balance training (55)
	Transcutaneous electrical stimulation (56)
	Joint stabilizers (56, 57)

with cancer treatment and has also been documented to improve mood, relaxation, and quality of life (66). The studies predominantly deal with either active or passive types of music therapies (64–66). Here, the active therapy signifies playing musical instruments, improvisation, singing, and passive therapy signify listening to music, imagination (2, 3). Although the outcomes of these cumulative studies comprehend the beneficial psychological aspects of music therapy, the aim of this present study is to explore as to how motor rehabilitation might be facilitated by the application of music-based auditory stimulations?

Several studies have reported that a large component of motor (re)learning is dependent upon the extent of sensorimotor integration (67, 68). Here, amplification of sensorimotor representations by enhancing the salience of sensory afferent information while minimally engaging the deficit cognitive resources should be a major objective (69–71). This enhanced sensorimotor representations of body schematics and executed movements could facilitate the development of efficient internal models (46, 72). Thereby, enhancing the system's ability to acquire, process, and execute a skill in an efficient manner (73–75). In the published literature, movement sonification and rhythmic auditory cueing are two well-studied auditory stimulations that have been demonstrated to incur beneficial effects in motor performance by jointly targeting sensorimotor and cognitive deficits (76–83).

Rhythmic auditory cueing can be defined as a repetitive isosynchronous auditory stimulation applied with an aim to simultaneously synchronize motor execution (74, 84). Real-time kinematic auditory feedback (movement sonification) on the other hand is a comparatively new approach (85). Such type of an intervention involves mapping of movement parameters on the sound components, such as pitch, amplitude with a very minimal or no latency (72) [for differential effects of auditory cueing and sonification please see (82)]. Recent systematic reviews and meta-analyses have conclusively demonstrated the benefits of these auditory stimulations on gait and postural stability with aging (77), in neurological disorders such as stroke (82, 83, 86), parkinsonism (78), cerebral palsy (80), and multiple sclerosis (81). Findings from these reviews can have widespread implications for counteracting neurotoxicity related motor deficits in cancer patients.

For instance, rhythmic auditory cueing has been reported to enhance gait, and postural stability performance across all age groups (77). We have previously stated that the majority of the affected cancer population groups are geriatrics and that this factor according to several studies accounts for the majority of fall-related morbidity and mortality (25). Likewise, stroke, a common neurotoxic manifestation also account for widespread movement, cognitive disorders (2). Ghai (82) has demonstrated that both rhythmic and real-time auditory stimulations can benefit stroke patients in recovering their motor and cognitive performances. Additionally, we also presume that damage induced by white matter deficits, which are a prominent manifestation of neurotoxicity can also be supplemented by the application of auditory stimulations (32, 87). Ghai and Ghai (81) recently demonstrated the beneficial effects of auditory cueing on patients with multiple sclerosis (a multifocal white matter disease). The authors stated evidence which supports the possibility of white matter re-organization with auditory-motor training [see (88)].

Likewise, Ghai et al. (78), demonstrated the beneficial effects of auditory cueing on movement disorders exhibited during parkinsonism. Chemotherapy, for instance with Metoclopramide (dopamine receptor antagonist) has been associated with inhibition of D_2 receptors in putamen (89). This disruption has been reported to result in movement disorders which are identical to that exhibited by a patient in Parkinson's disease (90). Here, dysfunctions between the striatopallidal projections could affect the internal timing mechanism of a patient in a similar manner as of a patient with Parkinson's disease. In this instance, the application of external auditory stimulations could assist in movement execution by providing an external cue to time movements. The external cueing can effectively bypass the deficit internal cueing pathway (Cerebellum-putamen-thalamus-pre supplementary motor area-supplementary motor area-primary motor area) through an alternative preserved pathway between (cerebellum-thalamus-parietal cortex-premotor area-primary motor area) and facilitate motor activity (91) (**Figure 1**).

Furthermore, we presume that the auditory stimulations could counteract sensory-perceptual deficits i.e., hearing, visual loss by enhancing the salience of sensory afferent information and aiding in the development of sensorimotor representations. For instance, Schmitz et al. (92) in a neuroimaging study reported that observation of a convergent sensory feedback can enhance activations in frontoparietal networks, action

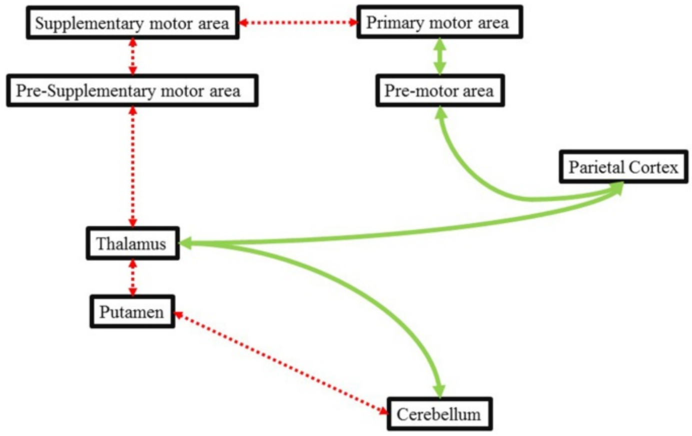

FIGURE 1 | Illustrating the deficit internal cueing pathways (dotted red line) and how external cueing might bypass this deficit pathway via an alternative route (green line). Adapted from Nombela et al. (91) and Ghai et al. (78).

observation system i.e., superior temporal sulcus, Broadman area 44, 6, insula, precentral gyrus, cerebellum, thalamus, and basal ganglia (92). The activations in these areas are associated with biological motion perception, thereby suggesting an enhancement in sensorimotor representation that might strengthen the perceptual analysis of a movement, ultimately resulting in efficient motor planning and execution (92).

Recent evidence has also demonstrated that auditory stimulations can even facilitate proprioceptive perceptions (93). Ghai et al. (94) demonstrated that concurrent auditory feedback can facilitate enhancements in knee-proprioception. Hasegawa et al. (95) too demonstrated that auditory biofeedback training resulted in enhanced spatiotemporal components of postural stability. Therefore, practical implications can be derived for cancer survivors, where deficits in proprioceptive perceptions are quite prominent (94, 96). According to Hasegawa et al. (95), auditory-motor training promoted a challenging environment that could have facilitated proprioceptive integration [for further insights on neuroimaging data see (97)]. Additional mechanisms by which auditory stimulations can facilitate motor performance are that they can provide explicit guidance to time/execute movements (94), reduce variability in musculoskeletal co-activation (98, 99), provide error feedback (100), enhance auditory-motor imagery (101, 102), allow cortical re-organization (103, 104), facilitate neural plasticity (105, 106), and even facilitate neural regeneration (107–109).

We would also like to draw the reader's attention toward literature suggesting how auditory stimulations might act by counteracting deficits in cognitive processing. Firstly, auditory stimulations have been suggested to strengthen attentional allocation (97). This might allow a patient to effectively switch between different tasks at hand without experiencing cognitive overload and/or movement failure. Secondly, enhanced cross-modal processing between auditory and proprioceptive signals can also circumvent cognitive overload and alleviate motor performance (94, 110). Thirdly, adjoining auditory stimulations with music can be an additional way to overcome cognitive deficits. For instance, coupling the auditory stimulations with musical mnemonics might facilitate synchronization of the oscillatory network in the prefrontal regions (111). Here, Thaut et al. (111) has reported that mnemonics might facilitate "deep encoding" during the acquisition phase of learning and might also amplify the internal timings of neural dynamics in the brain which are normally degraded by demyelination process in multiple sclerosis [also see (81)]. As demyelination is also a prominent neurotoxic manifestation of radiotherapy (8), transferrable beneficial effects on cognitive performance could be expected. Moreover, recent research also suggests that in addition to reducing cognitive overload in patients with stroke, the external auditory cueing via music might facilitate, reorganize deficit cortical structures (107–109). For instance, merging the external auditory stimuli with music can allow facilitation of neural network including prefrontal, and limbic cortex this, in turn, has been associated with cognitive and emotional recovery (109). Likewise, incorporating the component of music with external auditory stimulations might yield additional benefits in terms of reducing anxiety and stress (112). Studies have demonstrated that music therapy can allow a reduction in pain, fear-related stress [reduced salivary cortisol (113)], and anxiety outcomes (112). This can allow increased patient adherence toward medical procedures involved during cancer therapies and screening, for instance, screening mammography (114), sigmoidoscopy (115), colonoscopy (113), and even prostate biopsy (112, 116). Facilitation in the functioning of these mechanisms can have widespread influence on the regulation of cancer patient-related outcome and even the disease progression.

An additional outcome that can have important implications in management with auditory stimulations is the length of auditory-motor training duration. Here, interpretations can be drawn from neuroimaging research by Bangert and Altenmüller (117), and Ross et al. (106). Both the studies report that an auditory-motor training facilitates learning by acting on the rich neuroanatomical interconnectivity between the respective regions. The authors report a brief training duration lasting between 20 and 30 min to facilitate plasticity. Likewise, several of the published reviews and meta-analyses have also suggested a similar temporal course i.e., training session lasting for 25–40 min for auditory-motor training regimens (77, 78, 118). This training duration is relatively smaller as compared to conventional physiotherapy and physical exercise strategies discussed in the review by Duregon et al. (21). Therefore, beneficial implications in terms of cost-effectiveness and an enhanced prognosis in cancer survivors can be expected. Furthermore, we would also like to emphasize on the viability of the auditory stimulations, as a home-based intervention. Developing home-based interventions, are efficient for population groups in developing countries where lack of proper medical exposure accounts for widespread cancer-related morbidity and mortality (23). Wonders et al. (61) have also reported that home-based interventions can indeed impart beneficial effects in cancer survivors by reducing the peripheral neuropathic symptoms and enhancing the quality of life. We propose that in a home-based scenario patients can be taught by medical experts to utilize established smartphone rhythmic auditory cueing applications, such as Walkmate (119) to train gait effectively.

Finally, this perspective is a preliminary attempt to instigate scientific discussions for developing efficient rehabilitation protocols while using auditory neuroprosthetics based rehabilitation approach for enhancing motor recovery in patients with cancer. Incorporating these rehabilitation protocols with other sensory augmentation strategies such as virtual reality (120), joint prostheses (121–123), electrical stimulations (124) might have additional implications for enhancing the prognosis during cancer therapy. We have mentioned several mechanisms and findings from our previous review work, which could serve as the groundwork for future studies that could help design sensorimotor training regimens for the benefit of cancer population groups. Future studies are strongly recommended to analyze the effects of gait training with music-based auditory neuroprosthetics as a possible mechanism to counteract neurotoxic deficits because of cancer treatment.

AUTHOR CONTRIBUTIONS

SG conceptualized the perspective article. IG contributed in the formulation of the manuscript. Both authors approved the final draft.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix

Ethical approval document for the experimental studies

Leibniz
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20.10.2017

Ethikvotum

EV LUH 12/2017

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Die Zentrale Ethikkommission der Leibniz Universität Hannover bescheinigt nach eingehender Prüfung hiermit unter Auflagen die ethische Unbedenklichkeit des Vorhabens zum Thema

"socSMCs"

von Herrn Prof. Dr. Alfred Effenberg (Eingangsdatum des Antrags: 11.07.2017).
Die verpflichtenden Auflagen sind in der Anlage aufgeführt.

Mit freundlichen Grüßen,

Prof. Dr. H. Blume
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Chapter 1: Effect of rhythmic auditory cueing on aging gait: A systematic review and meta-analysis

Supplemental Data

Supplemental Table 1. Sample search strategy EMBASE.

DATABSE	**EMBASE**
DATE	**10/07/2017**
STRATEGY	**#1 AND #2 AND #3 AND #4 AND #5**
#1	(‘rhythmic auditory feedback’ OR ‘rhythmic auditory cueing’ OR ‘rhythmic acoustic feedback’ OR ‘rhythmic auditory entrainment’ OR ‘metronome feedback’ OR ‘metronome’ OR ‘rhythmic metronome feedback’ OR ‘acoustic stimulus’ OR ‘acoustic feedback’ OR ‘acoustic cueing’ OR ‘external stimuli’ OR ‘external feedback’ OR ‘external cueing’ OR ‘music therapy’ OR ‘Neurological music therapy’ OR ‘tempo’ OR ‘beat’ OR ‘rhythm’ OR ‘RAC’ OR ‘NMT’)/de OR (rhythmic auditory feedback OR rhythmic auditory cueing OR rhythmic acoustic feedback OR rhythmic auditory entrainment OR metronome feedback OR metronome OR rhythmic metronome feedback OR acoustic stimulus OR acoustic feedback OR acoustic cueing OR external stimuli OR external feedback OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT)ti,ab
#2	(‘cognitive task’ OR ‘concurrent task’ OR ‘dual task’ OR ‘dual task’ OR ‘dual task paradigm’ OR ‘dual task paradigm’ OR ‘cognitive task training’ OR ‘dual task training’ OR ‘dual task training’)/de OR (cognitive task OR concurrent task OR dual task OR dual task OR dual task paradigm OR dual task paradigm OR cognitive task training OR dual task training OR dual task training’):ti,ab
#3	(‘rehabilitation’ OR ‘treatment’ OR ‘rehab’ OR ‘management’ OR ‘therapy’ OR ‘physiotherapy’ OR ‘physical therapy’ OR ‘prevention’ OR ‘risk prevention’)/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
#4	(‘age groups’ OR ‘adolescent’ OR ‘young’ OR ‘elderly’ OR ‘old’ AND (‘gender’ OR ‘male’ OR ‘female’)/de OR (age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female));ti;ab
#5	clinical trial/exp OR (‘intervention study’ OR ‘cohort analysis’ OR ‘longitudinal study’ OR ‘cluster analysis’ OR ‘crossover trial’ OR ‘cluster analysis’ OR ‘randomized trial’ OR ‘major clinical study’)/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab

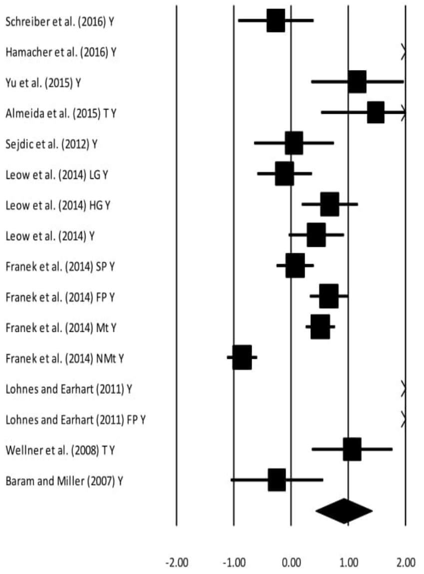
Supplemental Table 2. Individual Pedro scores.

Study	Total PEDRO	Point estimates & variability	Between group comparison	Intention to treat	Adequate follow-up	Blind assessors	Blind therapists	Blind subjects	Baseline comparability	Concealed allocation	Random allocation	Eligibility criteria
Dotov et al. (2017)	6	1	1	0	1	0	0	0	1	1	1	1
Maculewicz et al. (2016)	4	1	1	0	1	0	0	0	0	0	1	1
Terrier (2016)	4	1	1	0	1	0	0	0	0	0	1	1
Schreiber et al. (2016)	4	1	1	0	1	0	0	0	0	0	1	1
Hamacher et al. (2016)	5	1	1	0	1	0	0	0	1	0	1	1
Yu et al. (2015)	5	1	1	0	1	0	0	0	1	0	1	1
Almeida et al. (2015)	4	1	1	0	1	0	0	0	0	0	1	1
Kennel et al. (2015)	5	1	1	0	1	0	0	0	1	0	1	1
Roerdink et al. (2015)	5	1	1	0	1	0	0	0	1	0	1	1
Leow et al. (2014)	5	1	1	0	1	0	0	0	1	0	1	1
Franek et al. (2014)	4	1	1	0	1	0	0	0	0	0	1	1
Marmelat et al. (2014)	5	1	1	0	1	0	0	0	1	0	1	1
Hunt et al. (2014)	4	1	1	0	1	0	0	0	0	0	1	1
Wright et al. (2014)	5	1	1	0	1	0	0	0	1	0	1	1
Wittwer et al. (2013b)	4	1	1	0	1	0	0	0	0	0	1	1
Leman et al. (2013)	4	1	1	0	1	0	0	0	0	0	1	1
Bank et al. (2011)	5	1	1	0	1	0	0	0	1	0	1	1
Peper et al. (2012)	5	1	1	0	1	0	0	0	1	0	1	1
Sejdic et al. (2012)	5	1	1	0	1	0	0	0	1	0	1	1
Terrier and Dériaz (2012a)	4	1	1	0	1	0	0	0	0	0	1	1
Trombetti et al. (2011)	8	1	1	0	1	1	0	0	1	1	1	1
Roerdink et al. (2011)	5	1	1	0	1	0	0	0	1	0	1	1
Lohnes and	5	1	1	0	1	0	0	0	1	0	1	1

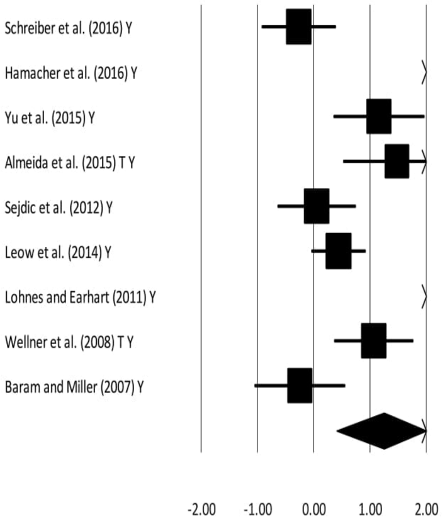
Earhart (2011)												
Baker et al. (2008)	6	1	1	0	1	0	0	0	1	1	1	1
Arias and Cudeiro (2008)	4	1	1	0	1	0	0	0	0	0	1	1
Wellner et al. (2008)	4	1	1	0	1	0	0	0	0	0	1	1
A.-M. Willems et al. (2007)	5	1	1	0	1	0	0	0	1	0	1	1
Baker et al. (2007)	6	1	1	0	1	0	0	0	1	1	1	1
Baram and Miller (2007)	4	1	1	0	1	0	0	0	0	0	1	1
Hausdorff et al. (2007)	5	1	1	0	1	0	0	0	1	0	1	1
A.-M. Willems et al. (2006)	4	1	1	0	1	0	0	0	0	0	1	1
Chen et al. (2006a)	4	1	1	0	1	0	0	0	0	0	1	1
Rochester et al. (2005)	6	1	1	0	1	0	0	0	1	1	1	1
McIntosh et al. (1997)	4	1	1	0	1	0	0	0	0	0	1	1
Thaut et al. (1992)	4	1	1	0	1	0	0	0	0	0	1	1

1: Point awarded, 0: Point not awarded

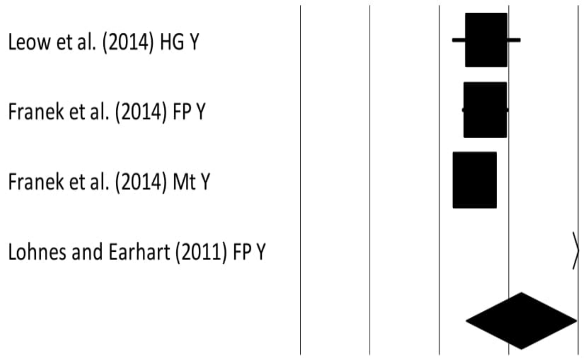
Meta-analysis Supplemental Figures



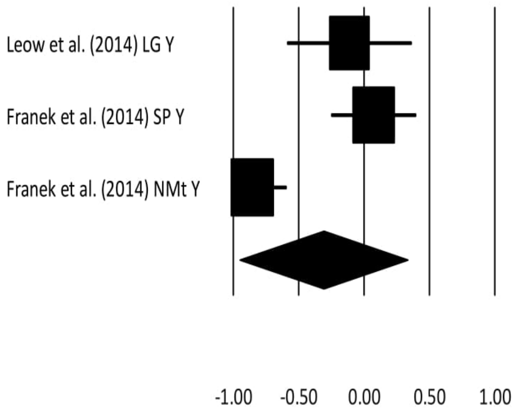
Supplemental Figure 1. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young participants. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



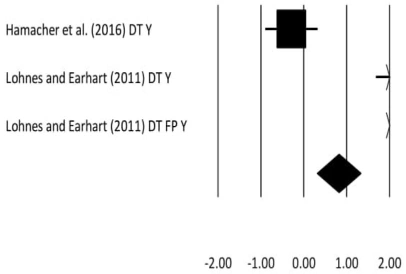
Supplemental Figure 2. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young participants, un-modulated rhythmic auditory cueing. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



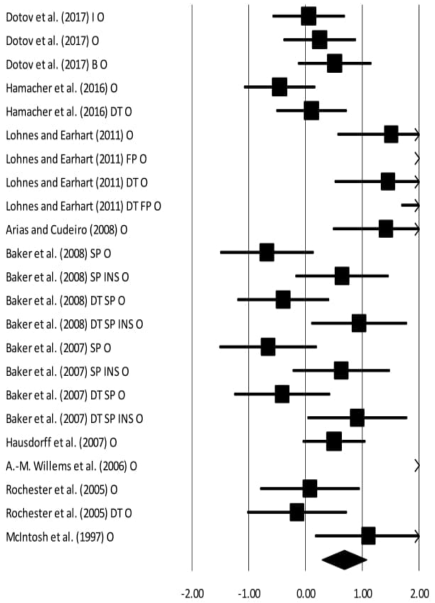
Supplemental Figure 3 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young participants with fast paced modified stimuli (measured according to preferred cadence). A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



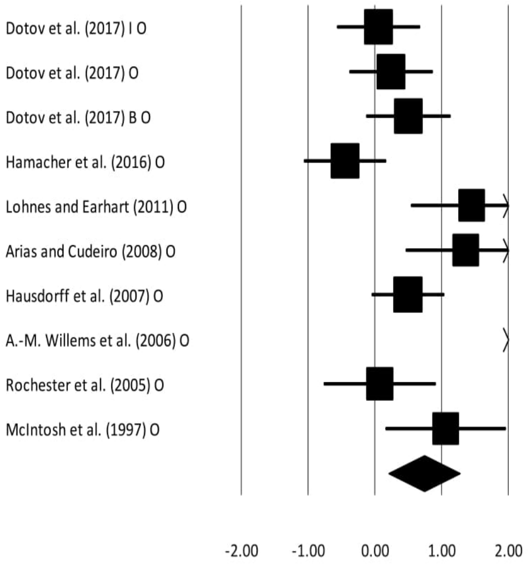
Supplemental Figure 4 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young participants with slow paced modified stimuli (measured according to preferred cadence). A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



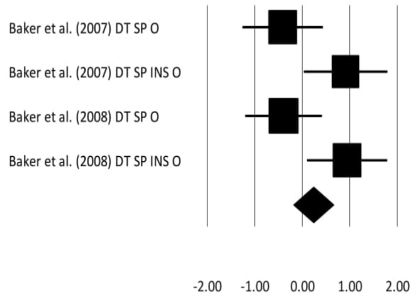
Supplemental Figure 5. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy young participants under dual-task conditions. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



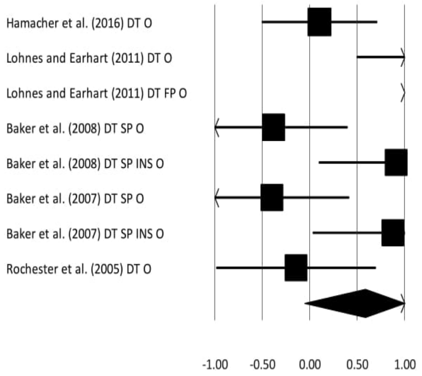
Supplemental Figure 6. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy old participants. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



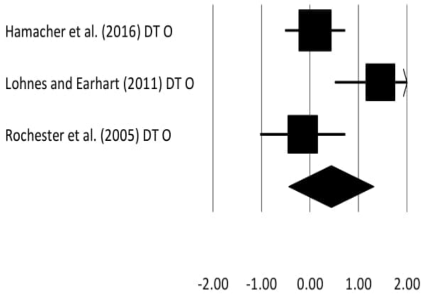
Supplemental Figure 7. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy old participants, un-modulated rhythmic auditory cueing. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



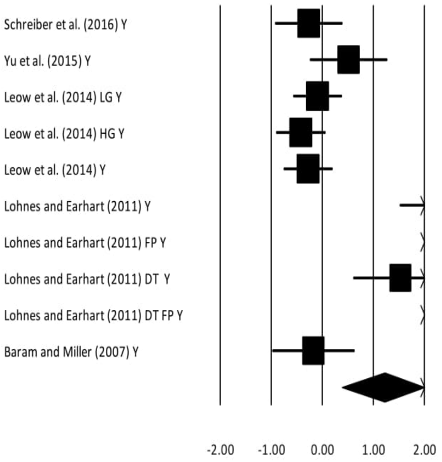
Supplemental Figure 8. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy old participants with slow paced modified stimuli (measured according to preferred cadence). A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback).



