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Review

Future perspectives on neural mechanisms underlying rhythm and music based neurorehabilitation in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is characterized primarily by a dysfunctional basal ganglia (BG) system, producing motor and non-motor symptoms. A significant number of studies have demonstrated that rhythmic auditory stimulation can improve gait and other motor behaviors in PD that are not well managed by the conventional therapy. As music, being highly complex stimulus, can modulate brain activity/function in distributed areas of brain, the therapeutic properties of music potentially extend to alleviate non-motor symptoms of PD. Despite the clinical, behavioral evidence and promises of rhythm and music based interventions, the neural substrates underlying the effectiveness are poorly understood. The goal of this review is to appraise the current state of knowledge in order to direct further neuroimaging studies that help to determine the therapeutic effects of rhythm and music based interventions for motor and non-motor symptoms of PD.

1. Introduction

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease after Alzheimer's disease (AD) and the most common movement disorder. It affects about 1% of the population aged over 60 years and 4% of those over 80 in industrial countries. The primary treatment for the cardinal motor symptoms of PD include dopamine (DA) replacement therapy employing Levodopa and DA agonists. Alternative treatment strategies include deep brain stimulation in more advanced stages of the disease. However, these conventional therapeutic interventions show limited efficacy to alleviate some of the motor impairment such as gait disturbances and freezing of gait (FOG) as well as non-motor symptoms. They can also impair some of the cognitive function, as well as develop impulse control disorders in some of the people with PD, and motor complications such as involuntary dyskinesia with advancing disease. Because of these limitations, non-conventional therapeutic interventions are of growing interest for PD. Rhythm and music based interventions for mobility training have shown their promises as they are sensory-based, non-invasive, safe, and easily accessible without adverse effects (Ashoori et al., 2015; Dalla Bella et al., 2015; de Dreu et al., 2012).

Among them, rhythmic auditory stimulation (RAS) has proven its efficacy to improve gait and upper limb disturbances in clinical populations including PD since it was first demonstrated to entrain movement patterns nearly two decades ago (McIntosh et al., 1997; Miller et al., 1996; Thaut et al., 1999b, 1996). Entrainment refers to the frequency locking of two oscillating bodies (Thaut et al., 2015b). In clinical application of rhythmic entrainment, rhythmic cues serve as continuous time reference to initiate and continue motor behaviors. For example, rhythmic auditory cues such as metronome tones, or salient beat embedded in music can help regulate timing and pace in walking (Thaut et al., 2001). Auditory entrainment is superior to the entrainment using other sensory systems such as visual and tactile systems because firstly, the auditory system is faster and more precise than the visual and tactile systems to detect temporal patterns (Shelton and Kumar, 2010; Thaut et al., 1999a); secondly, the interactions between auditory and motor systems are immediate and stable even below the conscious perception (Thaut et al., 1998); and thirdly, the auditory system is closely and diffusely connected to the motor system (Thaut et al., 2015a).

In PD, meta-analyses and systematic reviews conveyed general consensus that RAS significantly improved gait parameters such as gait velocity, cadence, and stride length (Ghai et al., 2018; Lim et al., 2005; Rocha et al., 2014; Spaulding et al., 2013). In addition, improvement of other motor parameters such as symmetry, gait timing variability (del Olmo and Cudeiro, 2005; McIntosh et al., 1997; Miller et al., 1996; Willems et al., 2006), step amplitude (Arias and Cudeiro, 2008; Rochester et al., 2010), pedaling rate (Gallagher et al., 2016), Unified

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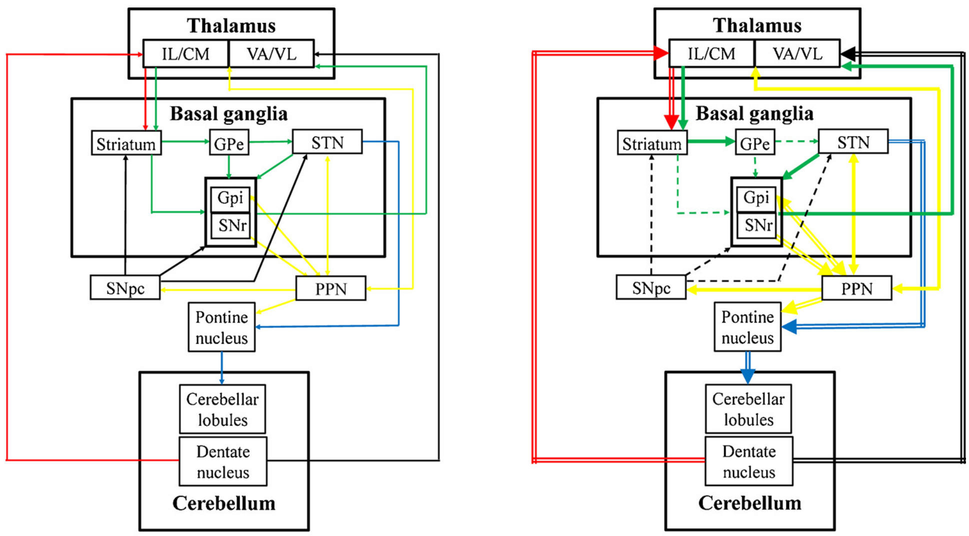