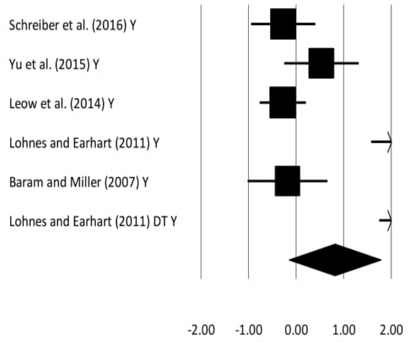
Supplemental Figure 9. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy old participants under dual-task conditions (fast & slow-paced cueing). A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



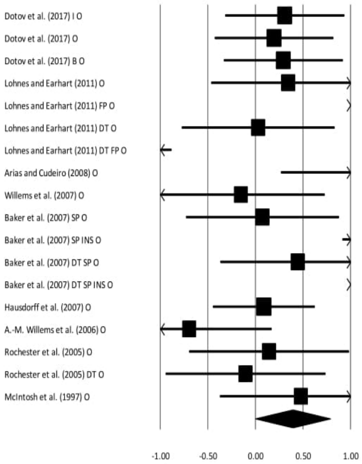
Supplemental Figure 10. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity among healthy old participants under dual-task conditions (un-modulated rhythmic auditory cueing). A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



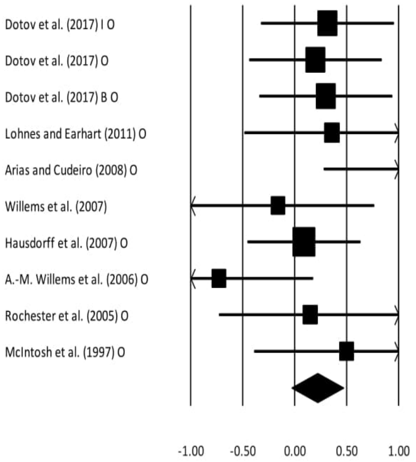
Supplemental Figure 11 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among healthy young participants. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



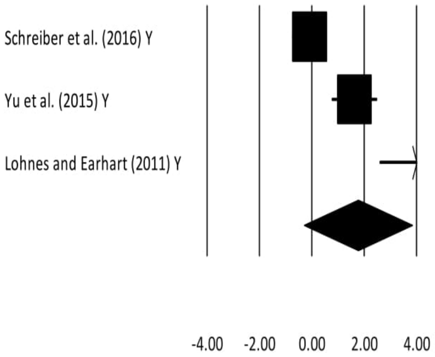
Supplemental Figure 12. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among healthy young participants (non-modulated rhythmic auditory cueing). A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



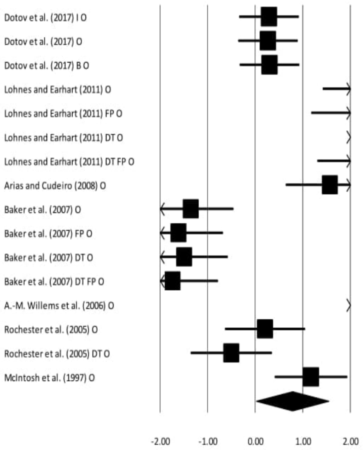
Supplemental Figure 13. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among healthy old participants. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



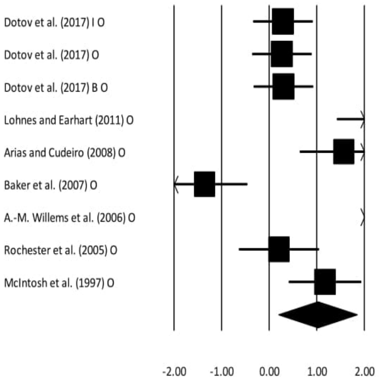
Supplemental Figure 14. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length among healthy old participants (non-modulated rhythmic auditory cueing). A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



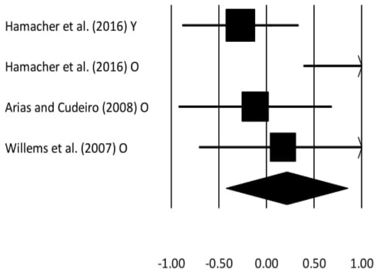
Supplemental Figure 15. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence among healthy young participants. A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



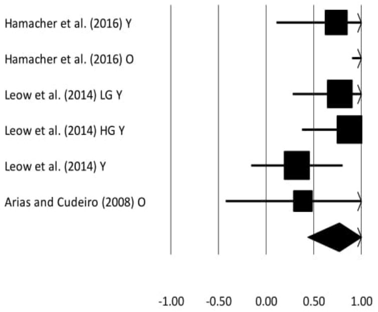
Supplemental Figure 16. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence among healthy old participants. A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



Supplemental Figure 17. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on cadence among healthy old participants (un-modulated rhythmic auditory cueing). A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



Supplemental Figure 18. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on Coefficient of variability for stride time among healthy young & old participants. A negative effect size indicated reduction in Coefficient of variability for stride time; a positive effect size indicated enhancement in Coefficient of variability for stride time. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)



Supplemental Figure 19. Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on Coefficient of variability for stride length among healthy young & old participants. A negative effect size indicated reduction in Coefficient of variability for stride length; a positive effect size indicated enhancement in Coefficient of variability for stride length. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative mean difference indicates a favorable outcome for control groups; a positive mean difference indicates a favorable outcome for experimental groups. (O: Old, Y: Young, FP: Fast paced, SP: Slow paced, DT: Dual-task, I: Isosynchronous, B: Biological variability, LG: Low groove, HG: High groove, INS: Instructions, Mt: Motivating feedback, NMt: Non-motivating feedback)

Chapter 2: Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis

Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review & meta-analysis

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Table 1 Studies analysing the effects of rhythmic auditory cueing on gait

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro score	Disease duration	Assessment tools	Research design	Sonified elements	Conclusion
Dotov, et al. [91]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 7F, 12M (60) Ct: 7F, 12M (60)	6	Exp: 6 (3-20 years)	Coefficient of variation of inter stride interval, cadence, gait velocity, stride length, deterended fluctuation analysis of short-long term series of inter-response-interval correlations, circular statistics for synchronization of footfall and beat	Pre-test, gait performance with/without rhythmic auditory cueing (no variability, biological variability, non-biological variability; randomized), post-test	Rhythmic auditory cueing with no variability, biological variability and non-biological variability at +10% of preferred cadence Magnitude of biological and non-biological variability: 2% of inter-beat-interval Metronome sequence: triangle timbre Musical excerpts Amplitude modulated noise: Modulated on musical excerpt with drum ensemble, discarding tonal information	Significant enhancement in cadence and coefficient of variation for inter stride interval after rhythmic auditory cueing in all conditions for both Exp and Ct. Significant effect of rhythmic auditory cueing that was amplitude modulated for biological variability as compared to isosynchronous metronome cueing on short-long term correlation for term series of inter-response-interval correlations in both Exp and Ct. Enhanced synchronization, but reduced short-long term correlation for term series of inter-response-interval correlations during metronome based isosynchronous cueing as compared to cueing with amplitude modulated for biological variability in both Exp and Ct.
Dalla Bella, et al. [93]	Effects of auditory cueing on gait in patients affected from Parkinsonism	Exp: 5F, 9M (66.5±7.2) Ct: 10F, 10M (66.4±7.8)	6	Exp: 8.0±2.8 years	Gait: Cadence, stride length, stride length variability, gait speed, stride time, stride time variability, synchronization accuracy and inter-step interval Hand tapping: Adaptation Index, phase correction, synchronization accuracy and variability	I: Pre-test, 3 training session/ week for 1 month. Three trials, 30 minutes each with 3 phases (10 minutes each) i.e. 1st and 3rd phase cued with music for 8 min, followed by 2 min of no feedback gait, post-test, follow-up 1 month after training II: Hand-tapping in isochronous sequence of 60 piano tones, same procedure above	Music beat rhythm adjusted to patient's preferred cadence Patients trained with beat frequency -10%, +10% of their preferred cadence Piano tones (tone frequency: 1319Hz) Inter-onset arrival: 600, 450 and 750ms.	Significant enhancement in gait speed in both Exp and Ct after training and with follow-up. Significant reduction in stride time variability after training, however, effect not seen at follow-up. Significantly shorter inter-step interval with -10% input as compared to +10%, however synchronization variability significantly increased with +10%. No effects on synchronization accuracy. Significantly reduced synchronization variability in hand tapping task with auditory input. Significant enhancement in adaptation index, and phase correction relative to group average was reported.
Chen, et al. [87]	Effects of auditory cueing on walking turns in patients affected from Parkinsonism	6F, 8M (57-67.3)	4	10.6± 5.8 years	Gait velocity, step length, cadence and freezing of gait score	Gait performance with clock and counter clockwise turns, with/without auditory and/or visual cueing and with/without dual task (carrying a tray with cup of water)	Rhythmic auditory cueing at -10% or +10% of preferred cadence	Significant enhancement in gait velocity, freezing of gait score with auditory cueing in both single and dual task conditions. Significant enhancement in gait velocity (dual-task only), step length, cadence and freezing of gait score in audio-visual condition in both single and dual task conditions.
Pau, et al. [119]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	6F, 20 M (70.4±9)	4	7.5±5.4 years	Gait speed, cadence, stance phase %, swing phase % and double support %, step length, step width, dynamic range of motion for hip flexion/extension, knee flexion/extension, ankle dorsiflexion/plantarflexion, gait variable score (pelvic tilt, pelvic rotation, pelvic obliquity, hip flexion-extension, hip abduction-adduction, hip rotation, knee flexion-extension, ankle dorsi-plantarflexion, foot progression) and gait profile score	Pre-test, gait training for 45 minutes' session, twice/week for 5 weeks, post-test Home training for 30 minutes' session, 5 days/ week for 12 weeks, follow up post-test after 17 weeks	Rhythmic auditory cueing (beats) for +10% (if cadence below normality), less than 10% difference (if cadence below but close to normality), at preferred cadence (if cadence above normality)	Significant enhancement in step length, gait speed, cadence, swing phase % after 5 weeks of supervised training and 17 weeks of home training with rhythmic auditory cueing as compared to baseline. Significant enhancement in step width after 17 weeks of training with rhythmic auditory cueing as compared to baseline and 5-week training. Significant reduction in stance phase % (5-week only) and double support % after 5 weeks of supervised training and 17 weeks of home training with rhythmic auditory cueing as compared to baseline. Significant reduction in gait profile score, gait variable score (hip flexion-extension) after 17 weeks of training with rhythmic auditory cueing as compared to baseline and 5-week training. Significant enhancement in gait variable score for (ankle dorsi-plantarflexion) after 17 weeks of training with rhythmic auditory cueing as compared to baseline and 5-week training. Significant enhancement in dynamic range of motion at hip flexion-extension (17-week> 5-week), knee flexion-extension after 5 weeks of supervised training and 17 weeks of home training with rhythmic auditory cueing as compared to baseline.
Zhao, et al. [198]	Effect of rhythmic auditory cueing with google glass on gait in patients affected from Parkinson's disease	3F, 9M (66.8±6.8)	5	13.6± 6.7 years	Cadence, deviation in cadence, stride length, stride length variability, gait speed and freezing of gait (duration/trial)	Gait performance in a wide/narrow 180° turn, full 360° turn, 90° turn track, across a doorway with/without rhythmic metronome cueing at preferred cadence, visual (LED/optic flow)	Rhythmic metronome cueing (80-124 steps/min i.e. preferred cadence)	Significant enhancement in stride length, gait speed (doorway course) with rhythmic metronome cueing. Significant reduction in stride length variability, cadence (narrow and full turn course) with rhythmic metronome cueing. No effect on freezing of gait with rhythmic metronome cueing. Rhythmic metronome cueing preferred as compared to visual cueing by patients.
Baram, et al. [199]	Effects of auditory feedback on gait in patients affected from Parkinson's disease	2F, 14M (69.9±7.8)	5	6.1±4.6 years	Gait speed, stride length, 10 metres walking test	Pre-test, followed by rhythmic auditory feedback and 15 min follow-up short term residual performance test	Clicking sound generated with gait step	Significant enhancement in gait speed and stride length with rhythmic auditory cueing. Significant enhancement in short-term residual performance with auditory cueing.

Son and Kim[197]	Effect of rhythmic auditory cueing on arm and trunk kinematics during gait in patients affected from Parkinson's disease	8F, 5M (64.8±6.8)	4	64.2± 37.8 months	Arm swing amplitude and trunk rotation	Gait performance with/without rhythmic auditory cueing and/or visual cueing (strips at 40% distance of participant's height)	Rhythmic metronome cueing +20% faster than preferred cadence	Significant enhancement in arm swing amplitude with auditory cueing as compared to visual, audio-visual and no stimuli condition Enhancement in trunk rotation range with audio-visual input as compared to visual, auditory and no stimuli condition.
Song, et al.[120]	Effect of rhythmic auditory cueing on gait and balance in patients affected from Parkinson's disease	Exp: 26F, 30M (65.7±8.1) Ct: 27F, 29M (66.1±7.9)	5	Exp: 6.9± 2.9 years Ct: 6.7± 3.1 years	Stride length, cadence, gait velocity, Unified Parkinson's disease rating scale II, III, 6 minutes walking test and berg balance score	Pre-test, gait training with rhythmic auditory and visual cueing for 30 minutes' session, 5 times/week, for 8 weeks, post-tests at 4 and 8 weeks	Rhythmic auditory cueing (beats) at preferred cadence	Significant enhancements in stride length, gait velocity, six minutes walking distance, berg balance score after 4, 8 weeks of training training with rhythmic auditory cueing and in Exp as compared to Ct. Significant reduction in unified parkinsons disease rating score II and III after 4, 8 weeks of training with rhythmic auditory cueing and in Exp as compared to Ct.
De Icco, et al.[123]	Effect of auditory cueing on gait in patients affected from Parkinson's disease	Exp: Acoustic: 4F, 7M (78.1±6.1) Visual: 6F, 5M (73.2±69) Ct: 12F, 12M (72.1±7.3)	4	Exp: 10±3.1 years Visual: 9± 2.4 years Ct: 10.5± 5.2 years	Number of stride, stride duration, stride length, stance % of stride, swing % of stride and gait speed	Pre-test, gait training with/without acoustic, visual stimulus 20 minutes session for 5 sessions/ week for 4 weeks, post-test, 3 months follow up post-test	Rhythmic metronome cueing with frequency between 60-120Hz at preferred cadence	Significant enhancement of gait speed, stride length and reduction in number of strides post acoustic cueing training. However, the effects reduced in the 3 months follow up post-test.
Bukowska, et al.[54]	Effect of auditory cueing on gait and postural stability performance in patients affected from Parkinson's disease	Exp: 15F, 15M (63.4±10.6) Ct: 10F, 15M (63.4±9.6)	4	Exp: 5.5± 3.9 years Ct: 6.7± 4.3 years	Gait velocity, step length, stride length, step width, Stance phase, swing phase, double support %, stride time, cadence, spatial (elongation of step, stride length, increase of velocity, step width), temporal (shortening of stance phase, double support, stride time, increase of cadence, extension of swing phase) parameters and Rhomberg's test	Pre-test, gait training and postural stability (with eyes closed/open) with auditory cueing for 45 minutes' session, 4 times a week for 4 weeks, therapeutic instrument music performance, patterned sensory enhancement facilitated gait phases, step length, body weight distribution, coordination and reciprocated movements of upper and lower limbs. Rhythmic auditory cueing enhanced gait speed, step length, walking up and down stairs	Auditory cueing by rhythmic metronome cueing, therapeutic instrument music performance, patterned sensory enhancement Percussion instruments for rhythmic cueing, metronome tone embedded in music	Significant enhancement in swing phase, cadence, step length, gait velocity and stride length after training in Exp as compared to Ct. Significant reduction in postural sway (eyes open, sagittal plane) stance phase, double support, stride time, after training in Exp as compared to Ct.
Benoit, et al.[94]	Effect of auditory cueing on gait and motor task performance in patients affected from Parkinson's disease	Exp: 5F, 10M (67.2±7.5) Ct: 10F, 10M (66.4±7.8)	5	Exp: 7.9± 2.7 years	Gait: Cadence, stride length, stride length variability, gait speed, stride time, stride time variability, synchronization accuracy and inter-step interval Hand tapping (BAASTA: Battery for the assessment of auditory sensorimotor timing abilities): Adaptation Index, phase correction, synchronization accuracy and variability	I: Pre-test, 3 training session/ week for 1 month. Three trials, 30 minutes each with 3 phases (10 minutes each) i.e. 1st and 3rd phase cued with music for 8 min, followed by 2 min of no feedback gait, post-test, follow-up 1 month after training II: Hand-tapping BAASTA: Anisochrony detection without tone/music, paced tapping to isochronous sequence/music, synchronization continuation	Music beat cueing adjusted to patient's preferred cadence Patients trained with beat frequency -10%, +10% of their preferred cadence Piano tones (tone frequency: 1319Hz) Inter-onset arrival: 600, 450 and 750ms.	Significant enhancement in gait speed and step length with auditory inputs in Exp, even during the follow-up test. Significant enhancement in synchronization accuracy with isochronous sequences after training. No significant differences in synchronization variability before training and synchronization accuracy and variability with music. Significant enhancement in detection of misaligned beat enhanced after training with follow-up. Exp group had higher thresholds than CT in duration discrimination and improved with training.
Harro, et al.[110]	Effect of rhythmic auditory cueing on gait in patients affected from Parkinson's disease	Exp: 2F, 8M (67.31±1.4) Ct:5F, 5M (46.9±9.4)	8	Exp: 3.7±2.2 years Ct: 4.2±2.4 years	Functional gait assessment, comfortable gait speed, fast gait speed, 6-minute walking distance test	Pre-test, gait training with rhythmic auditory cueing on ground (Exp), speed gait training on treadmill (Ct) for 30 minutes' session/week, for 6 week, 3-month follow up post-test	Rhythmic auditory cueing (+5-10bpm than preferred cadence in following sessions i.e. 105-144bpm)	Significant enhancement in comfortable gait speed, 6-minute walking distance, functional gait assessment after training with rhythmic auditory cueing. Significant enhancement in retention performance for functional gait assessment, comfortable gait speed, fast gait speed, 6-minute walking distance test during 3-month follow up post-test after training with rhythmic auditory cueing. No difference in between Exp and Ct.
Lopez, et al.[88]	Effect of rhythmic auditory cueing on gait in patients affected from Parkinson's disease	3F, 7M (45-65)	6	-	Cadence, stride length, gait speed	Gait performance with/without rhythmic auditory cueing at +25% of preferred cadence	Rhythmic auditory cueing at +25% of preferred cadence (Listenmee®)	Significant enhancement in cadence, stride length, gait speed with rhythmic auditory cueing.
Young, et al.[92]	Effect of rhythmic auditory cueing on gait in	I: Exp: 6F, 4M (64.6±5)	5	3.1± 1.3 years	I: Mean step length, % change stride length, mean step duration, %	I: Gait performance with/without verbal instruction, verbal instruction-metronome cueing, stepping	I: Rhythmic auditory cueing (Ct: 550-649ms, Exp: 600-700ms), foot step feedback on gravel (500, 600, 700ms)	I: Significant reduction in stride length variability, stride duration variability for stepping sound and stepping sound-verbal instructions as compared to

	patients affected from Parkinson's disease	Ct: Healthy 6F, 4M (63.9±4) II: same as I III: same as I			change in variability of stride length, duration II: same as I III: same as I	sound, stepping sound-verbal instructions, for small and wide stride length (randomized) II: Gait performance with/without stepping sound, verbal instruction-stepping sound feedback, synthesized gravel sound, synthesized gravel sound-verbal instructions, for small and wide stride length (randomized) III: Gait performance with/without motor imagery, motor imagery-stepping sound feedback, synthesized gravel sound, synthesized gravel sound-motor imagery, for small and wide stride length (randomized)	II: Rhythmic auditory cueing (Ct: 550-649ms, Exp: 600-700ms), foot step feedback on gravel (500, 600, 700ms), synthesized gravel step sound corresponding to plantar force (developed by using ground reaction forces vector to modulate both intensity envelop and central frequency of bandpass filter applied to stochastic noise impulse signal) III: same as II	metronome and metronome-verbal instructions in Exp. Significant reduction in stride length variability for stepping sound and stepping sound-verbal instructions and metronome-verbal instructions in Exp as compared to Ct. No effect of auditory cueing or instructions on mean step duration. II: Significant enhancement in step length with metronome-verbal instruction as compared to synthesized sound, synthesized sound-verbal instructions. No effect of auditory cueing or instructions on mean step duration. Significant reduction in stride length variability with synthesized feedback as compared to footstep feedback-verbal instruction, synthesized feedback-verbal instructions, and Ct group. Significant reduction in stride duration variability in Exp as compared to Ct. III: Significant enhancement in step length (long steps) with stepping sound, stepping sound-verbal instruction as compared to synthesized feedback, synthesized-verbal instructions. Significant enhancement in step length with synthesized feedback in Ct as compared to Exp. No effect of acoustic feedback or instructions on mean step duration. Significant reduction in stride length variability with stepping, synthesized feedback, stepping-verbal instructions. Significant enhancements in stride length with rhythmic auditory cueing (synthesized) and motor imagery together. No effect on stride duration parameters.
Hove, et al. [154]	Effect of auditory cueing on gait performance in patients affected from Parkinson's disease	Exp: 12F, 8M (69.2±7.7) Ct: 2F, 16M (24.7±2.7)	4	Exp: 3.6 years	Step-tone synchronization, Deterended fluctual analysis and self-reported stability on Likert scale (1-7)	Pre-test, gait performance with under counterbalanced: no auditory, fixed rhythmic auditory tempo, interactive rhythmic auditory tempo (Walkmate), post-test for retention	100ms sine-tone from 523-700 Hz Interactive rhythmic cueing directed at period and phase adjustment	Significantly enhanced step-tone synchronization, fractal scaling and self-reported stability in both Exp and Ct groups when interactive auditory input was present as compared to fixed rhythmic auditory input.
Kadivar, et al. [200]	Effect of auditory cueing on gait performance in patients affected from Parkinson's disease	Exp: 3F, 5M (73.2±2.2) Ct: 2F, 6M (70.5±2.2)	5	Exp: 8.9± 1.8 years Ct: 7.5± 1.2 years	Dynamic gait index, unified parkinson's disease rating scale, Tinetti gait and balance tests, time up and go test and freezing of gait questionnaire.	Pre-test, gait training with rhythmic auditory input at 0%, ±10%, ±20% of preferred cadence, for front, side and back steps for 45-60 min, 3 times per week, for 6 weeks, post-test (last day of training, follow up tests 1 week, 4 weeks and 8 weeks)	Rhythmic tone cueing at 0%, ±10%, ±20% of preferred cadence	Significant enhancement in dynamic gait index, Tinetti gait and balance tests and time up and go test with enhancements persisting in post-tests for last day of training, follow up tests 1 week, 4 weeks and 8 weeks. Significant enhancements in unified Parkinson's disease rating scale, freezing of gait questionnaire score in post-tests for last day of training, follow up tests 1 week, 4 weeks.
Rochester, et al. [68]	Effects of rhythmic auditory cueing on gait in patients affected from Parkinson's disease during "on" and "off" medications	19F, 31M (69.2±8.7)	6	8.6± 5.1 years	Gait velocity, stride amplitude, cadence, coefficient of variability for (stride time, double leg support)	Gait performed in "on" and "off" phase of medication cycle (2 weeks apart), with verbal instruction for taking larger steps and with/without rhythmic auditory cueing at preferred cadence	Rhythmic metronome cueing at preferred cadence	Significant enhancement in gait velocity, stride amplitude (no feedback only), cadence during the "off" phase of medication with rhythmic auditory cueing as compared to no feedback and verbal instructions. Significant reduction in coefficient of variability for (stride time, double limb support) during the "off" phase of dopaminergic medication with rhythmic auditory cueing as compared to no feedback. Significant enhancement in gait velocity, stride amplitude (no feedback only), cadence (verbal instruction only) during the "on" phase of medication with rhythmic auditory cueing as compared to no feedback and verbal instructions. Significant reduction in coefficient of variability for (stride time, double limb support) during the "on" phase of medication with rhythmic auditory cueing as compared to no feedback.
Lohnes and Earhart [106]	Effect of auditory cueing and dual-task on gait performance in participants affected from Parkinson's disease	Exp: 7F, 4M (70.2±6.8) Ct: 7F, 4M (70.8±10.4) 7F, 4M (24±0.8)	5	Exp: 9±5.3 years	Gait velocity, cadence and stride length	Patients performed gait with/without rhythmic auditory cueing at -10%, +10% of preferred cadence alone or with additional cueing strategy "think about larger strides" with/without -10% and +10% of auditory inputs tone, with/without dual-task "word generation task"	Metronomic cueing at -10% or +10% of preferred cadence.	Significantly enhanced gait velocity and stride length in Exp within combined condition of additional cues and auditory inputs. Significant increase in stride length in the dual-task setting wit auditory input and additional cues. Modulated auditory input affected gait parameters of Ct.
Ford, et al. [141]	Effects of auditory cueing on gait and treadmill	Exp I: 10M (67.1±4) Exp II: 10M (67.9±6.3)	7	Exp I: 3.7± 4.1 years	Step length, stride length, cadence, 6-meter walk time, distance, gait speed	Participants trained in gait on a treadmill with (Exp I)/without (Ct) rhythmic music cueing for 3 days/ week	Rhythmic music cueing	Significant enhancement in step length, stride length, 6 metre walk time and time up and go test (8th week only) for both 4th and 8th week post-tests after training with auditory cueing and treadmill training.

	training in patients affected from Parkinson's disease	Ct: 10M (68.6±5.2)		Exp II: 4.4± 2.3 years Ct: 7.4± 3.4 years	and time up and go test	and home training 3 days/week for 4 weeks, followed by 4 weeks of self-training Exp II. Ct group trained for walking 6 days/ week for 4 weeks.		Enhancement in gait speed, 6-minute walk distance, cadence (8th week only) for both 4th and 8th week post-tests after training with auditory cueing and treadmill training.
Espay, et al. [89]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	5F, 9M (50-79)	5	-	Gait velocity, cadence and stride length	Gait training for 30 minutes a session (evaluation and training in each session i.e. total 24 sessions), 3 sessions/ week for 8 weeks, gait training by auditory cueing tempo increased in middle of training by +10bpm	Rhythmic auditory cueing (5 parts: melody, chords, bass, percussion) music superimposed by metronome +5 beat increments from 60-165bpm	Significant enhancement in gait velocity, cadence and stride length after training with rhythmic auditory cueing.
Lim, et al. [11]	Effect of rhythmic auditory and visual cueing in gait for patients affected from Parkinson's disease	9F, 6M (73.3±11.7)	4	12.1± 4.2 years	Gait velocity, stride length, cadence	Pre-test, home gait training for 30 minutes' session/day for (at least) 2 weeks with virtual reality device, testing with/without device, visual, audio-visual cueing, post-test after 2 weeks training	Rhythmic auditory cueing for stepping sound at preferred cadence	Significant enhancement in gait velocity and stride length with combined audio-visual cueing. Significant enhancement in immediate retention measurement without device for gait velocity and stride length.
Arias and Cudeiro [29]	Effects of rhythmic auditory cueing on gait and physical activity for patients affected from Parkinson's disease	Early: 28F, 48M (67.5) Late: 37F, 40M (69)	7	Early: 4-11 years Late: 4-12 years	Percentage of time on static, dynamic activity, sitting, standing, gait, walking periods (>5, >10 seconds/hour)	Pre-test, gait training at home with rhythmic audio-visual cueing for 9 sessions of 30 minutes each over 3 weeks, under the supervision of therapist, post-test follow up at 9 weeks (early), 6 weeks (late)	Rhythmic auditory cueing (beep)	Significant enhancement in dynamic, static activities, gait and walking periods (>5, >10 seconds/hour) with rhythmic auditory cueing. Patients preferred rhythmic auditory cueing as the medium for cueing as compared to visual cueing modality.
Chaiwanichsiri, et al. [82]	Effects of auditory cueing on gait in patients affected from parkinso Parkinson's disease nism	Exp: Freezing of gait: 4F, 6M (68.2±8) Exp: No freezing: 3F, 6M (64.4±9.5) Ct: 2F, 8M (70.2±6.8)	6	-	Gait velocity, cadence, step length, turnaround time and freezing episodes	Patients performed gait at preferred cadence, followed by trials at +10% cadence with/without auditory cueing	Tone with wave frequency 4.625 Hz, deliver at pulses of 50ms and inter-pulse duration customized to obtain desired stimulation frequency	Significantly enhanced gait velocity, stride length and cadence in presence of auditory input +10% as compared baseline auditory feedback at preferred cadence. Significantly reduced episodes of freezing in presence of auditory cueing. Significantly reduced turnaround time in all groups in presence of auditory input.
de Bruin, et al. [95]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 5F, 6M (64.1±8.1) Ct: 6F, 5M (67±8.1)	8	Exp: 6.4± 4.2 years Ct: 4.5± 3.3 years	Gait velocity, cadence, stride time, stride length and Unified Parkinson's diseases rating scale	Pre-test, gait training 30 min session, 3times/week for 13 weeks, post-test With/without auditory cueing, dual-task (arithmetic task)	Music with tempo to cadence matched characteristics	Significant enhancements in gait velocity, stride time, cadence and motor symptoms with auditory cueing in Exp as compared to Ct. Enhancement in gait velocity and cadence with dual task with auditory cueing.
Elston, et al. [96]	Effects of auditory cueing on gait and quality of life in patients affected from Parkinson's disease	Early intervention: 8F, 13M (71.5±11.3) Late intervention: 5F, 15M (70.4±8.7)	8	-	Gait speed, Parkinson's disease questionnaire, fall assessment and Short form 34 version questionnaires	Pre-test, patients in early intervention acquainted to metronome for 5-10 min, tests at 4, 10, 14 weeks, Post-test Late intervention group introduced to metronome at week 10	Metronome cueing with beat frequency adjusted to preferred cadence	Enhancement in gait speed in early intervention group as compared to late intervention. No differences in outcomes from parkinson's disease questionnaire, fall assessment and Short form 34 version questionnaires
Rochester, et al. [85]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Early intervention: 28F, 48M (61.5-72) Late intervention: 37F, 40M (62.5-73)	8	Early: 7 (4-11) years Late: 8 (4-12) years	Gait speed, step length and cadence	Visual, auditory and somatosensory input (randomized) with/without dual task (carrying a tray) Early intervention: 30min for 9 sessions over 3 weeks, the next 3 weeks no training was given. Late intervention: No training for first 3 weeks, 30min for 9 sessions over 3 last weeks 6-week follow-up for both groups	Rhythmic beep cueing at preferred cadence	Significant enhancement in step length and gait speed in dual/ single task condition with training by auditory input. Enhancement of cadence with training by auditory input. Retention evident in 6 weeks follow up for the gait parameters.
Picelli, et al. [102]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	3F, 5M (65.1±4.7)	4	6.5± 1.5 years	Stride length, stride time, cadence, gait speed, single support duration, double support duration, single/double support duration, coefficient of variation of stride time, hip, knee, ankle sagittal plane range of motion and maximal values within pull, push-off phase of hip	Gait performed with/without auditory cueing at -10%, 0%, +10% of preferred cadence	Rhythmic metronome cueing at -10%, 0%, +10% of preferred cadence	Significant enhancement on stride length, stride time, cadence, gait speed, double support duration, single/double support duration and coefficient of variation of stride time. With highest effect of +10% auditory cueing. Significant reduction in ankle sagittal plane range of motion, and enhancement in pull-off phase hip joint power.

Rochester, et al. [122]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	3F, 18M (76.4±12.9)	6	-	Gait speed, step amplitude, step frequency, tandem stance and unified parkinsonian disease rating scale II and III	Pre-test, 30 min intervention for 9 sessions for 3 weeks with auditory cueing and with/without dual task (carrying a tray with glass of water), post-test With instructions "take a big step in beat time"	Rhythmic metronome cueing at preferred cadence	Significant enhancement in gait speed, for both single/ dual task condition with auditory input. Significant enhancement in step frequency in single task condition with auditory input. Significant reduction in step amplitude in both single and dual task condition with auditory input. Enhancement in step frequency with dual task and auditory input. Significant enhancement in unified parkinsonian disease rating scale II and III. Enhancement in tandem stance after treatment intervention.
Frazzitta, et al. [103]	Effects of auditory cueing with treadmill training on gait in patients affected from Parkinson's disease	Exp: I: 12F, 8M (71±8) II: 11F, 9M (71±7)	6	Exp I: 13.2± 4.1 years Exp II: 12.9±4.6 years	6-minute walking test distance, gait speed, Unified parkinson's disease rating scale, stride cycle and freezing of gait questionnaire	Pre-test, gait training on treadmill for 20 minutes/day for 4 weeks (28 sessions) with (Exp I)/without treadmill (Exp II) and with visual and auditory cueing, post-test	Rhythmic auditory cueing (synchronized with visual cueing)	Significant enhancement in 6-minute walking test distance, gait speed and stride cycle in Exp I as compared to Exp 2. Significant reduction in freezing of gait score in Exp I as compared to Exp II. No effect on unified parkinsons disease rating scale on both Exp I and Exp II.
Rochester, et al. [81]	Effects of cueing k on gait in patients affected from Parkinson's disease	9M (74.8±6.4)	4	6.1± 6.1 years	Gait speed, stride amplitude, cadence, coefficient of variation of step time, double limb support time	Pre-test, gait performance with/without auditory input, with/without dual task (carrying a tray with glass of water) With different instructions "step in beat time", "take big step in beat time"	Rhythmic beep cueing at preferred cadence	Significant enhancement in gait speed, stride amplitude with walking instructions "big step in beat time" and auditory input in both single and dual task conditions. The enhancements were higher for single task as compared to dual task setting. Reduced coefficient of variation of step time and coefficient of variation of double limb support time with auditory input, single/dual task, and additional instructions. Higher reduction for "big steps in beat time". Enhanced cadence for auditory input in both single and dual task conditions.
Bryant, et al. [108]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	4F, 17M (72±10.3)	4	6.6±4.3 years	Gait speed, cadence, stride length, double support time and base of support	Gait performed with rhythmic auditory cueing at 0%, +25% of preferred cadence, followed by 1 week of self-home training, 30 minutes per day, post-test	Rhythmic auditory cueing at 0% and +25% of preferred cadence	Significant enhancement in gait speed, stride length with rhythmic auditory cueing. Significant retention in gait speed, stride length, double support time, 1 week follow up test with auditory cueing training. Enhancement in cadence with auditory cueing both during initial testing and post 1-week training with auditory cueing.
Ma, et al. [97]	Effects of auditory cueing on rhythmic reach movements in patients affected from Parkinson's disease	11F, 9M (66.4±6.2)		3.7± 2.5 years	Movement time, amplitude of peak velocity, deceleration time and number of movement units	Participants performed reaching task with/without auditory input (marching, weather forecast sound), and with/without paying attention to the sound	Rhythmic marching auditory input (96-100 bpm), volume (62.4±3.2 decibels) and random weather forecast auditory input, volume (67.4±4.2 decibels)	No effect on movement variables with marching auditory input as compared to no attention, no sound conditions. Significantly poorer performance in weather forecast condition on arm movement variables with as compared to no attention, no sound conditions.
Nieuwboer, et al. [28]	Effects of auditory cueing on turn speed in patients affected from Parkinson's disease	Freezers: 29F, 39M (67.3±6.9) Non-freezers: 26F, 39M (66±8.1)	7	Freezers: 8.7± 4.7 years Non-freezers: 7.8± 5.1 years	Mean turning time	Pre-test, functional gait performed, participants picked up a tray with a cup of water and turned 180º while walking, with auditory, visual, somatosensory input (randomized), post-test	Rhythmic auditory cueing at preferred cadence	Significantly enhanced turning time with auditory input as compared to visual input, but no difference with somatosensory input. Short term carry-over evident after the treatment duration in post-test (with all three inputs trained).
Arias and Cudeiro [101]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 10F, 15M (65.9±7.6)- 9 patients' severe (71.3±3.2), 16 patients' mild (62.8±7.8) Ct: 6F, 5M (65.7±7.6)	5	Severe: 12.8± 7 years Mild: 6.7±4.6 years	Cadence, gait velocity, step amplitude, coefficient of variation for step amplitude and stride time	Patients performed gait with/without sensory rhythmic input from auditory, visual and audio-visual condition, with frequency ranging from 70-110% increment/decrement at ±10%	Rhythmic tone with wave frequency of 4625 Hz delivered at frequency ranging from 70-110% increment/decrement at ±10%	Significantly enhanced cadence, step amplitude in severely affected Parkinson's patients with auditory and audio-visual cueing. Significantly enhanced gait cadence, velocity, stride length with increased auditory input i.e. 70%, 80%, 90%... Significantly reduced coefficient of variation for stride time in severely affected Parkinson's patients with auditory and audio-visual cueing. Significant enhancement in cadence, step amplitude in Ct with auditory cueing. Reduced coefficient of variation of step amplitude and enhanced gait velocity in severely affected Parkinson's patients with auditory and audio-visual cueing.
Baker, et al. [114]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 9F, 5M (69.2±3.3) Ct: 7F, 5M (71.5±2.5)	7	Exp: 6.6± 3.2 years	Gait speed, coefficient of velocity for (step time, double limb support time)	Pre-test, functional gait performance with/without auditory cueing -10% of preferred cadence, attentional cue instructions "try to take big steps", together "take a big step with the beat", and with/without a dual task (a tray with 2 cups of water on top), post-test	Rhythmic auditory cueing at -10% of preferred cadence	Significant enhancement in gait speed for Exp with rhythmic auditory cueing and verbal instructions together under both single and dual task conditions. Significant reduction in coefficient of variability [step time, double limb support (single task only)] for Exp with rhythmic auditory cueing and verbal instructions together under both single and dual task conditions. Significant enhancement in gait speed for Ct with rhythmic auditory cueing and verbal instructions together under single task condition.
Rochester, et al. [118]	Effects of auditory cueing on gait in patients affected from	65F, 88M (67±7.5)	8	8.2±5 years	Gait velocity, step amplitude and step frequency	Pre-test, functional gait performed with/without auditory, visual or somatosensory cueing (randomized), with/without	Rhythmic auditory cueing at preferred cadence	Significant enhancement in step amplitude (dual task only), gait velocity and step frequency with auditory cueing and under both single and dual task conditions, as compared to no auditory cueing.

	Parkinson's disease					dual task (tray with two cups of water), Post-test, 3-weeks post-test		No effects evitable in 3-weeks post-test retention measurement.
Baker, et al. [113]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 9F, 6M (68.8±3.3) Ct: 7F, 4M (71.5±2.5)		6.5±3.2 years	Gait speed, step amplitude and step frequency	Pre-test, functional gait performance with/without auditory cueing -10% of preferred cadence, attentional cue instructions "try to take big steps", together "take a big step with the beat", and with/without a dual task (a tray with 2 cups of water on top), post-test	Rhythmic auditory cueing at -10% of preferred cadence	Significant effect of auditory cueing and attentional cue "big steps with beat" on step frequency in gait speed, step amplitude, step frequency (dual task only) in Exp in both single and dual task conditions. Significant effect of auditory cueing and attentional cue "big steps with beat" on step frequency in gait speed (single task only), step amplitude, step frequency in Ct in both single and dual task conditions. Non-significant effects on gait speed, step amplitude and step frequency with auditory cueing only. Effects not evitable once the auditory cueing was removed, in post-test.
Hausdorff, et al. [111]	Effects of auditory cueing on gait performance in patients affected from Parkinson's disease	Exp: 13F, 16M (67.2±9.1) Ct: 14F, 12M (64.6±6.8)	5	-	Stride time, gait speed, stride length, swing time, stride time variability and swing time variability	Pre-test, gait performance with/without rhythmic auditory cueing at preferred cadence, +10%, Post-test 2 and 15 min short term retention test	Rhythmic auditory cueing at 0% and +10% of preferred cadence	Significant enhancement in gait speed, stride length and swing time with auditory input in Exp. Significant enhancement in Stride time, gait speed, stride length, swing time at +10% input. Significant reduction in stride time variability and swing time variability in Exp at +10% input. Significant enhancement in Stride time, gait speed, stride length, swing time for immediate retention measurements for Exp for auditory cueing and at +10% input.
Nieuwboer, et al. [86]	Effects of auditory cueing on gait and posture in patients affected from Parkinson's disease	Early intervention: 28F, 48M (61.5-72) Late intervention: 37F, 40M (62.5-73)	8	Early: 7 (4-11) Late: 8 (4-12)	Posture and gait score, walking speed, step length, step frequency, functional reach, single stance, tandem stance, time-up and go test, freezing of gait questionnaire, Nottingham extended activities of daily life scale, falls efficacy scale, Parkinson's disease questionnaire, carer stain index and number of fall recording	Similar therapy in early and late intervention groups Early intervention: 30min for 9 sessions over 3 weeks, the next 3 weeks no training was given. Late intervention: No training for first 3 weeks, 30min for 9 sessions over 3 last weeks 6-week follow-up for both groups With auditory, visual, somatosensory input (randomized) at preferred cadence Tests at 1, 3, 6 and 12 weeks	Rhythmic auditory cueing at preferred cadence	Significant enhancement in posture and gait score for early and late intervention group. Significant reduction in severity of freezing. Significant enhancement in gait speed, step length and times balance tests for both groups. Significantly enhanced confidence for carrying out functional activities post training. Patients had higher compliance with auditory cueing (67%).
Willems, et al. [84]	Effects of rhythmic auditory cueing on turning in patients affected from Parkinson's disease	Exp: Freezers: 9 (62.6±3.9) Non-freezers: 10 (6.6±6.2) Ct: 9 (68.1±7.3)	5	Non-freezers: 6.2± 3 years Freezers: 11.8± 5.7 years	Steps (number, time, height, width, length), step length, step width, step duration, coefficient of variation of step duration	Gait performance while turning with/without rhythmic auditory cueing	Rhythmic metronome cueing at preferred cadence	Significant reduction in coefficient of variation of step duration for both Exp I and II with auditory cueing. No effects on step length, width and duration.
Chester, et al. [107]	Effects of auditory cueing on gait performance in patients affected from Parkinson's disease	10F, 19M (67.8±10.9)	5	-	Gait speed, relative gait speed stride time, stride length and single, double limb support	Gait performed with rhythmic auditory cueing at -10% and +10% of preferred cadence (randomized).	Rhythmic auditory cueing at ±10% of auditory cueing.	Significant enhancement of gait speed, relative gait speed, stride length, and single limb support with +10% of auditory cueing. Reduction in double limb support and stride time. Significant reduction of gait speed, relative gait speed and enhancement in stride time for -10% of auditory cueing.
Willems, et al. [83]	Effects of auditory cueing on gait performance in patients affected from Parkinson's disease	Exp: Non-freezers: 10 (60.6±6.2) Freezers: 10 (68.4±6.9) Ct: 10 (67.2±9.1)	4	Non-freezers: 6.2±3 years Freezers: 11.8±5.7 years	Step frequency, gait speed, stride length and double support %	Pre-test, gait performance at 0%, -20%, -10%, +10%, +20% of rhythmic auditory input (randomized), post-test	Rhythmic metronome cueing at preferred cadence i.e. 0%, -20%, -10%, +10%, +20%	Significant enhancement in gait speed, step frequency, stride length in Exp with auditory input at 0%, step frequency significantly enhanced in +10%, +20% and significantly reduced in -10%. Similarly, for the Ct in both step frequency and gait speed at 0%, -10%, +10%, +20%. Freezers and non-freezers showed similar response to rhythmic auditory inputs.
del Olmo, et al. [99]	Effects of auditory cueing on gait and finger tapping in patients affected from Parkinson's disease	Exp: 4F, 5M (61.2±5.5) Ct: 3F, 2M (63.2. ±4.8)	4	Exp: 5.7± 1.9 years	Gait velocity, cadence, step length, coefficient of variability of 2 consecutive steps, tapping frequency, coefficient of variation of interval of 2 consecutive taps, PET scan	Pre-test, gait training with rhythmic auditory cueing, rehabilitation for 1 hour/day, 5 days/ week for 4 weeks	Metronome cueing at rates between 30 and 150 bpm for gait Metronome at rates between 0.5 and 4 Hz for finger tapping.	Significantly reduced coefficient of variability for steps and finger tapping with auditory input as compared to Ct. No effect on gait velocity, cadence and step length. Significant hypo metabolism for Exp in right parietal and temporal lobes, left temporal and frontal lobes. Significant hypermetabolism in Exp in left cerebellum. Significant metabolic increment in Exp in right cerebellum, right parietal and temporal lobes.