a. Normal state

b. Parkinsonian state

Fig. 1. Subcortical motor pathways associated with rhythmic movement in (a) normal and (b) parkinsonian states. The red lines indicate the projection from the dentate nucleus to the striatum. The blue lines indicate the projection from the subthalamic nucleus to the cerebellar cortex. The yellow lines indicate connections between pedunculopointine nucleus to basal ganglia. The green lines indicate connections in the basal ganglia motor pathway. The black lines indicate the rest of connections. The thicker and dashed lines indicate increased and decreased activities associated with the disease. The double lines indicate potentially altered activities due to the disease. CM: centromedian; GPe: external globus pallidus; GPi: internal globus pallidus; IL: intralaminar; PPN: pedunculopointine nucleus; SNpc: substantia nigra pars compacta; SNr: substantia nigra parc reticularis; STN: subthalamic nucleus; VA: ventroanterior; VL: ventrolateral.

Parkinson's Disease Scale (UPDRS) scores (de Bruin et al., 2010; De Icco et al., 2015; Lim et al., 2005), and FOG (Arias and Cudeiro, 2010; Kadivar et al., 2011; Lee et al., 2012; Nieuwboer et al., 2009) were reported. Furthermore, gait training with auditory cueing led to some improvement on the motor and perceptual timing tasks in people with PD (Benoit et al., 2014). The carry over effects of auditory-cueing motor training ranged from four to eight weeks (Benoit et al., 2014; Dalla Bella et al., 2017; Kadivar et al., 2011; Nieuwboer et al., 2007), but not three months (De Icco et al., 2015) after the completion of the intervention. Regardless of the status of antiparkinsonian medication, people with PD could benefit from the motor training with RAS (McIntosh et al., 1997; Rochester et al., 2010). Although both studies showed that the improvement in motor behaviors was greater when the auditory cue was used in the on-medication (ON) state compared to the off-medication (OFF) state, the differences were not statistically significant. A recent meta-analysis reported that an application of auditory cueing in the ON state yielded large effect sizes for stride length and gait velocity while the application of auditory cueing in the OFF state yielded a large effect size for stride length and a medium effect size for gait velocity (Ghai et al., 2018). These observations suggest that the restored dopaminergic function contribute to greater effectiveness in auditory-motor entrainment.

The use of rhythmic timing has been extended to dance interventions in people with PD (Bloem et al., 2015; Sihvonen et al., 2017). Tango (Hackney and Earhart, 2009; McKee and Hackney, 2014), Argentine tango or adapted tango (Allen et al., 2017), Irish setting dance (Volpe et al., 2013; but see Shanahan et al., 2017), and music based movement therapy (Pohl et al., 2013) alleviated disease severity (Allen et al., 2017; McKee and Hackney, 2014; Pohl et al., 2013; Volpe et al., 2013), as well as improved balance (Allen et al., 2017; Volpe et al., 2013), gait (Allen et al., 2017), FOG (Volpe et al., 2013), cognitive function (McKee and Hackney, 2014; Pohl et al., 2013), and quality of life (Pohl et al., 2013).

Despite the clinical behavioral evidence and promises of rhythm and music based mobility training, the neural substrates underlying the effectiveness are poorly understood. This is of particular interest in people with PD who are characterized by dysfunctional BG as the structure subserves important functions in rhythmic motor timing (Leow and Grahn, 2014; McIntosh et al., 1997). Thus, a question arises how people with PD can benefit from RAS? PD literature hypothesizes that RAS recruits a 'bypass' network such as cerebello-thalamo-cortical (CTC) motor network (Morris et al., 1996). However, literature suggests that RAS may also be able to influence the residual dopaminergic function and BG-thalamo-cortical (BGTC) network, and/or the activity in the motor pathway between pedunculopontine nucleus (PPN) and BG to improve gait impairment in PD. In this review paper, we discuss the motor pathways/networks associated with rhythmic movement (e.g., gait) in PD, how auditory stimuli can exert influence on them, summarizes published neuroimaging data in PD, and presents future directions of research in the field of neural plasticity induced by auditory-motor entrainment, implicating the therapeutic effects in PD. Additionaly, we discuss the potential of music based interventions to alleviate non-motor symptoms of PD.