Jiang and Norman [98]	Effects of auditory cueing on gait-initiation in patients affected from Parkinson's disease	Freeze history: 5F, 2M (67±13) No-freeze history: 7M (70±7)	5	Freeze: 6.1± 5.4 years No-freeze: 3.4± 1.4 years	Measures of magnitude: Posterior horizontal force, length of 1st and 2nd step, gait velocity and push-off force during gait initiation	Gait initiation and performance for 30 metres	High pitched beep at 40ms duration, interval set in auditory inputs per preferred gait.	No effect of auditory inputs on measures of magnitude, push-off force and gait velocity. No effects of auditory inputs on key events timing in gait initiation Significant enhancement in coefficient of variability with auditory cueing in between pre-posttests. No difference in coefficient of variability in Exp and Ct group. Significant enhancement in gait velocity, step length and cadence with auditory cueing.
del Olmo and Cudeiro [109]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 7F, 8M (61.7±5.2) Ct: 4F, 11M (63.1±4.2)		Exp: 7.2± 4.3 years	Gait velocity, step length, cadence, coefficient of variability i.e. temporal variability of gait	Gait performed at preferred and fast speed with and without a dual-motor task (thumb apposition task) for 1 hour/day for 5 days/week for 4 weeks while reproducing heard auditory cueing or while receiving auditory cueing	Metronome cueing: 60, 90, 120, 150 bpm during reproduction task and synchronized task.	Significant enhancement in coefficient of variability with auditory cueing in between pre-posttests. No difference in coefficient of variability in Exp and Ct group. Decrease in gait velocity, step length and cadence with auditory cueing.
Rochester, et al. [116]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 8F, 12M (64.6±7.9) Ct: 4F, 6M (63.5±7)	6	Exp: 10± 1.6 years	Step length, step frequency, walking speed, time duration and cadence	Complex functional walking and sitting task under single and dual-motor task (carrying a tray) condition	Rhythmic auditory cueing generated according to preferred speed of patients.	Significant enhancement in step length of dual-motor task with auditory cueing as compared to Ct group. Enhancement in walking speed for patients in dual-motor task with auditory cueing. No difference in step length and walking speed in single task conditions. No difference in step frequency, time duration and cadence in both single and dual-motor conditions.
Suteerawattananon, et al. [112]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	10F, 14M (68.9±10.4)	5	6.9±4.4 years	Gait speed, cadence and stride length	Gait performed with/without visual and/or auditory cueing	Rhythmic metronome cueing +25% of preferred cadence	Significant enhancement of gait speed and cadence with auditory input. No effect on stride length with auditory input
Cubo, et al. [201]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	4F, 8M (65.8±11.2)	8	12.4± 7.3 years	Total freezing instances, time, average duration of a freeze, gait time, total procedure time	Pre-test, gait performance with rhythmic auditory cueing at preferred cadence (post-test 1) and home training daily for 1 week, post-test 2	Rhythmic metronome cueing at preferred cadence	Significant reduction in walking time during post-test 2 as compared to post-test 1 with rhythmic auditory cueing Reduction in total procedure time, average duration of freeze during post-test 2 as compared to post-test 1 with rhythmic auditory cueing. Significant enhancement in walking time during post-test 1 with rhythmic auditory cueing Reduction in number of freeze instances during post-test 1 with rhythmic auditory cueing.
Howe, et al. [90]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	2F, 9M (30-67)	6	-	Cadence, gait velocity and stride length	Patients performed gait with auditory input and at 85%, 92.5%, 100%, 107.5%, 115% of mean preferred cadence	Music motor cueing adjusted for speed by time interval adjusted between consecutive heel strikes	Significant enhancement in gait velocity, stride length, heel on-toe-off distance. Significantly reduced symmetry deviation. Enhanced cadence with auditory cueing.
Freedland, et al. [202]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	5F, 11M (74±7.2)	4	-	Gait cycle time, double support, step length, base of support, cadence, step-extremity ratio, Functional ambulation performance score, mean normalized velocity	Pre-test, gait performed with rhythmic auditory input at 0% and +10% of preferred cadence, post-test	Rhythmic metronome cueing at 0% and +10% of preferred cadence	Significant enhancement in step length, and step extremity ratio and reduction in gait cycle time, double support with auditory cueing.
McIntosh, et al. [104]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	With meds: 6F, 15 M (71±4) 24h post meds: 4F, 6M (73±3) Ct: 6F, 4M (72±5)	4	Exp: 7.5 years	Gait velocity, stride length, cadence and cadence-auditory stimulus synchronization	Gait performance by participants with pre-test, with and without normalized auditory and at +10% of preferred cadence, post-test.	0%, +10% of basic tempo for metronome adjusted at patients preferred cadence.	Significant enhancement in gait velocity, cadence and stride length with +10% auditory stimulus. Significantly enhanced synchronization in Ct, but synchronization not evident in both Exp groups.
Thaut, et al. [105]	Effects of auditory cueing on gait in patients affected from Parkinson's disease	Exp: 5F, 10M (69±8) Ct: Self-paced: 3F, 11M (74±3) No training: 3F, 11M (71±8)	5	Exp: 7.2±4 years Ct: 5.4±3 years No training: 8.5±4 years	Gait velocity, stride length, cadence and Electromyogram amplitude variability (Gastrocnemius, tibialis anterior, vastus medialis)	Pre-test/ training for 30 min/day for 3 weeks/ post-tests Walking with rhythmic auditory cueing on flat surface, incline stair steps	Rhythmic auditory cueing embedded in music beat structure for: preferred cadence, quick (normal +5-10%), fast (quick +5-10%) pace	Significant enhancement in gait velocity, stride length and cadence in Exp. Re-production of performance parameters evident after training in absence of auditory stimuli. Significant reduction in electromyogram amplitude variability of tibialis anterior and vastus medialis muscle.

Exp: experimental group, Ct: Control group

Table 2 Individual Pedro scores

Study	**PEDRO Score**	**Point estimates & variability**	**Between group comparison**	**Intention to treat**	**Adequate follow-up**	**Blind assessors**	**Blind therapists**	**Blind subjects**	**Baseline comparability**	**Concealed allocation**	**Random allocation**	**Eligibility criteria**
Dotov et al. (2017)	6	1	1	0	1	0	0	0	1	1	1	1
Dalla Bella et al. (2017)	6	1	1	0	1	0	0	0	1	1	1	1
Pau et al. (2016)	4	1	1	0	1	0	0	0	0	0	1	1
P.-H. Chen et al. (2016)	4	1	1	0	1	0	0	0	0	0	1	1
Baram et al. (2016)	4	1	1	0	1	0	0	0	0	0	1	1
Zhao et al. (2016)	5	1	1	0	1	0	0	0	1	0	1	1
Bukowska et al. (2015)	4	1	1	0	1	0	0	0	0	0	1	1
De Icco et al. (2015)	6	1	1	0	1	0	0	0	1	1	1	1
J. Song et al. (2015)	5	1	1	0	1	0	0	0	1	0	1	1
Son and Kim (2015)	4	1	1	0	1	0	0	0	0	0	1	1
Benoit et al. (2014)	6	1	1	0	1	0	0	0	1	1	1	1
Harro et al. (2014)	8	1	1	0	1	1	1	0	1	1	1	1
Lopez et al. (2014)	6	1	1	0	1	0	0	0	1	1	1	1
Young et al. (2014)	5	1	1	0	1	0	0	0	1	0	1	1
Hove et al. (2012)	4	1	1	0	1	0	0	0	0	0	1	1
Kadivar et al. (2011)	5	1	1	0	1	0	0	0	1	0	1	1
Lohnes and Earhart (2011)	5	1	1	0	1	0	0	0	1	0	1	1
Rochester et al. (2011)	6	1	1	0	1	0	0	0	1	1	1	1
Chaiwanichsiri et al. (2011)	7	1	1	0	1	1	0	0	1	1	1	1
Arias and Cudeiro (2010)	5	1	1	0	1	0	0	0	1	0	1	1
de Bruin et al. (2010)	8	1	1	0	1	1	1	0	1	1	1	1
Elston et al. (2010)	8	1	1	0	1	1	1	0	1	1	1	1
Espay et al. (2010)	4	1	1	0	1	0	0	0	0	0	1	1
Ford et al. (2010)	5	1	1	0	1	0	0	0	1	0	1	1
Picelli et al. (2010)	4	1	1	0	1	0	0	0	0	0	1	1
Rochester, Baker, et al. (2010)	8	1	1	0	1	1	1	0	1	1	1	1
Rochester, et al. (2010)	6	1	1	0	1	0	0	0	1	1	1	1
Bryant et al. (2009)	4	1	1	0	1	0	0	0	0	0	1	1
Rochester et al. (2009)	4	1	1	0	1	0	0	0	0	0	1	1
Nieuwboer et al. (2009)	7	1	1	0	1	1	0	0	1	1	1	1
Frazzitta et al. (2009)	6	1	1	0	1	0	0	0	1	1	1	1
Arias and Cudeiro (2008)	4	1	1	0	1	0	0	0	0	0	1	1
Baker et al. (2008)	6	1	1	0	1	0	0	0	1	1	1	1
Nieuwboer et al. (2007)	8	1	1	0	1	1	1	0	1	1	1	1
Baker et al. (2007)	6	1	1	0	1	0	0	0	1	1	1	1
A.-M. Willems et al. (2007)	5	1	1	0	1	0	0	0	1	0	1	1
Hausdorff et al. (2007)	5	1	1	0	1	0	0	0	1	0	1	1
Rochester et al. (2007)	8	1	1	0	1	1	1	0	1	1	1	1
Y. Jiang and Norman (2006)	5	1	1	0	1	0	0	0	1	0	1	1

Chester et al. (2006)	5	1	1	0	1	0	0	0	1	0	1	1
del Olmo et al. (2006)	4	1	1	0	1	0	0	0	0	0	1	1
A.-M. Willems et al. (2006)	4	1	1	0	1	0	0	0	0	0	1	1
del Olmo and Cudeiro (2005)	4	1	1	0	1	0	0	0	0	0	1	1
Rochester et al. (2005)	6	1	1	0	1	0	0	0	1	1	1	1
Cubo et al. (2004)	8	1	1	0	1	1	1	0	1	1	1	1
Suteerawattananon et al. (2004)	5	1	1	0	1	0	0	0	1	0	1	1
Howe et al. (2003)	6	1	1	0	1	0	0	0	1	1	1	1
Freedland et al. (2002)	4	1	1	0	1	0	0	0	0	0	1	1
McIntosh et al. (1997)	4	1	1	0	1	0	0	0	0	0	1	1
M. H. Thaut et al. (1996)	5	1	1	0	1	0	0	0	1	0	1	1

1: point awarded, 0: no points awarded

Meta-analysis Figures

on individual
ge’s g (boxes) and 95%
d) represents pooled
positive effect size
rs, NFz: Non-Freezers,
: Fast paced training, I:
ep frequency: number

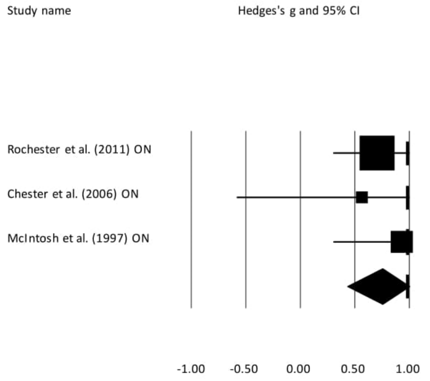

Figure 1 Gait velocity evaluated in ON medication condition

Favours A Favours B

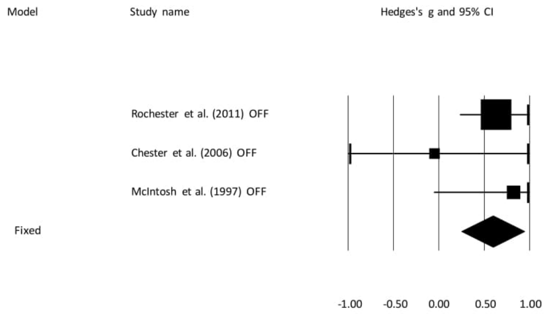

Figure 2 Gait velocity evaluated in OFF medication condition with rhythmic auditory cueing

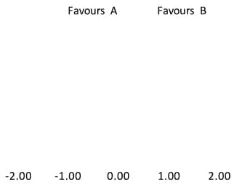

Figure 3 Gait velocity evaluated on treadmill with rhythmic auditory cueing

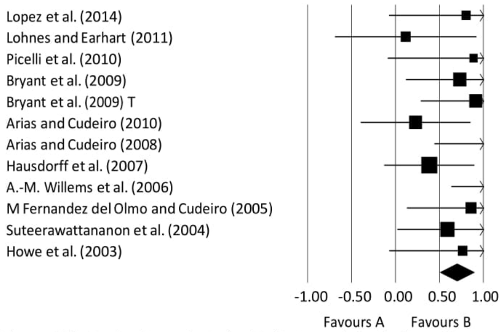

Figure 4 Gait velocity evaluated with fast paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

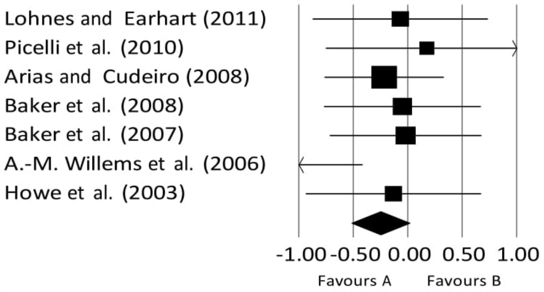

Figure 5 Gait velocity evaluated with slow paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

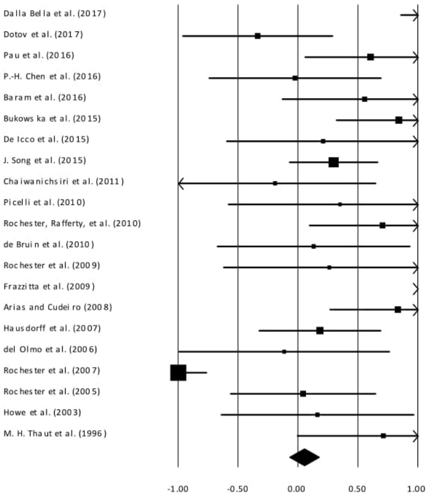

Figure 6 Gait velocity evaluated with un-modulated rhythmic auditory cueing

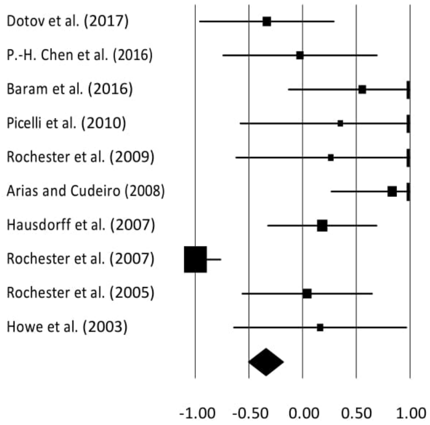

Figure 7 Gait velocity analysed with un-modulated rhythmic auditory cueing without training

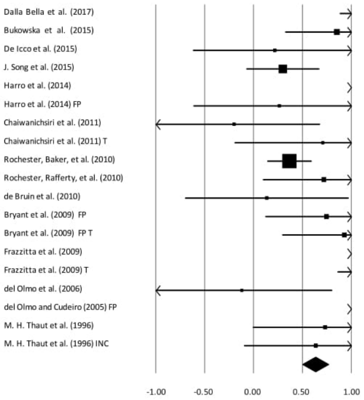

Figure 8 Gait velocity analysed with rhythmic auditory cueing with training

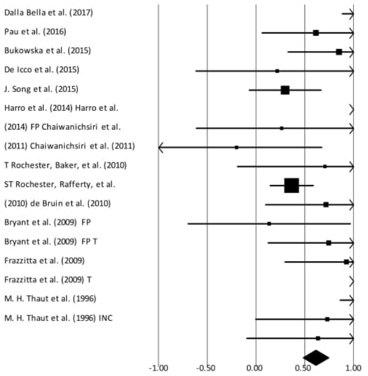

Figure 9 Gait velocity analysed with training for more than 45 minutes with rhythmic auditory cueing

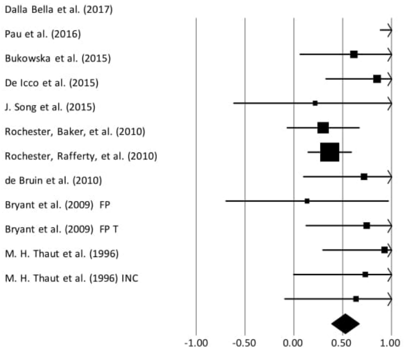

Figure 10 Gait velocity analysed with training for 30-45 minutes with rhythmic auditory cueing

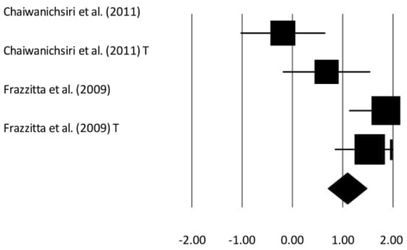

Figure 11 Gait velocity analysed with training for 20 minutes with rhythmic auditory cueing

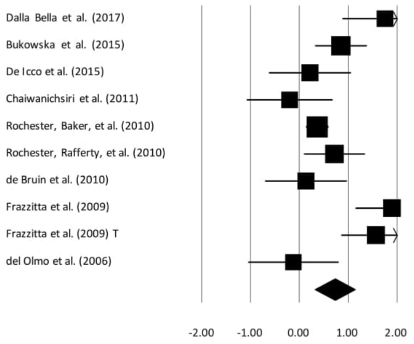

Figure 12 Gait velocity analysed with training for less than 5 weeks with rhythmic auditory cueing

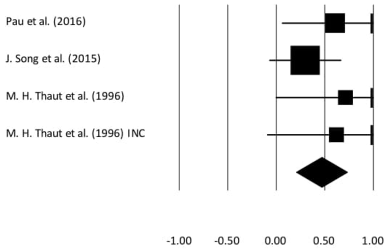

Figure 13 Gait velocity analysed with training for more than 5 weeks with rhythmic auditory cueing

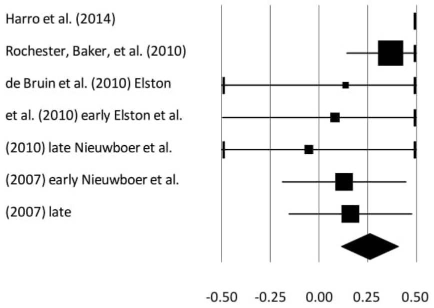

Figure 14 Gait velocity analysed in randomized controlled trials with rhythmic auditory cueing

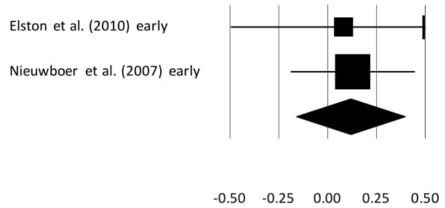

Figure 15 Gait velocity analysed in early group with rhythmic auditory cueing

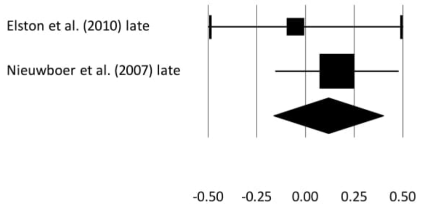

Figure 16 Gait velocity analysed in late group with rhythmic auditory cueing

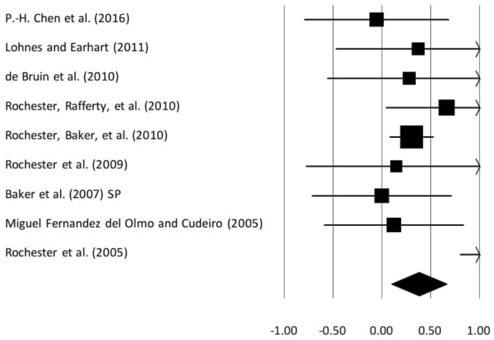

Figure 17 Gait velocity analysed with rhythmic auditory cueing and a dual task performed simultaneously

Stride length

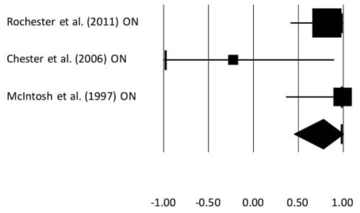

Figure 18 Stride length evaluated in ON medication condition with rhythmic auditory cueing

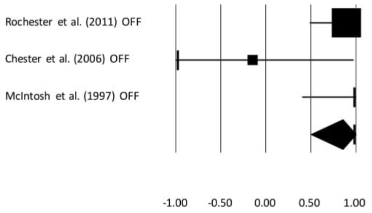

Figure 19 Stride length evaluated in ON medication condition with rhythmic auditory cueing

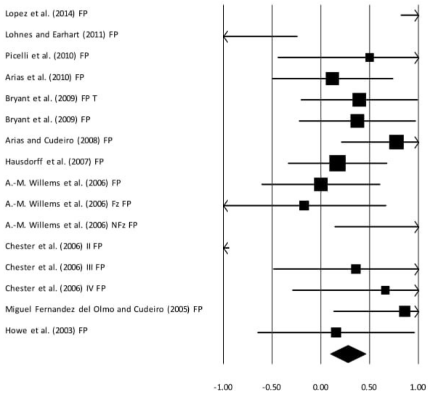

Figure 20 Stride length evaluated with fast paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

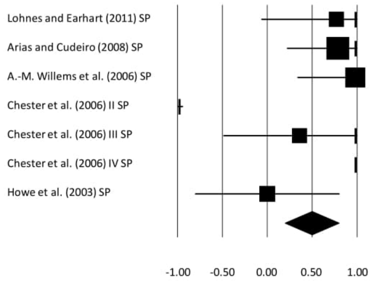

Figure 21 Stride length evaluated with slow paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

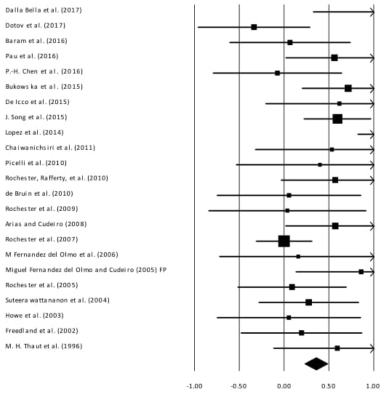

Figure 22 Stride length evaluated with un-modulated rhythmic auditory cueing

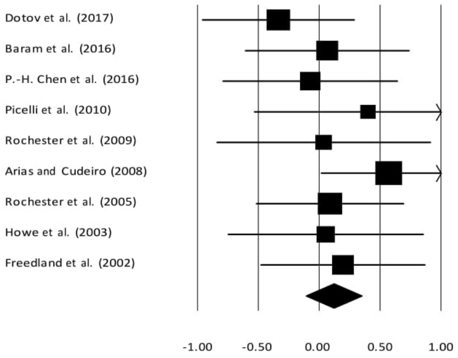

Figure 23 Stride length analysed with un-modulated rhythmic auditory cueing without training

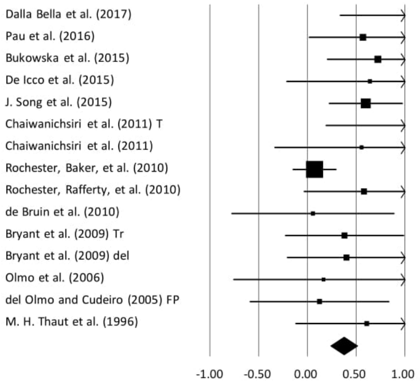

Figure 24 Stride length analysed with rhythmic auditory cueing with training

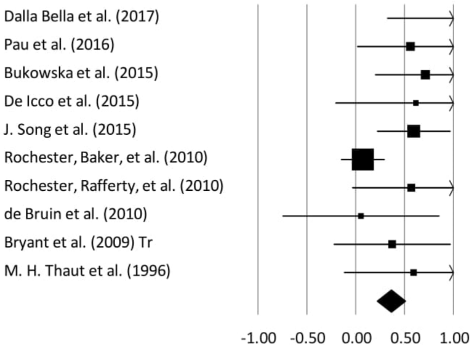

Figure 25 Stride length analysed with training for 30 minutes with rhythmic auditory cueing

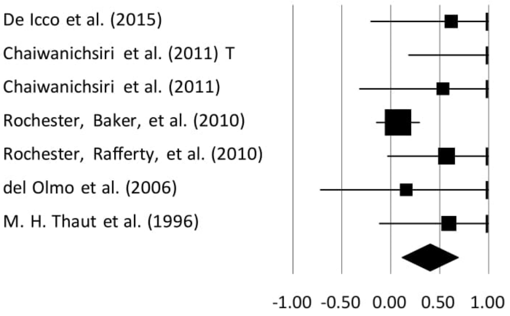

Figure 26 Stride length analysed with training for more than 5 sessions per week with rhythmic auditory cueing

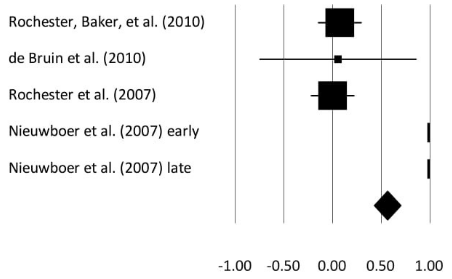

Figure 27 Stride length analysed in randomized controlled trials with rhythmic auditory cueing

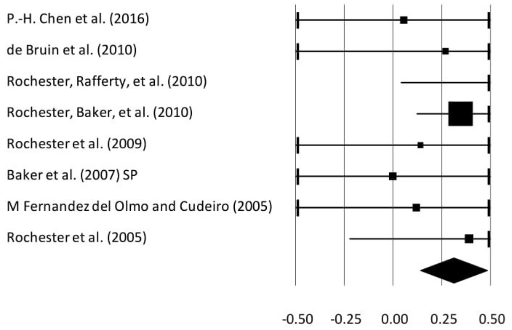

Figure 28 Stride length analysed with rhythmic auditory cueing and a dual task performed simultaneously

Cadence

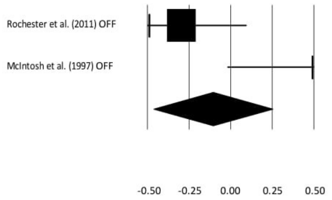

Figure 29 Cadence evaluated in OFF medication condition with rhythmic auditory cueing

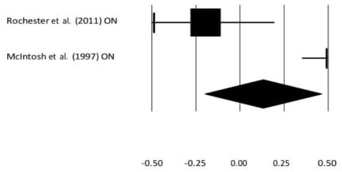

Figure 30 Cadence evaluated in ON medication condition with rhythmic auditory cueing

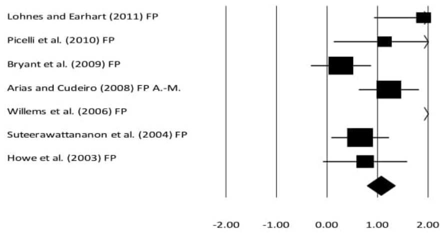

Figure 31 Cadence evaluated with fast paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

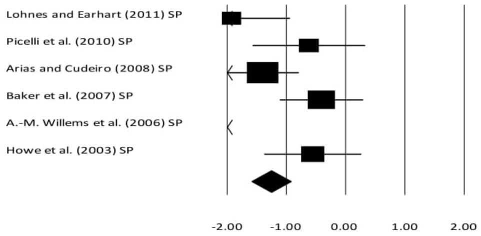

Figure 32 Cadence evaluated with slow paced rhythmic auditory cueing (pace of stimuli determined with reference to patient's preferred cadence)

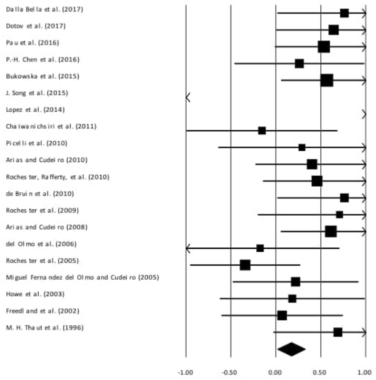

Figure 33 Cadence evaluated with un-modulated rhythmic auditory cueing

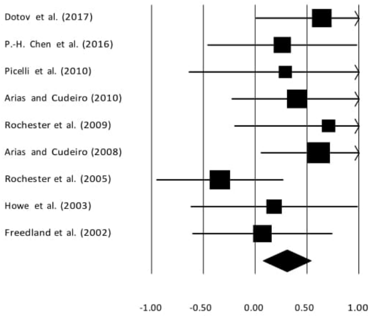

Figure 34 Cadence analysed with un-modulated rhythmic auditory cueing without training

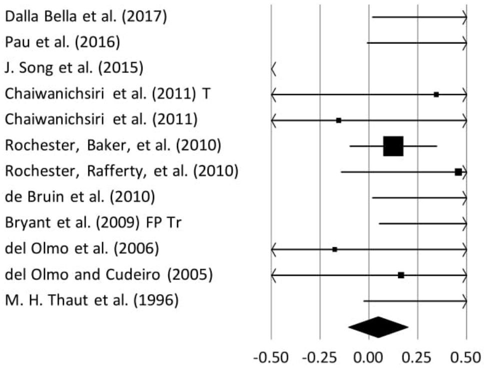

Figure 35 Cadence analysed with rhythmic auditory cueing with training

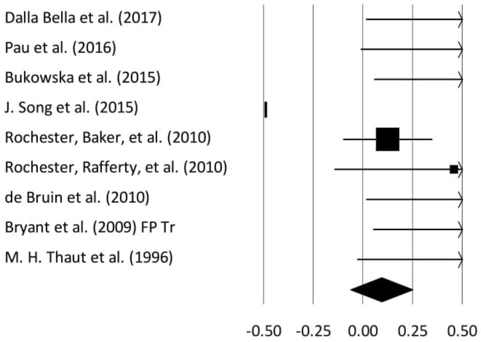

Figure 36 Cadence evaluated with training for 30 minutes with rhythmic auditory cueing

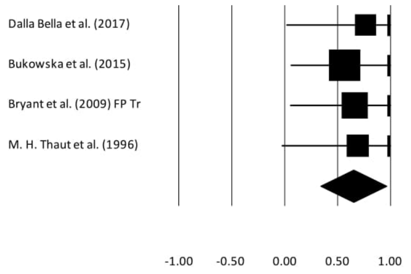

Figure 37 Cadence evaluated with training for less than 5 weeks training with rhythmic auditory cueing

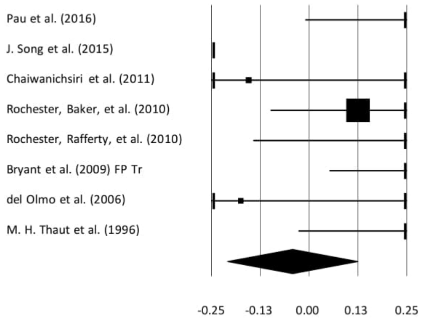

Figure 38 Cadence evaluated with training for more than 5 weeks training with rhythmic auditory cueing

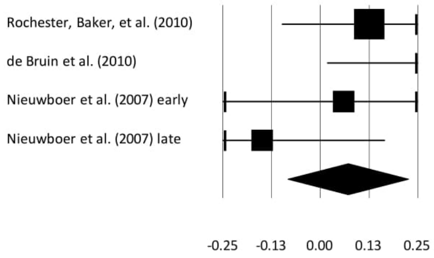

Figure 39 Cadence analysed in randomized controlled trials with rhythmic auditory cueing

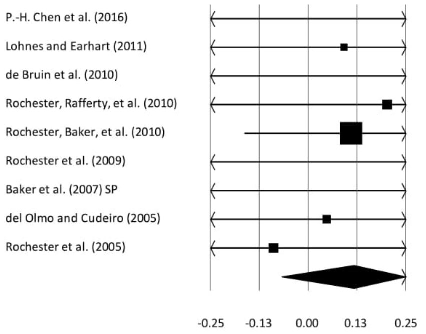

Figure 40 Cadence analysed with rhythmic auditory cueing and a dual task performed simultaneously

Double limb support

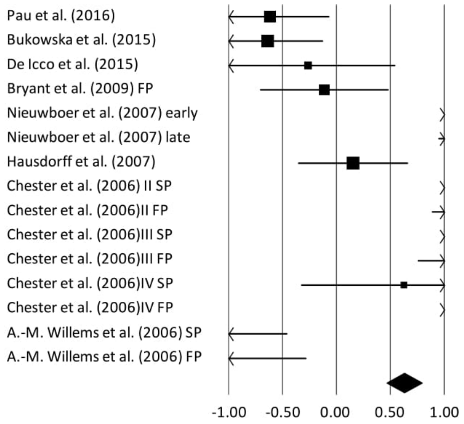

Figure 41 Double limb support duration analysed with rhythmic auditory cueing

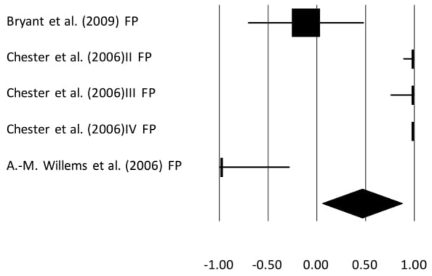

Figure 42 Double limb support duration analysed with fast paced rhythmic auditory cueing (reference patient's preferred cadence)

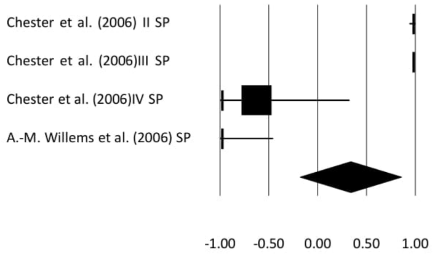

Figure 43 Double limb support duration analysed with slow paced rhythmic auditory cueing (reference patient’s preferred cadence)

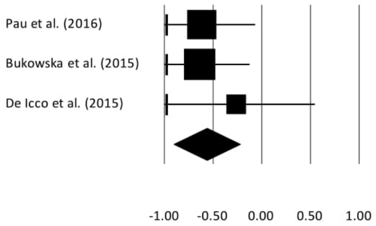

Figure 44 Double limb support duration analysed with un-modulated rhythmic auditory cueing

Turn time

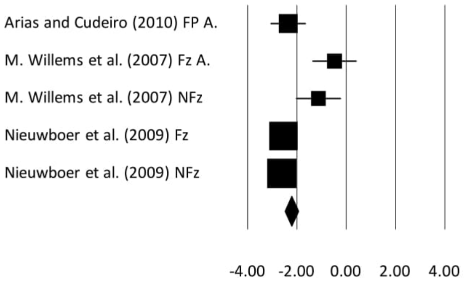

Figure 45 Turn time analysed with rhythmic auditory cueing

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Chapter 3: Effect of (music-based) rhythmic auditory cueing training on gait and posture post-stroke: A systematic review and dose-response meta-analysis

Influence of music-based auditory cueing training on gait and balance recovery post stroke: A systematic review & meta-analysis

Supplementary File

Shashank Ghai*, Ishan Ghai

Table 1 Individual Pedro scores for studies (1: point awarded, 0: no point awarded)

Study	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention to treat	Between group comparison	Point estimates & variability	PEDro score
Kobinata, et al. [1]	1	0	0	1	0	0	0	1	0	1	1	5
Ko, et al. [2]	1	0	0	1	0	0	0	1	0	1	1	5
Fouad and Mousa [3]	1	0	0	0	0	0	0	1	0	1	1	4
Song and Ryu [4]	1	0	0	1	0	0	0	1	1	1	1	6
Park and Chung [5]	1	1	1	1	0	0	0	1	1	1	1	8
Yang, et al. [6]	1	0	0	0	0	0	0	1	0	1	1	4
Yoon and Kang [7]	1	1	0	1	0	0	0	1	1	1	1	7
Brasileiro, et al. [8]	1	0	0	1	0	0	0	1	1	1	1	6
Shin, et al. [9]	1	0	0	1	0	0	0	1	0	1	1	5

Ki, et al. [10]	1	0	0	1	0	0	0	1	1	1	1	6
Jung, et al. [11]	1	0	0	1	0	0	0	1	0	1	1	5
Yoon and Kang [12]	1	0	0	1	0	0	0	1	1	1	1	6
Park, et al. [13]	1	0	0	1	0	0	0	1	0	1	1	5
Oh, et al. [14]	1	1	0	1	0	0	0	1	1	1	1	7
Hashiguchi, et al. [15]	1	1	0	1	0	0	0	1	1	1	1	7
Cha, et al. [16]	1	1	0	1	0	0	0	1	1	1	1	7
Suh, et al. [17]	1	1	0	1	0	0	0	1	1	1	1	7
Cha, et al. [18]	1	1	0	1	0	0	0	1	0	1	1	6
Wright, et al. [19]	1	0	0	0	0	0	0	1	0	1	1	4
Lee, et al. [20]	1	1	1	1	0	0	0	1	1	1	1	8
Chouhan and Kumar [21]	1	1	0	1	0	0	0	1	0	1	1	6
Muto, et al. [22]	1	0	0	1	0	0	0	1	0	1	1	5

Jung-Hee, et al. [23]	1	1	0	1	0	0	0	1	1	1	1	7
Kim and Oh [24]	1	1	0	1	0	0	0	1	1	1	1	7
Jung, et al. [25]	1	0	1	1	0	0	0	1	0	1	1	6
Johannsen, et al. [26]	1	0	0	1	0	0	0	1	0	1	1	5
Park, et al. [27]	1	0	0	1	0	0	0	1	0	1	1	5
Pelton, et al. [28]	1	1	0	1	0	0	0	1	0	1	1	6
Roerdink, et al. [29]	1	1	0	1	0	0	0	1	1	1	1	7
Hayden, et al. [30]	1	0	0	1	0	0	0	1	0	1	1	5
Roerdink, et al. [31]	1	0	0	1	0	0	0	1	0	1	1	5
Argstatter, et al. [32]	1	0	0	0	0	0	0	1	0	1	1	4
Thaut, et al. [33]	1	1	0	1	0	0	0	1	1	1	1	7
Schauer and Mauritz [34]	1	0	0	0	0	0	0	1	0	1	1	4

Thaut, et al. [35]	1	0	0	0	0	0	0	1	0	1	1	4
Prassas, et al. [36]	1	0	0	1	0	0	0	1	0	1	1	5
Thaut, et al. [37]	1	0	0	1	0	0	0	1	0	1	1	5

Table 2 Effects of rhythmic auditory cueing on gait and postural stability in stroke patients

Author	**Research question(s)/ hypothesis**	**Sample description, age: (M ± S.D)**	**PEDro**	**Disease duration**	**Assessment tools**	**Research design**	**Auditory characteristics**	**Conclusion**
Kobinata, et al. [1]	Effects of auditory cueing on gait in patients affected from stroke	Lesion site: Cerebellum 5F, 15M (71.3±9.5) Pons & medulla: 5F, 21M (67.4±10.9) Thalamus: 4F, 18M (64±9.2)	5	Cerebellum: 40.8± 30.6 days Pons & medulla: 38.4± 22.8 days Thalamus: 61± 33 days	Gait velocity & stride length	Pre-test, gait training with gradually enhanced frequency to achieve increased cadence, rhythm, post-test	Rhythmic metronome cueing (drum or autoharp) at preferred cadence	Significant enhancement in gait velocity, stride length in patients with lesion sites at cerebellum, pons & medulla, thalamus after auditory training. Enhancement in gait velocity, stride length in patients with lesion sites at putamen, corona radiata after auditory training.

		Putamen: 7F, 11M (64.3±13.4) Corona radiata: 7F, 12M (72.8±9.4)		Putamen: 42.7± 19.5 days Corona radiata: 39.2± 23.2 days				
Sangita and Remya [38]	Effects of auditory cueing on gait in patients affected from stroke	Exp: 15 Ct: 15	4	-	10-metre walk test, cadence	3-week training	Rhythmic metronome cueing at preferred cadence	Significant enhancement in 10-metre walk test performance and cadence in Exp as compared to Ct.
Ko, et al. [2]	Effects of auditory cueing on	4F, 11M (56±7.4)	5	81.9± 87.8 months	Gait speed, cadence, stride length, gait	Pre-test/7 min of gait training, with rhythmic auditory	(C-E-G, C-F-A, A-D-G, clap, click, gun & robot sound) at -10%, -5%,	Significant enhancement in cadence, step-length, 10MWT & DGI post

	gait in patients affected from stroke				cycle duration, step length affected & unaffected side & symmetry ratio	cueing at -10%, -5%, 0%, +5%, +10% of patient's preferred pace "applied randomly" /post-test	0%, +5%, +10% of patient's preferred pace	training with auditory cueing as compared to Ct group.
Fouad and Mousa [3]	Effect of rhythmic auditory cueing on treadmill gait in patients affected from stroke	30 stroke patients Exp: 15 Ct: 15	4	-	Stride length	Pre-test, treadmill training with (Exp)/without (Ct) rhythmic auditory cueing for 6 weeks, post-test	Rhythmic auditory cueing	Significant enhancement in stride length for both the affected & non-affected side for Exp as compared to Ct.
Song and Ryu [4]	Effects of auditory cueing on gait in patients	Exp: 8F, 12M (57.1±7.8)	6	Exp: 12.3± 3.4 months	Cadence, step length, 10 metres walking	Pre-test, Gait training with/without rhythmic auditory cueing for 30 minutes session, 5 times a week for 4	Rhythmic auditory cueing	Significant enhancement in cadence, step-length, 10MWT & DGI post training with auditory cueing as compared to Ct group.

	affected from stroke	Ct: 11F, 9M (60.1±6.8)		Ct: 14.7± 6 months	test & Dynamic gait index	weeks with rehabilitation/post-test		
Park and Chung [5]	Effects of auditory cueing on robot-assisted gait in patients affected from stroke	Visual cueing: 2F, 3M (52.4±12) Auditory cueing: 2F, 3M (55±5) Ct: 3F, 2M (57.2±11.5)	8	Visual: 9.2± 1.3 months Auditory: 9.2± 2.2 Ct: 9.0± 1.5	Berg balance scale, time-up & go test & 10 metres walking test	Pre-post intervention with robot assisted gait training (40-50% weight supported) for 45 min, 3 times a week for 2 weeks.	Rhythmic auditory cues generated per preferred speed of patients.	Significantly enhanced performance in BBS, TUG, & 10 MWT when participants received auditory cueing as compared to Ct.
Yang, et al. [6]	Effects of real-time auditory cueing on gait &	Exp: 2F, 9M (51.9±13.3)	4	Exp: 11.1± 3.6 months	Gait speed, cadence, step length, stride length, single limb support,	Pre-test, gait on treadmill training for 30 minutes/ session, 3 sessions/week for 4 weeks with real-time	Rhythmic auditory cueing at preferred cadence, tempo modified in two sounds of different pitch, reduced	Significant enhancement in gait speed, cadence, step length, stride length, single limb support in Exp as compared

	balance in patients affected from stroke	Ct: 2F, 9M (55.8±13.5)		Ct: 11.9± 3.5 months	gait asymmetry, average perturbation velocity, average total perturbation distance & time up & go test	auditory cueing at 0% & 5% input from preferred cadence, post-test	speed by half of averaged gait speed from initial contact of 6th phase of gait cycle at 0% & 5%.	to Ct. Significant reduction in gait asymmetry in Exp. Significant reduction in average perturbation velocity (eye open only), average total permutation distance & time up & go test duration in Exp as compared to Ct with both eyes closed and open performance.
Yoon and Kang [7]	Effects of auditory cueing on gait performance on treadmill, postural stability in patients affected	Exp: 4F, 6M (50.8±14.4) Ct I: 3F, 6M (56.3±7.1) Ct II: 4F, 5M (61.2±13)	7	Exp: 16.4± 10.3 months Ct I: 13.6± 8.5 months Ct II: 17.1±	Time up & go test, berg balance score, 6-minute walking test time, gait speed, cadence, single leg stance & symmetry index.	Pre-test, treadmill training at (5% incline, preferred cadence) initially, followed by (10% incline, +5% speed) in 2nd & 3rd weeks, rhythmic auditory cueing for Exp, no auditory cueing for Ct I & Ct II (normal treadmill training), training for 30 minutes' session, 5	Rhythmic metronome cueing at 0% & +5% of preferred cadence	Significant enhancement in berg balance score, gait speed, cadence, single leg stance & symmetry index after training with auditory cueing Significant reduction in time up & go test, 6-minute walking test time after training with auditory cueing Significant effects on time up & go test, berg balance score, 6-minute walking test time, gait speed & symmetry index in Exp as compared to Ct I, Ct II.

	from stroke			8.4 months		times/ week, for 4 weeks, post-test		
Brasileiro, et al. [8]	Effect of auditory cueing on treadmill gait in patients affected from stroke	12F, 18M Exp: 10 (58.8±7.9) Ct: 10 (57.9±4.9) Ct I: 10 (52.3±5.9)	6	Exp: 34.1±20.2 months Ct I: 37.8± 21.5 Ct: 27.4± 17.4 months	Gait speed, stride length, cadence, paretic stance time, symmetry ratio, maximum hip extension (stance), maximum hip flexion (swing), hip range of motion, knee angle initial contact, maximum knee flexion (swing), knee range of motion, ankle range of motion	Pre-test, treadmill training with 30% of supported body weight with/without rhythmic auditory cueing at +15% of preferred cadence (Exp), visual cueing (Ct I) for 20 minutes' session, post-test	Rhythmic auditory cueing at +15% of preferred cadence	Significant enhancement in gait speed, stride length, hip & ankle range of motion after training with rhythmic auditory cueing. No differences between Exp, Ct I & Ct II.

					& ankle angle at initial contact, toe off.			
Shin, et al. [9]	Effects of real-time auditory cueing on gait in patients affected from hemiplegia (stroke/cerebral palsy)	Cerebral palsy: 4F, 3M (30.1±4.1) Stroke: 4F, 7M (44.2±7)	5	Stroke patients: 3.5±2.2 years	Cadence, gait speed, stride length, stride time, step time, single/double support time, stance/swing phase (temporo-spatial deviation & side to side comparison), pelvis, hip, knee, ankle, foot kinematics & gait deviation index	Pre-test, gait training with rhythmic auditory cueing for 30 minutes/ session, 3 sessions/ week for 4 weeks, post-test	Rhythmic auditory cueing by four-chord progression with metronome beat on keyboard	Significantly reduced ankle plantar flexion at initial contact & push off. Reduced anterior pelvic tilt in sagittal plane after training with auditory cueing. Significantly enhanced kinematic improvements in stroke patients as compared to cerebral palsy. Significant enhancement in gait deviation index & kinematics for patients affected from sub-acute stroke as compared to chronic stroke. No effect on gait parameters after training from auditory cueing. Enhanced side to side symmetry after training from auditory cueing.

								Significant enhancement in gait deviation index, hip adduction in mid stance, maximal knee flexion in mid swing, ankle dorsiflexion in terminal stance after training from rhythmic auditory cueing.
Ki, et al. [10]	Effects of rhythmic auditory on weight bearing phase in gait training and dynamic posture for patients affected	Exp: 4F, 8M (55.3±9.2) Ct: 2F, 11M (60.1±12.3)	7	Exp: 19.1± 8.2 months Ct: 22± 9.9 months	Gait parameters (double limb stance, single limb stance phase), time up and go test	Pre (4 weeks training i.e. neurodevelopmental-with/without auditory cueing) post-test analysis	Auditory cueing engaged by pressure gauge when more than 50% weight procured on the healthy.	Significant enhancements in double leg, single leg stance phase and time up & go tests with auditory cueing as compared to control group.

	from stroke							
Jung, et al.[11]	Effect of auditory cueing by cane pressure during gait in patients affected from stroke	Exp: 4F, 7M (56.4±11.1) Ct: 3F, 7M (56.3±17.1)	7	Exp: 6.2± 2.5 months Ct: 7.0± 2.5 months	Vertical peak force of cane, electromyographip activity of gluteus medius, vastus medialis oblique, single support phase of gait, gait velocity	Pre-test, assisted gait training with/without auditory cueing (calculated by dividing peak vertical force by patients' body weight) with -10% threshold reduction/week, for 30 minutes' session/day, 5 times/week for 4 weeks, post-test	Real-time auditory cueing at initial threshold of 60% of level of dependency, -10% every week (if comfortable with patient)	Significant enhancement in gait velocity, electromyographic activity of gluteus medius, vastus medialis oblique, single support phase of gait in Exp as compared to Ct. Significant reduction in vertical peak force of cane in Exp as compared to Ct.
Yoon and Kang[12]	Effects of auditory cueing on gait performance on	Exp: 3F, 2M (60.6±9)	5	Exp: 10.4± 2.4 months Ct I: 9.8±	Time up & go test, berg balance score, 6-minute walking test time, gait speed,	Pre-test, incline treadmill training with rhythmic auditory cueing for Exp, no auditory cueing for Ct I & Ct II (normal	Rhythmic metronome cueing at preferred cadence	Significant enhancement in berg balance score, gait speed, cadence, single leg stance & symmetry index after training with auditory cueing

	treadmill, postural stability in patients affected from stroke	Ct I: 2F, 3M (57.6±5.5) Ct II: 2F, 3M (52.8±5.6)		3.11 months Ct II: 11.8± 4.3 months	cadence, single leg stance & symmetry index.	treadmill training), training for 30 minutes' session, 5 times/ week, for 3 weeks, post-test		Significant reduction in time up & go test, 6-minute walking test time after training with auditory cueing
Park, et al. [13]	Effect of rhythmic auditory cueing & treadmill training on gait in patients affected from stroke	Exp I: 5F, 4M (51.8±12. 5) Exp II: 4F, 6M (55±9.8)	6	Exp I: 10.3± 3.3 months Exp II: 12.5± 4.2 months	Gait speed, step cycle, step length (affected/unaffected side), coefficient of variation of gait cycle (affected/unaffected side), functional gait assessment, 6-minute walking	Pre-test, gait training with treadmill (Exp I), normal ground walking (Exp II) with rhythmic auditory cueing progressing at -10% (1st week), 0% (2nd week), +10% (3rd week) of preferred cadence, for 30 minutes' session, 5 times/week for 3 weeks, post-test	Rhythmic metronome cueing at -10%, 0%, +10% of preferred cadence	Significant reduction in coefficient of variation of gait cycle (affected/unaffected side), step cycle in Exp I & Exp II. Significant enhancement in functional gait assessment, 6-minute walking distance test, gait speed, step length (affected/unaffected side) in Exp I & Exp II. Reduction in time up & go test time in Exp I & Exp II.

					distance test & timed up & go test			
Oh, et al. [14]	Effects of auditory cueing on gait, postural stability in patients affected from stroke	Exp I: 8F, 6M (55.8±8) Exp II: 7F, 7M (57.4±8)	5	Exp I: 8.3± 2.3 months Exp II: 8.9± 1.9 months	Gait velocity, cadence, stride length, double limb support, time up & go test, functional gait assessment & centre of body sway angle (x, y, z axis)	Pre-test, gait training with rhythmic auditory cueing (Exp I: music, Exp II: metronome) at preferred cadence for first week followed by +10% for the second & third week, training for 30 minutes' session, 5 times/ week, for 3 weeks, post-test	Exp I: Rhythmic auditory cueing on music (2/4 & 4/4-time signature) Exp II: Rhythmic metronome cueing	Significant enhancement in Gait velocity, cadence, stride length, functional gait assessment (music>metronome) after training with auditory cueing. Significant reduction in time up & go test (music> metronome), centre of body sway, double limb support after training with auditory cueing
Hashiguchi, et al. [15]	Effect of rhythmic auditory cueing on gait &	14 patients	4	-	Gait velocity, coefficient of variation for stride time, coefficient of	Pre-test, gait performance with rhythmic auditory cueing at 0%, +10% of preferred cadence,	Rhythmic auditory cueing at 0%, +10% of preferred cadence, adjusted for stride-to-	Significant enhancement in gait velocity, electromyographic activity of gastrocnemius with rhythmic auditory cueing at +10% of preferred cadence as compared to baseline.

	muscle activity in patients affected from stroke				variation of duration time, electromyographic activity of gastrocnemius & tibialis anterior	adjusted for stride-to-stride tempo for paretic/non-paretic limb, post-test	stride tempo for paretic/non-paretic limb	Significant reduction in coefficient of variation of stride time, coefficient of variation of duration time with rhythmic auditory cueing at +10% of preferred cadence as compared to baseline.
Cha, et al. [16]	Effect of auditory cueing on gait in patients affected from stroke	17F, 24M (60.8±19.8)	7	8.68± 2.35 months	Patients walked at preferred speed followed by rhythmic auditory cueing applied randomly at -10%, 0%, +10%, +20% of basic tempo while performing gait.	Gait velocity, cadence, stride length, double limb support, double single limb support Gait symmetry ratio	-10%, 0%, +10%, +20% of basic tempo for metronome adjusted at patients preferred pace.	Significantly reduced gait velocity, cadence & stride length with -10% of rhythmic auditory stimuli as compared to 0% Significant enhancement of gait symmetry with normalized auditory stimulus. Significant enhancement in gait velocity & cadence in +10% & +20% auditory stimuli. However reduced gait symmetry as compared to 0% condition.

Suh, et al.[17]	Effect of auditory cueing on gait & balance in patients affected from stroke	Exp: 5F, 3M (61±14.4) Ct: 5F, 3M (70.6±12.4)	6	Exp: 386.3±283.2 days Ct: 224.2±213 days	Cadence, gait velocity, stride length, overall stability index & anterior-posterior, mediolateral stability index	Pre-test, gait training with rhythmic auditory cueing at 0%, +5%, +10% of preferred cadence for 30 minutes/day, 5 times a week for 3 weeks, post-test	Rhythmic tone cueing, with single tone series in 4/4-time signature, 60dB, 40-100bpm, at 0%, +5% & +10% of preferred cadence	Significant enhancement in gait velocity, overall stability index & anterior-posterior, mediolateral stability index after training in Exp as compared to before training & Ct. Enhancement in cadenceafter training in Exp as compared to before training & Ct. No effect on stride length.
Cha, et al.[18]	Effects of rhythmic auditory cueing on gait & posture in patients affected from stroke	Exp: 4F, 6M (59.8±11.7) Ct: 4F, 6M (631±4.1)	7	Exp: 14.5±5.5 Ct: 14.7±5.4	Berg balance scale, gait velocity, cadence, stride length (affected/unaffected side), double stance period (affected/unaffected side),	Pre-test, gait training with rhythmic auditory cueing at 0% of preferred cadence for 30 minutes/session, 5 times/week, for 6 weeks (+5% of preferred cadence on 3rd & 5th week), post-test	Rhythmic auditory cueing, metronome superimposed on music at 0%, +5% of preferred cadence	Significant enhancement in berg balance score, gait velocity, cadence, stride length (affected/unaffected side), stroke specific quality of life scale after training with rhythmic auditory cueing, in Exp as compared to Ct. Significant reduction in double stance period (affected/unaffected side) after training with rhythmic auditory cueing, in Exp as compared to Ct.

					stroke specific quality of life scale			
Wright, et al. [19]	Effect of rhythmic auditory cueing on gait in patients affected from stroke	4F, 6M (61±16)	6	6± 2 years	Step time asymmetry, paretic step time variability, nonparetic step time variability & time up & go test	Pre-test, gait performance with/without rhythmic auditory cueing of single & dual tones (randomized)	Rhythmic metronome cueing at single tone (700Hz) Rhythmic metronome cueing at dual tone (700Hz & 1400Hz)	Significant reduction in step time asymmetry (single tone only) & paretic step time variability with both single & dual tone rhythmic auditory cueing. Reduction in non-paretic step time variability with both single & dual tone rhythmic auditory cueing.
Lee, et al. [20]	Effect of auditory cueing on gait & in patients affected	11F, 14M (64.3±8.2)	8	12.8± 7.5 months	Gait velocity, cadence, symmetry index, symmetry ratio & gait asymmetry	Gait performance with rhythmic auditory cueing at preferred cadence, paretic/non-paretic leg footfall with auditory cueing at preferred cadence,	Rhythmic metronome cueing at 0% & ±30% of preferred cadence	Significant enhancement in gait velocity, symmetry & cadence when auditory cueing was directed at paretic limb at 0% & ±30% of preferred cadence.

	from stroke					±30% of preferred cadence		
Chouhan and Kumar [21]	Effect of rhythmic auditory cueing on gait & arm reaching in patients affected from stroke	Exp: 3F, 12M (56.7±5.9) Ct I: 3F, 12M (58.1±4.1) Ct II: 3F, 12M (57.3±5.5)	6	-	Dynamic gait index & Fugyl meyer motor scale score	Pre-test, gait, reaching task training with rhythmic auditory cueing (0% of preferred cadence initially, increased by +10% every week if comfortable for patient: for gait) (Exp) or visual cueing (Ct I) for 2 hours training, 3 time/week session for 3 weeks, post-tests at 7, 14, 21, 28 days	Rhythmic auditory cueing at 0% & +10% on following weeks of preferred cadence	Significant enhancements in dynamic gait index & Fugyl meyer motor scale (14, 21, 28 days only) after 7, 14, 21, 28 days of training with rhythmic auditory cueing & in Exp as compared to Ct II.
Muto, et al. [22]	Effect of rhythmic auditory cueing in gait for	Exp: 3F, 5M (57.5±12.6)	5	Exp: 11.8± 14.3 months	Left-right phase difference (gait asymmetry), (fluctuation in gait tempo)	Gait training for 9 sessions with rhythmic auditory cueing at +5% of preferred cadence(Ct), walk-	Walkmate auditory cueing (real-time): Continuous rhythmic	Significant reduction gait asymmetry in Exp during training with walk-mate auditory cueing, improvements not retained after training.

	patients affected from stroke	Ct: 3F, 5M (57.1±15.6)		Ct: 15.1± 18.8 months	standard deviation of ground contact period during leg motion	mate (rhythmic real-time auditory cueing) (Ct), pre-test & post-tests at the beginning & end of 9 sessions	auditory cueing according to gait pattern Stable phase difference computed with gait pattern Internal model modulates frequency by target phase difference to adapt to changing gait pattern Rhythmic auditory cueing (dual-dynamics model) +5% of preferred cadence	No effect on gait asymmetry with rhythmic auditory cueing at +5% of preferred cadence. Significant reduction in fluctuation in gait tempo for for Exp during>after walk-mate auditory training. Significant reduction in fluctuation in gait tempo for Ct during gait training with rhythmic auditory cueing at +5% of preferred cadence.
Jung-Hee, et al. [23]	Effect of auditory cueing on gait & postural stability in patients	Exp: 4F, 6M (58.3±11.8) Ct: 3F, 7M	7	Exp: 5.68± 1.04 months	Activities specific balance confidence scale, dynamic gait index, four square step tests, functional	Pre-test, functional gait training with rhythmic auditory cueing for 30 minutes training session, 3	Rhythmic metronome cueing at +5% for normal preferred cadence (-20% when gait was unmatched with given	Significant enhancement in gait velocity, activities specific balance confidence scale, dynamic gait index, cadence, functional ambulation category score, stride length (affected &

	affected from stroke	(51.8±13.7)		Ct: 4.76± 2.65	ambulation category score, timed up & go test, stair up & down steps/sec gait velocity, stride length, gait cycle time & cadence	times per week for 5 weeks, post-test	rhythmic auditory cueing)	unaffected side) after training with auditory cueing. Significant reduction in gait cycle time on unaffected side, four square step test, time up & go test, stair up & down steps/sec after training with auditory cueing. Significantly enhanced performance in activities specific balance confidence scale, dynamic gait index & timed up & go test in Exp as compared to Ct. Reduction in gait cycle time on affected side after training with auditory cueing.
Kim and Oh [24]	Effect of rhythmic auditory cueing on gait in patients affected	Exp: 10 (65.2±6.8) Ct: 10 (64.5±8.1)	7	Exp: 15.2± 2.3 months	Stride length (affected/unaffected side), stride length ratio, support time (affected/unaffected side),	Pre-test, gait training for 10 minutes' session, 3 times/week for 6 weeks with rhythmic auditory cueing at 20, 40, 60, 80, & 100 bpm	Rhythmic metronome cueing at 20, 40, 60, 80, & 100 bpm	Significant enhancement in stride length (affected/unaffected side), support time (affected/unaffected side) & gait velocity in Exp as compared to Ct.

	from stroke			Ct: 15.3± 3 months	single support time ratio & gait velocity	incremented at 0, 2, 4, 6 & 8 minutes of training, post-test		Significant reduction in single support time ratio & stride length ratio in Exp as compared to Ct.
Jung, et al. [25]	Effect of rhythmic auditory cueing on gait in patients affected from stroke	5F, 7M (52.5±12.4)	6	15.5± 8.5 months	Gait velocity, cadence, stride length & step length	Gait performance with visual & rhythmic auditory cueing at 0%, ±50% of preferred cadence	Rhythmic auditory cueing at 0%, ±50% of preferred cadence	Significant effect of combined visual-auditory cueing on gait velocity i.e. reduced gait parameters with reduced cueing (-50% cueing of preferred cadence) & vice versa for enhanced cueing (+50% cueing of preferred cadence)
Johannsen, et al. [26]	Effect of rhythmic auditory cueing on arm reaching & gait in	Exp I: 3F, 8M (59.513.4) Exp II: 3F, 7M (68.110.1)	7	62.5± 50.9 months	Fugyl meyer motor assessment (upper/lower extremity), 10-meter walking test, treadmill	Pre-test, bilateral (arm: Exp I/leg: Exp II) training with rhythmic auditory cueing for 45 minutes' session, 2 times/week for 5 weeks, post-test,	Rhythmic auditory cueing at preferred pace of physical activity (increased at patient's preference) bilateral leg training with rhythmic auditory	Significant enhancement in treadmill step length on both paretic & non-paretic side after bilateral leg training in Exp II as compared to Exp I (no effects), during immediate follow-up test. No effects in follow up post-test.

patients affected from stroke		(step length), repetitive foot/hand aiming task	follow up post-test after 18 weeks	cueing: increased during training from 36.7±6.5-45.9±9.5 bilateral arm training with rhythmic auditory cueing: increased during training from 39.8±5.6-46.3±5.9	Enhancement in fugl meyer motor test for lower extremity in Exp II> Exp I at post-test. No enhancements in follow up post-test Enhancement in fugl meyer motor test for upper extremity in Exp I> Exp II at post-test. No enhancements in follow up post-test Enhancement in treadmill step length on both paretic & non-paretic side after bilateral arm training in Exp I as compared to Exp II during 18 week follow up post-test. Enhancement in repetitive foot & arm aiming task on both paretic & non-paretic side after bilateral leg training in Exp II during immediate post-tests. No effects on follow up post-tests.

Park, et al. [27]	Effects of auditory cueing on gait in patients affected from stroke	Exp: 5F, 8M (59.2±11) Ct: 4F, 8M (52.9±13)	7	Exp: 15.5± 5 months Ct: 14± 8 months	Gait speed, number of steps & Wisconsin gait scale	Pre-test, gait training with rhythmic auditory cueing at 30 minutes' session, twice a day, 5 days/week, for 2 weeks, post-test	Rhythmic auditory cueing (120 bpm) embedded in music	Significant enhancement in gait speed in Exp as compared to Ct. Significant reduction in number of steps & Wisconsin gait scale in Exp as compared to Ct.
Pelton, et al. [28]	Effects of auditory cueing on treadmill gait in patients affected from stroke	3F, 5M (70±12)	5	41.5± 32.2 months	Baseline asynchrony, percentage proportional error in period control, limb symmetry, correction parameter & relative asymptope	Gait performance with 20 metronome pulses without phase shift, followed by 80 pulses with random 1 phase shift (counterbalanced for paretic & non-paretic limb) i.e. delayed metronome cueing	Rhythmic metronome cueing, 1 phase shift: 20% of inter pulse interval i.e. 36º of gait cycle	Significant reduced correction for phase shifts when error occurred on nonparetic limb (correction required on paretic side) as compared to paretic limb, vice versa with rhythmic auditory cueing (with phase shifts)

Roerdink, et al. [29]	Effects of auditory stimuli on gait performance in patients affected from stroke	Exp: 4F, 7M 60 (42-71) Ct (healthy): 4F, 6M 60(46-79)	5	Exp: 18.5± 17.5 months	Mean phase relation between footfall & acoustic stimuli, step width, spatial-temporal gait asymmetry, variability of relative timing between footfall & metronome beat	Patients performed gait with/without auditory pacing input for single (paretic/non-paretic limb), double (both limbs) metronome, thereafter gait performed and auditory input delivered off-time & patients synchronized with tone.	Single & double paced rhythmic auditory cueing, sampled at 1000Hz.	Significantly enhanced auditory-motor synchronization in condition of double as compared to single-metronome condition. Patients had slower step response to restore synchronization when auditory stimuli were presented later as compared to before. Ct group had better & faster step response as compared to Exp. Step width increased with acoustic pacing for both Exp & Ct.
Hayden, et al. [30]	Effects of auditory cueing on gait & postural stability in patients affected	Exp I: 1F, 4M (55-72 years) Exp II: 4F, 1M (55-72 years)	5	-	One limb stance, cadence, gait velocity, stride length, timed up & go test, functional reach test & postural	Pre-test, Gait training for (Exp I: 30 sessions with auditory cueing, Exp II: 20 sessions with auditory cueing, Exp III: 10 sessions with auditory cueing) 8-10minutes day 1,	Rhythmic auditory “music” cueing at preferred cadence & increased by 1-3 bpm (when patient comfortable)	Significant improvements for the timed up and go test and the functional reach test. Significantly enhanced one-limb stance and cadence with earlier implementations of rhythmic auditory cueing in treatment protocol

	from stroke	Exp III: 3F, 2M (55-72 years)			changes by head tilt measurement	after 10 sessions, after 20 sessions, post-tests at 1st, 11th, 21st & 30th session		
Roerdink, et al. [31]	Effect of rhythmic auditory cueing on treadmill gait in patients affected from stroke	Exp: 2F, 8M (63, 46-78) Ct (healthy): 5F, 4M (69, 60-78)	5	Exp: 37.7± 32.6 months	Stride frequency, stride length, step length (paretic, nonparetic side), spatial asymmetry, stride time, step time (paretic, nonparetic side), step width, interlimb coordination	Gait performance on treadmill with (Exp)/without (Ct) with rhythmic auditory cueing at 0%, ±10% of preferred cadence	Rhythmic auditory cueing (0%, ±10% of preferred cadence) on alternate left & right ear	Significant effect of rhythmic auditory cueing on stride frequency (enhanced: +10%, reduced: -10%), stride length (reduced: +10%, enhanced: -10%), step length (paretic, non-paretic side: reduced: +10%, enhanced: -10%), stride time (reduced: +10%, enhanced: -10%), step time (paretic, non-paretic side: reduced: +10%, enhanced: -10%) & step width (reduced: +10%, enhanced: -10%)with rhythmic auditory cueing at 0% & 10% of preferred cadence for Exp.

					(relative phase difference, relative phase variability)			Significant enhancement in relative phase difference with pacing stimuli for Exp with rhythmic auditory cueing. Significant reduction in spatial asymmetry, temporal asymmetry with pacing rhythmic auditory cueing for Exp.
Argstatter, et al.[32]	Effects of rhythmic auditory cueing on gait in patients affected from stroke	Exp: 9F, 11M (69.3±10.2) Ct: 8F, 12M (69.2±9.5)	4	Exp: 20.7±0.2 days Ct: 24.2± 5.3 days	Gait velocity, stride length, cadence, gait cycle, gait symmetry, Barthel index, Fugl meyer motor assessment, functional independence measure	Pre-test, gait training with (Exp)/without (Ct) rhythmic auditory cueing at preferred cadence for a 30 minutes' session/day for 3 weeks, post-test	Rhythmic auditory cueing at preferred cadence (autoharp) with tempo changed according to patient's performance (2/4 pattern)	Significant enhancement in barthel index score, functional independence measure (no difference between Exp & Ct) in Exp after training with rhythmic auditory cueing & as compared to Ct. Significant enhancement in gait velocity, cadence, stride length in Exp after training with rhythmic auditory cueing, no difference with Ct. Enhancement in Fugyl meyer motor test, gait symmetry in Exp after training with rhythmic auditory cueing.

								Reduction in gait cycle in Exp after training with rhythmic auditory cueing.
Thaut, et al. [33]	Effects of auditory stimuli on gait performance in patients affected from stroke	Exp: 21F, 22M (69.2±11) Ct: 16F, 19M (69.7±11)	7	Exp: 21.3± 11 days Ct: 22.2± 12 days	Gait velocity, stride length, cadence, symmetry (swing ratio)	Pre-test, training with repeated auditory input for Exp & neurodevelopmental therapy/Bobath therapy for Ct for 30 min/5 times a week for 3 weeks, test after 3 weeks, 6-week post-test. Exp auditory input: Phases: 1st: preferred pace, 2nd: +5%, 3rd: ramp & step training, 4th fading auditory input.	Metronome input at preferred pace, +5%.	Significant enhancement in Gait velocity, stride length, cadence, symmetry as compared to Ct after 3 & 6 week training.

Schauer and Mauritz [34]	Effects of auditory cueing on gait in patients affected from stroke	23 patients Exp: (59±12) Ct: (61±12)	4	Exp: 53 days Ct: 67 days	Gait velocity, stride length, cadence, symmetry deviation, stride frequency & heel on-toe-off distance	Pre-test, gait training with music motor cueing for 20 min session, 5 days/week, 15 total sessions.	Music motor cueing adjusted for preferred cadence by time interval adjusted between consecutive heel strikes	Significant enhancement in gait velocity, stride length, heel on-toe-off distance. Significantly reduced symmetry deviation. Enhanced cadence with auditory cueing.
Thaut, et al. [35]	Effects of auditory cueing on gait & muscle activity in patients affected from stroke	Exp: 5F, 5M (73±7) Ct: 5F, 5M (72±8)	4	-	Gait velocity, stride length, gait symmetry cadence, Electromyogram amplitude variability (Gastrocnemius)	Pre-test/ training for 60 minutes with rhythmic auditory input/ post-tests Increased rhythmic auditory cueing by +5%, +10% of preferred cadence in the later stage of training.	Rhythmic metronome cueing superimposed on music for rhythmic input at 0%, +5%, +10% of preferred cadence, subdivided basic meter in ratios 1:2, 1:4.	Significant enhancement in gait velocity, stride length gait symmetry & cadence in Exp. Significant reduction in electromyogram amplitude variability of gastrocnemius in Exp.

Prassas, et al.[36]	Effects of auditory cueing on gait & muscle activity in patients affected from stroke	1F, 7M (69.6±11)	5	7.75± 7.24 months	Stride length, knee, hip joint range of motion, trunk angle, pelvic tilt, centre of mass displacement for vertical & lateral mass, centre of mass horizontal velocity & Electromyogram amplitude variability (Gastrocnemius)	Gait performance tested with/without rhythmic auditory cueing	Rhythmic auditory cueing at preferred cadence (original music composition allowed accentuation of 1st & 3rd beats)	Significant enhancement in stride length symmetry & symmetry of hip joint range of motion on both affected & non-affected side with rhythmic auditory cueing Significant reduction in centre of mass vertical displacement with rhythmic auditory cueing
Thaut, et al.[37]	Effects of auditory cueing on gait & muscle	2F, 8M (70.4±10.4)	5	6.5± 6.91 months	Stride variation, symmetry, weight bearing during stance, Electromyogra	Gait performance tested with/without rhythmic auditory cueing 3 times for 5 weeks	Rhythmic auditory cueing at 4/4-time signature (1st & 3rd beat accentuated by	Significant enhancement in weight bearing stance time on affected side & stride symmetry when rhythmic auditory cueing was received.

activity in patients affected from stroke	m amplitude variability (Gastrocnemius)	tambourine beat) at preferred cadence	Significant enhancement of magnitude of muscle activation during midstance/push-off on affected side & reduced on un-affected side. Significant reduction in electromyographic variability during swing phase on affected side (correlated with enhancement in stride symmetry). Significant reduction in variability of integrated amplitude ratios during midstance/push-off phase on affected side.

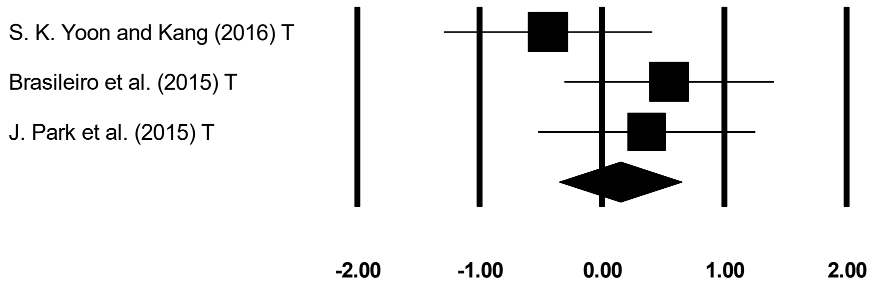

Figure 1 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity amongst post stroke patients with treadmill. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. (T: Treadmill)

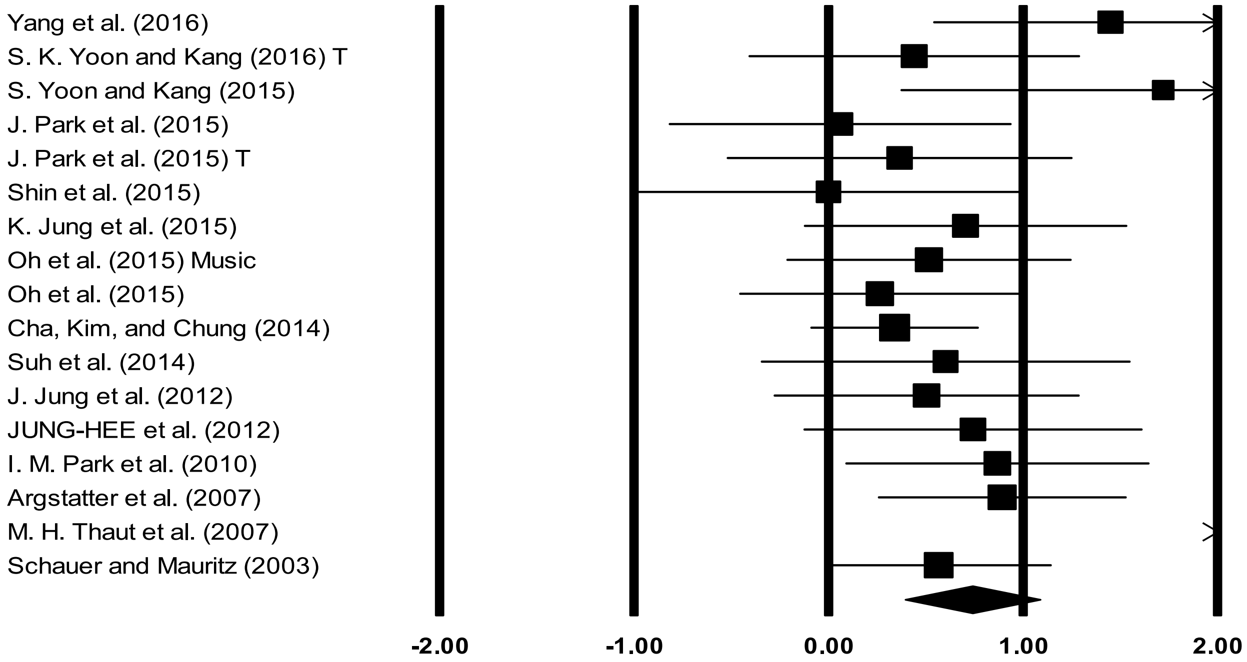

Figure 2 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with training on gait velocity amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill)

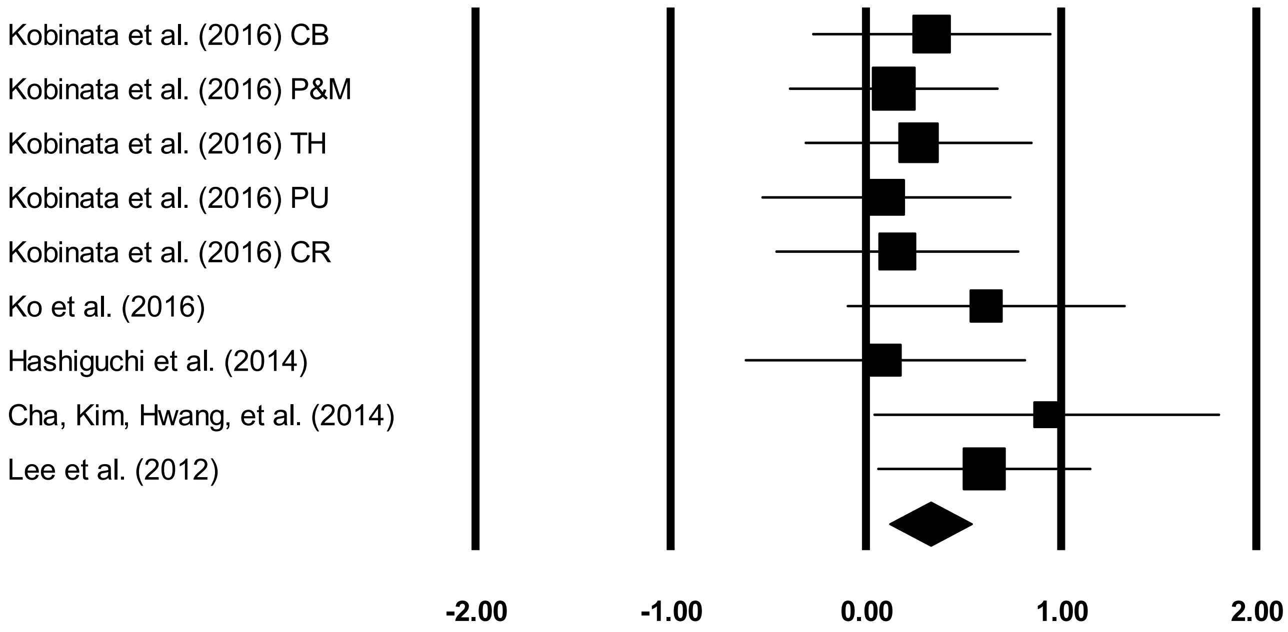

Figure 3 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with no training on gait velocity amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in gait velocity; a positive effect size indicated enhancement in gait velocity. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill)

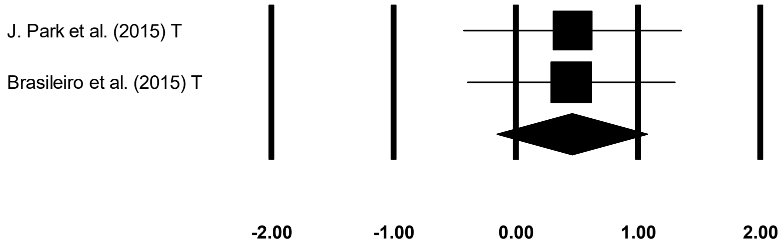

Figure 4 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with treadmill on stride length amongst post-stroke patients with treadmill. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. (T: Treadmill)

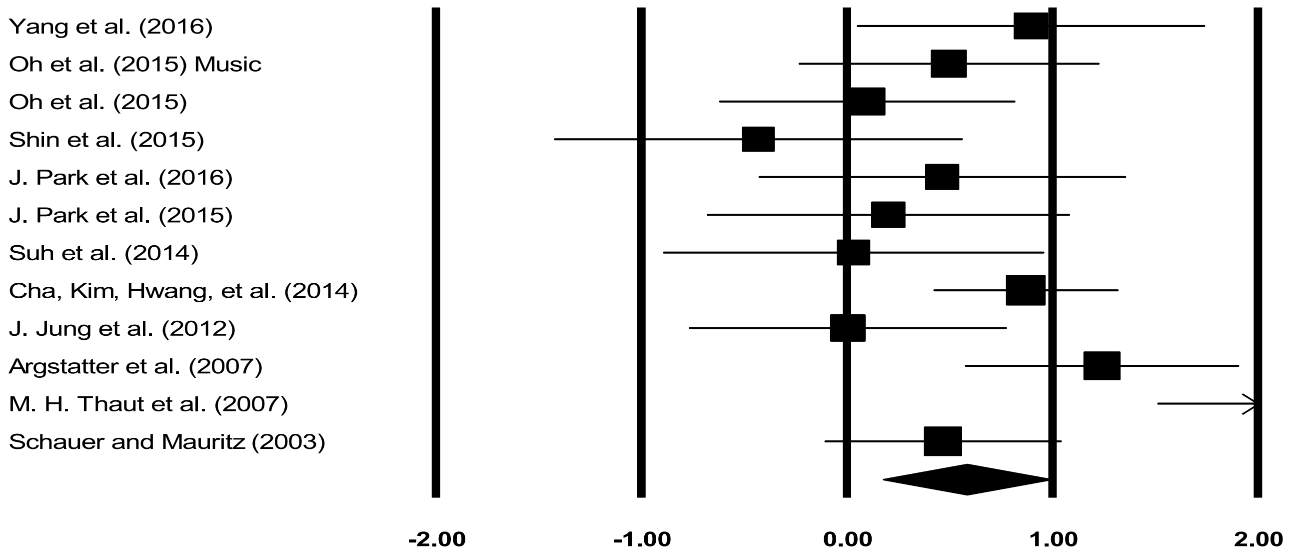

Figure 5 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with training on stride length amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill)

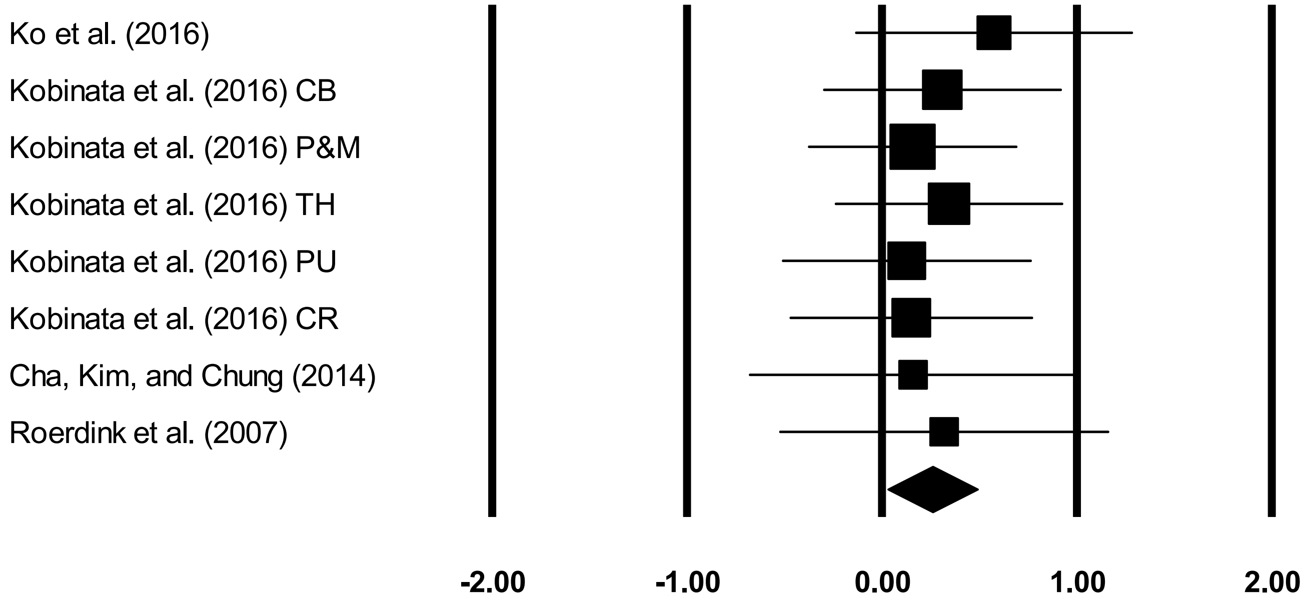

Figure 6 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with no training on stride length amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors

for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in stride length; a positive effect size indicated enhancement in stride length. (CB: Cerebellum, P&M: Pons & medulla, TH: Thalamus, PU: Putamen, CR: Corona radiata, T: Treadmill)

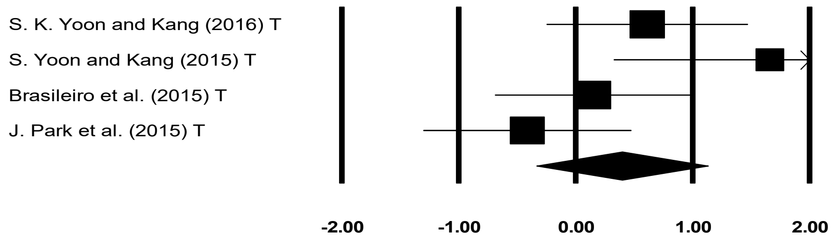

Figure 7 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on cadence amongst post stroke patients with treadmill. Weighted effect sizes; Hedge’s g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. (T: Treadmill)

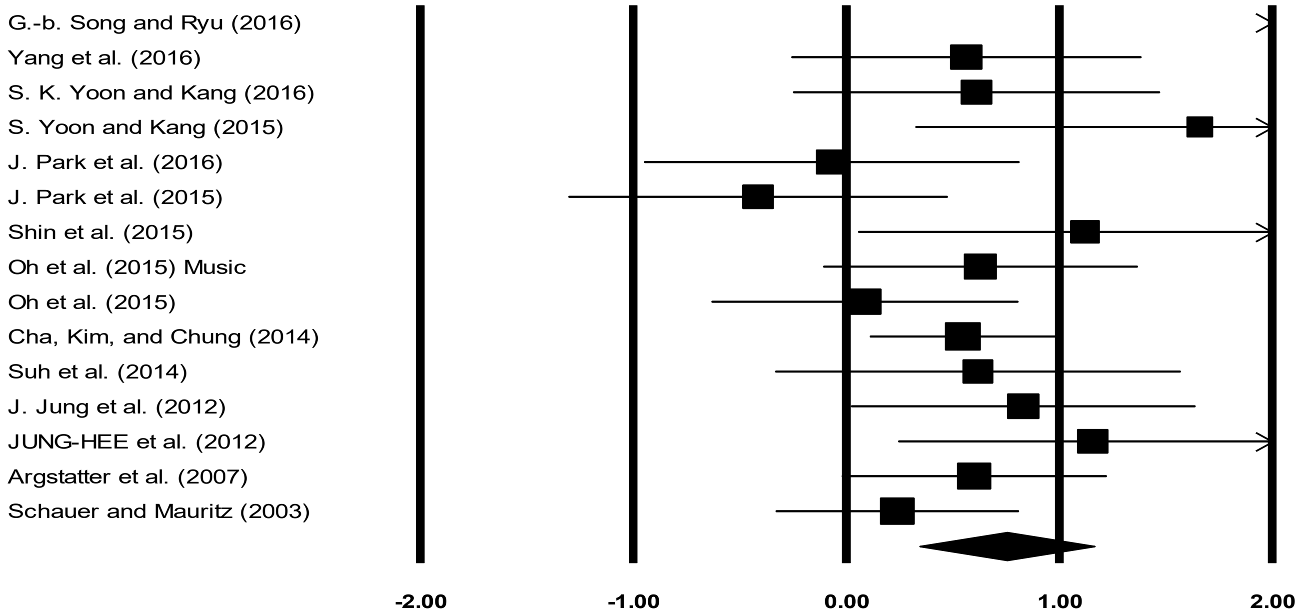

Figure 8 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with training on cadence amongst post-stroke patients. Weighted effect sizes; Hedge’s g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect

size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. (T: Treadmill)

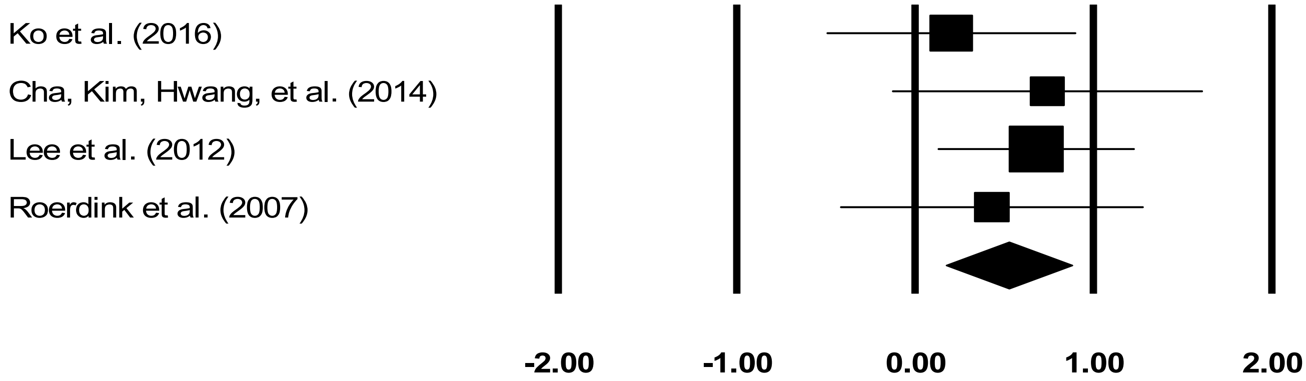

Figure 9 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing with no training on cadence amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in cadence; a positive effect size indicated enhancement in cadence. (T: Treadmill)

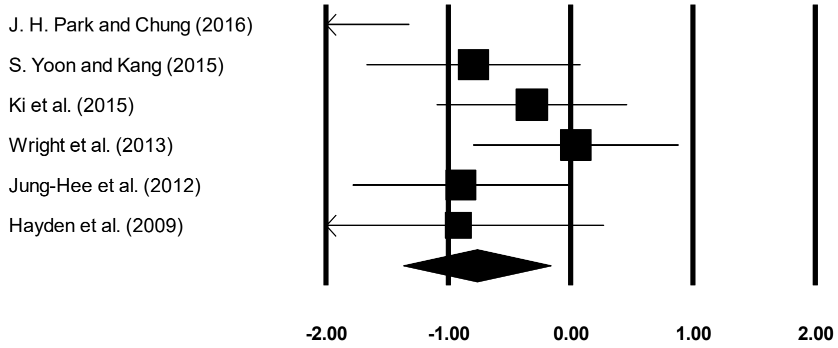

Figure 10 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, on time up and go test amongst post-stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in time up and go test (enhanced postural stability); a positive effect size indicated enhancement in time up and go test (reduced stability).

Table 3 PRISMA Checklist (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097)

Section/topic	**#**	**Checklist item**	**Reported on page #**
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1, 6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Table 1, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Page 1 of 2

Section/topic	**#**	**Checklist item**	**Reported on page #**

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, 2, 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table 2, 8-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2-3, 9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 1, 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-16
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

For more information, visit: **www.prisma-statement.org**.

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Chapter 5: Effects of rhythmic auditory cueing on gait in cerebral palsy: A systematic review and meta-analysis

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Supplementary materials

Table S1 Individual PEDro scores

Study	PEDro	Point estimates and variability	Between-group comparison	Intention to treat	Adequate follow-up	Blinded assessors	Blinded therapists	Blinded subjects	Baseline comparability	Concealed allocation	Random allocation	Eligibility criteria
Efraimidou et al[70]	4	1	1	0	1	0	0	0	0	0	1	1
Shin et al[38]	4	1	1	0	1	0	0	0	0	0	1	1
Wang et al[73]	7	1	1	0	1	1	0	0	1	1	1	1
Jiang[75]	7	1	1	0	1	1	0	0	1	1	1	1
Baram and Lenger[41]	4	1	1	0	1	0	0	0	0	0	1	1
Varsamis et al[77]	4	1	1	0	1	0	0	0	0	0	1	1
Kim et al[39]	7	1	1	0	1	1	0	0	1	1	1	1
Kim et al[76]	4	1	1	0	1	0	0	0	0	0	1	1
Kwak[74]	4	1	1	0	1	0	0	0	0	0	1	1

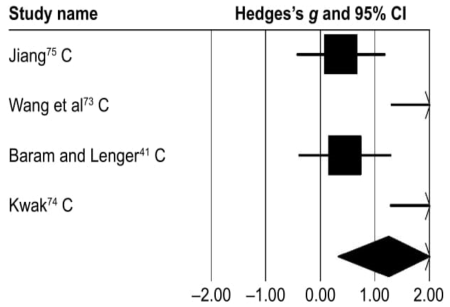

Figure S1 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity in children with cerebral palsy.

Notes: Negative effects indicate reduction in gait velocity, positive effects enhancement in gait velocity. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

Abbreviation: C, children.

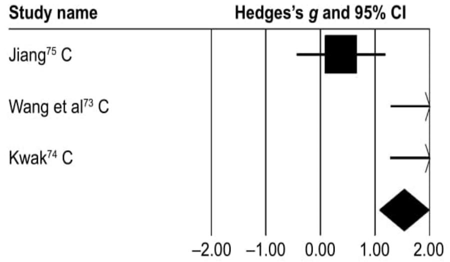

Figure S2 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on gait velocity in children with cerebral palsy posttraining.

Notes: Negative effects indicate reduction in gait velocity, positive effect sizes enhancement in gait velocity. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

Abbreviation: C, children.

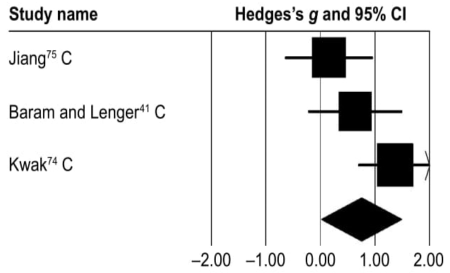

Figure S3 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on stride length in children with cerebral palsy.

Notes: Negative effects indicate reduction in stride length, positive effects enhancement in stride length. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean difference indicate favorable outcomes for control groups, positive mean difference favorable outcomes for experimental groups.

Abbreviation: C, children.

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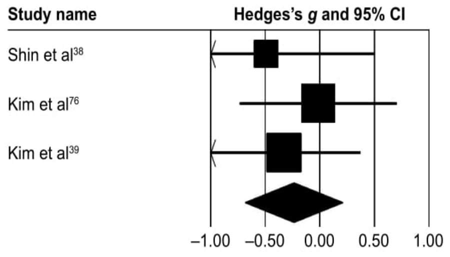


Figure S4 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on pelvic kinematics in adults with cerebral palsy.

Notes: Negative effects indicate reduction in pelvic kinematics, positive effects enhancement in pelvic kinematics. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicates favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

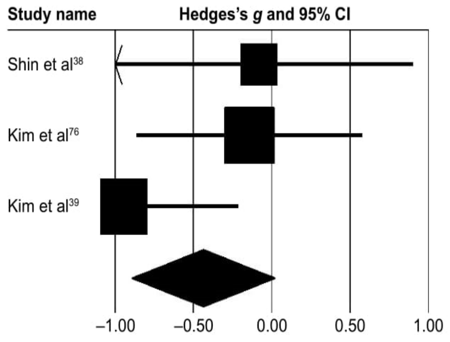


Figure S5 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on hip kinematics in adults with cerebral palsy.

Notes: Negative effects indicate reduction in hip kinematics, positive effects enhancement in hip kinematics. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

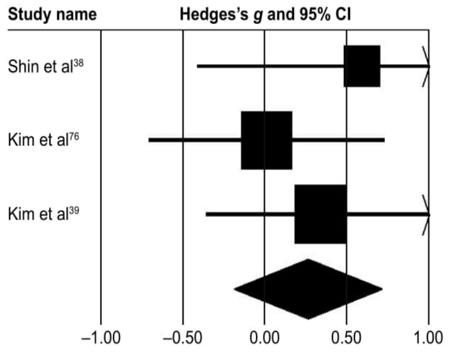


Figure S6 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on knee kinematics in adults with cerebral palsy.

Notes: Negative effects indicate reduction in knee kinematics, positive effects enhancement in knee kinematics. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

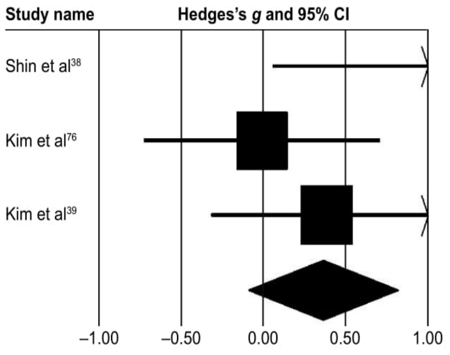


Figure S7 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on ankle kinematics in adults with cerebral palsy.

Notes: Negative effect sizes indicate reduction in ankle kinematics, positive effects enhancement in ankle kinematics. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrating repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean difference favorable outcomes for experimental groups.

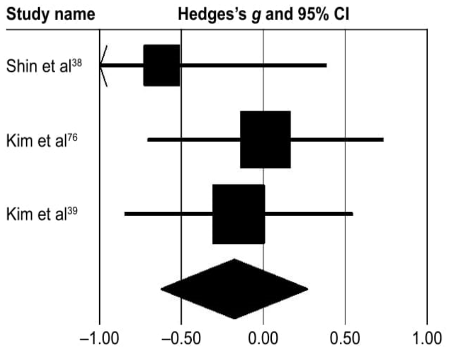


Figure S8 Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing on foot kinematics in adults with cerebral palsy.

Notes: Negative effects indicated reduction in foot kinematics, positive effects enhancement in foot kinematics. Weighted-effect sizes – Hedge's *g* (boxes) and 95% CI (whiskers) – demonstrate repositioning errors for individual studies. The diamond represents pooled effect sizes and 95% CI. Negative mean differences indicate favorable outcomes for control groups, positive mean differences favorable outcomes for experimental groups.

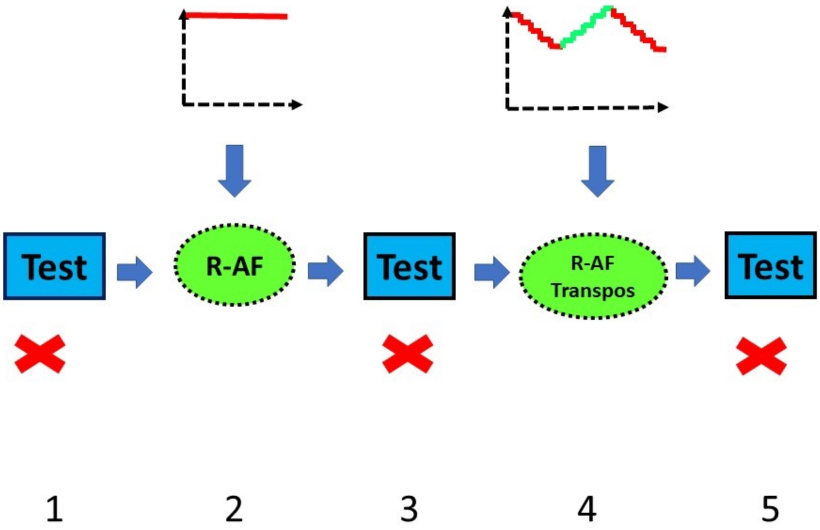
Chapter 9: Auditory Proprioceptive Integration: Effects of Real-Time Kinematic Auditory Feedback on Knee Proprioception

Supplementary material

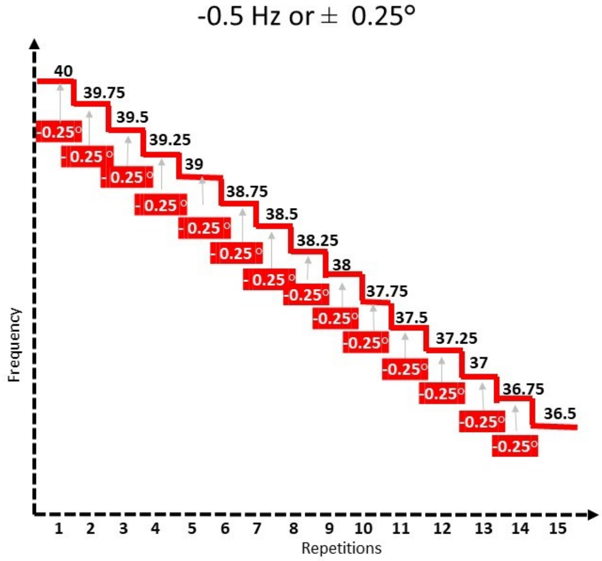
Effects of real-time auditory feedback on knee proprioception

[1]Shashank Ghai*, Gerd Schmitz, Tong-Hun Hwang, Alfred O. Effenberg
[1]Institute for Sports Science, Leibniz University Hannover, Germany
*Correspondence: Shashank Ghai, shashank.ghai@sportwiss.uni-hannover.de

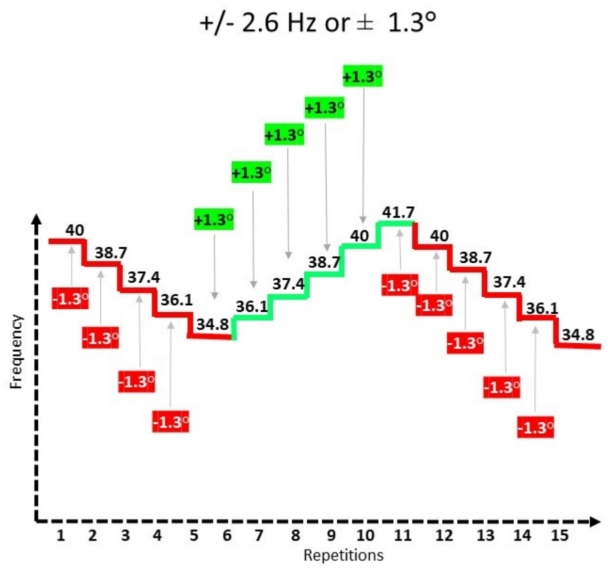
File 1. Illustrating the experimental setup and IMU sensor placements. (For representational purpose only)



File 2. Illustrating the experimental blocks, Green blocks represent presence of auditory feedback, and blue blocks represent no auditory feedback



File 3. Illustrating the step down transposition for 40° target angle across 15 repetitions during experiment I



File 4. Illustrating the step down-up transposition for 40° target angle across 15 repetitions for experiment II

For a sample auditory feedback please visit:

https://www.frontiersin.org/articles/10.3389/fnins.2018.00142/full#supplementary-material

Chapter 10: Training proprioception with sound: Effects of real-time auditory feedback on intermodal learning

Supplementary material

Training proprioception with sound: Effects of real-time auditory feedback on intermodal learning

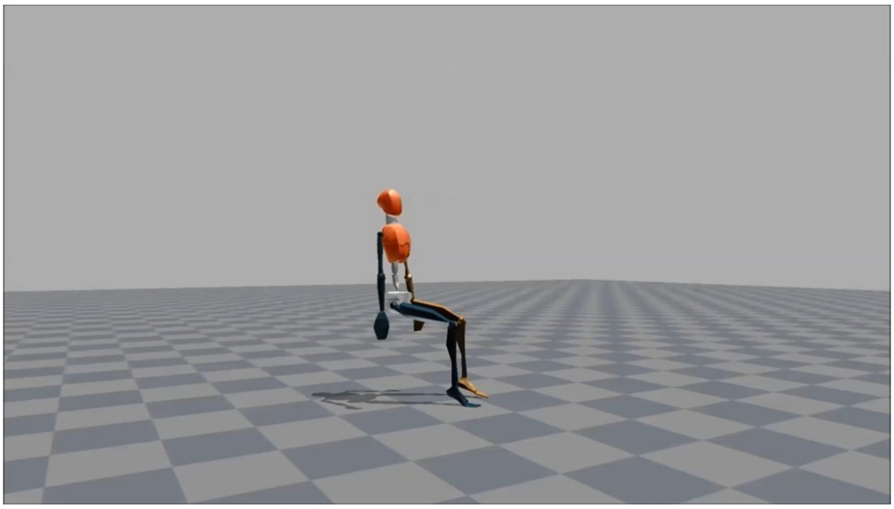
[1]Shashank Ghai*, [1]Gerd Schmitz, [1,2]Tong-Hun Hwang, [1]Alfred O. Effenberg

[1]Institute of Sports Science, Leibniz University Hannover, Germany

[2]Institute of Microelectronic Systems, Leibniz University Hannover, Germany

*Correspondence: Shashank Ghai, shashank.ghai@sportwiss.uni-hannover.de

File 1. Illustrating the experimental setup and IMU sensor placements. (For representational purpose only)



File 2. Sample MVN file depicting 4 repetitions for first right and then left knee for angle 1, 2, 3, 4 repetitions performed with real-time auditory feedback (the position of the trunk is not true position because the upper body was not tracked, the real-position is demonstrated in File 1)

- Pre-test: Angles- 20°, 40°, 60° and 80°, trials- 40, sound off
- PPT1: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- R-AF1: Angels- 20°, 40°, 60° and 80°, trials-96, sound on
- PPT2: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- R-AF2: Angels- 20°, 40°, 60° and 80°, trials-96, sound on
- PPT3: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- R-AF3: Angels- 20°, 40°, 60° and 80°, trials-96, sound on
- PPT-Final: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- RET-15min: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- RET-24 hours: Angles- 20°, 40°, 60° and 80°, trials-64, sound off
- G-Test: Angles- 15°, 35°, and 55°, trials-30, sound off

File 3. Demonstrates the breakdown of experimental blocks in terms of the angles trained in the block, the presence of sound i.e. on/off and total number of trials performed

Chapter 11: Auditory guidance of imagined movements: Effects of real-time auditory feedback (sonification) guided mental imagery on knee proprioception

Supplementary File

DRKS-ID: **DRKS00014244**
Date of Registration in DRKS: **2018/04/04**
Date of Registration in Partner Registry or other Primary Registry: **[---]***

Trial Description

Title

Effects of real-time auditory feedback and mental training on knee proprioception

Trial Acronym

Audioception 3

URL of the trial

[---]*

Brief Summary in Lay Language

Background: Proprioception is integral for efficient motor control and performance. Deficits in knee proprioception accuracy have been associated with a higher predisposition to injury, for instance, Anterior cruciate ligament injury, both in healthy and fall prone population groups. Recent research has demonstrated that real-time auditory feedback and auditory guided mental training can enhance knee proprioceptive perceptions, motor performance during a relatively short (20-30 minutes) training protocol, respectively.
Objective: We in the present study aim to analyze and compare the effects of mental practice performed with guided auditory feedback on knee proprioception.
Method: In the first steps, we train healthy participant's knee's bilaterally with real-time auditory feedback, and then ask them to perform mental practice of knee positions under two different conditions: a) with guided auditory feedback b) without auditory feedback. We also compare the effects of mental practice as compared to physical training.
Outcomes: The study for the first time will reveal outcomes of a novel rehabilitation protocol, where self-produced auditory feedback guides mental practice. Findings from this research later can be implemented in clinical fall prone population groups which manifest reduced physical activity due to fatigue. Here, mental practice might serve as an effective tool to maintain or even enhance the level of proprioceptive accuracy.

Brief Summary in Scientific Language

The aim of the study is to evaluate the effects of real-time auditory feedback and mental practise on knee propriocpetion.

Organizational Data

- DRKS-ID: **DRKS00014244**
- Date of Registration in DRKS: **2018/04/04**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
-

DRKS-ID: **DRKS00014244**

Date of Registration in DRKS: **2018/04/04**

Date of Registration in Partner Registry or other Primary Registry: **[---]***

Investigator Sponsored/Initiated Trial (IST/IIT): **yes**

Ethics Approval/Approval of the Ethics Committee: **Approved**

- (leading) Ethics Committee Nr.: **EV LUH 12/2017 , Ethikkommission der Leibniz Universität Hannover**

Secondary IDs

Health condition or Problem studied

- Free text: **Healthy participants will be analyzed**

Interventions/Observational Groups

- Arm 1: **Experimental group: The influence of mental training induced with guided real-time auditory feedback on knee proprioception**
- Arm 2: **Control group I: The influence of mental training induced without any guidance from real-time auditory feedback on knee proprioception.**
- Arm 3: **Control group II: The influence of no mental training on knee proprioception.**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, data analyst**
- Control: **Active control (effective treament of control group)**
- Purpose: **Prevention**
- Assignment: **Parallel**
- Phase: **IV**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

Influence of auditory feedback guided mental practise on knee proprioception will be primarily assessed. Here, a comparison between different mental practise strategies i.e. with/without auditory guidance would be made after a bilateral knee training regimen with real-time auditory feedback.

Secondary Outcome

The participants will also be evaluated based on the their Vividness of mental imagery capability evaluated with Movement Imagery Questionnaire-3.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- other **Institute of Sports Science, Leibniz University Hannover, Hannover**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/04/30**
- Target Sample Size: **40**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **20 Years**
- Maximum Age: **30 Years**

Additional Inclusion Criteria

1. No history of injuries on lower back, hip, knee and ankle joints.
2. Participants qualify the basic auditory hearing test (HTTS audiometry).
3. Participants having knee re-positioning errors (≤10 degrees)
4. Participants within the age group 20-30 years.

Exclusion criteria

1. Participants younger than 20 years or older than 30 years.
2. Participants who have acute injuries to either lower back, hip, knee, ankle joint.
3. Participants having a repositioning error of more than 10 degrees.
4. Participants who fail to qualify the basic auditory hearing test (HTTS audiometry).
5. Sedentary population group performing no physical activity.

Addresses

- **Primary Sponsor**

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  Fax: **+49 511.762-5511**
  E-mail: **alfred.effenberg at sportwiss.uni-hannover.de**
  URL: **https://www.sportwiss.uni-hannover.de/alfred_effenberg.html**

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  URL: **[---]***

Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

  European Commisson EC H2020-FETPROACT-2014 No. 641321.
  30173 Hannover
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2018/05/15**

Trial Publications, Results and other documents

- Approval of ethics comm. (mandatory for transfer to Studybox) **Ethical approval for the study**
- Background literature **Associated background literature**
- Background literature **Background literature**
- Background literature **Auditory Proprioceptive Integration: Effects of Real-Time Kinematic Auditory Feedback on Knee Proprioception**

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*