2. Motor pathways/networks associated with rhythmic movement

2.1. Basal ganglia-thalamo-cortical (BGTC) and cerebello-thalamo-cortical (CTC) networks

Two major motor networks associated with rhythmic movement include basal ganglia-thalamo-cortical (BGTC) and cerebello-thalamo-cortical (CTC) motor networks. The BGTC network consists of the post-commissural putamen, the internal segment of the globus pallidus, thalamus, and sensorimotor areas while the CTC network consists of the cerebellar cortex and dentate nucleus, thalamus, premotor cortex, and parietal regions. These two networks were considered distinct and their interactions were thought to occur only at the cortical level (Caligiore et al., 2017; Wu and Hallett, 2013). However, recent animal studies revealed the existence of disynaptic connections between BG and cerebellum (Fig. 1a): the dentate nucleus projecting to the striatum through the thalamus (Hoshi et al., 2005) and the subthalamic nucleus (STN) projecting to the cerebellum through the pontine nuclei (Bostan et al., 2010). The projection from the dentate nucleus to the striatum originates from both motor and non-motor domains of the dentate nucleus (Hoshi et al., 2005) and the projection from the STN to the cerebellum was topographically organized (Bostan et al., 2010). The reciprocal, topographically specific connections between the cerebellum and BG (Hoshi et al., 2005) indicates that the two structures are likely to interact to influence motor and non-motor functions.

A human neuroimaging study also supported the connectivity (Pelzer et al., 2013). In PD, the OFF state shows both increased and decreased coupling in the motor networks, commonly with decreases within the BGTC motor network and increases within other BGTC networks and/or CTC motor network (Fig. 1b), and the administration of dopaminergic medication restores at least partially the altered brain activity (Esposito et al., 2013; Wu et al., 2009). Furthermore, PD shows higher neural activity than normal in the STN (Schrock et al., 2009) whose neurons are excitatory using glutamatergic neurotransmission (Smith et al., 1998). The abnormal excitatory signals from the STN likely increase the cerebellar activity because the pontine nuclei are also largely glutamatergic (Beitz et al., 1986; Wu and Hallett, 2013) (Fig. 1b). Deep brain stimulation of the STN normalizes cerebellar activation and improves the motor symptoms (Grafton et al., 2006; Payoux et al., 2004). These observations also indicate close interactions between the two motor networks. Furthermore, a unified model of these two networks for timing processing, which is important for motor control is postulated (Petter et al., 2016), and degeneracy (Edelman and Gally, 2001; Tononi et al., 1999) occurs in PD, in which the CTC motor network performs similarly to the BGTC motor network.

2.2. Pedunculopontine nucleus to basal ganglia motor pathway

Pedunculopontine nucleus (PPN) is a target site for deep brain stimulation to alleviate gait and postural impairment as well as FOG of PD (Huang et al., 2018; Tsang et al., 2012) and has close connections with BG (Fig. 1a). PPN has connections from the substantia nigra pars reticularis and internal globus pallidus (GPi) and projects to the substantia nigra pars compacta (SNpc), GPi, dorsolateral striatum, intralaminar and ventral thalamus, and ventral tegmental area (Benarroch, 2013; Mena-Segovia and Bolam, 2017). The ascending projections of PPN may be able to induce locomotion by increasing DA neuronal activity in the SNpc, releasing DA in the striatum as well as by modulating the thalamic activity (Mena-Segovia and Bolam, 2017).

In summary, the anatomical and functional connectivity data suggest that the cerebellum, BG, and PPN may be able to communicate with one another (Fig. 1a) to modulate rhythmic motor behavior such as gait and that due to dysfunctional BG, PD shows differential use of the motor networks/pathways during motor behavior (Fig. 1b).

3. How do rhythmic auditory stimuli influence the motor regions? Anatomical and functional connectivity between auditory and motor areas

The auditory system is composed of a hierarchical, widely distributed brain pathway encompassing brain regions in the brainstem, subcortical and cortical regions. Auditory information is conveyed from the cochlear nuclei to the superior olivary nucleus, the nucleus of the lateral lemniscus and the inferior colliculus in the brain stem, the medial geniculate nucleus in the thalamus, and reaches the primary auditory cortex through the acoustic radiations originating from the medical geniculate nucleus (Pickles, 2015) (Fig. 2).

Auditory regions in the midbrain and brainstem play an important role in processing temporal regularity. Among them, the IC is most sensitive to changes in temporal regularity and has connections with PPN (Motts and Schofield, 2010) whose cholinergic neurons are responsive to click sounds with broad frequencies (Reese et al., 1995). These suggest that the PPN may involve in auditory-motor entrainment using RAS. There is also a network of the medial part of the MGN projecting to cholinergic and non-cholinergic neurons in the GP that project to the auditory cortex (Moriizumi and Hattori, 1992), which may also be associated with auditory motor functions. Furthermore, some neurons in the primary auditory cortex sends direct glutamatergic projections to the superior olivary complex, as well as the PPN (Motts and Schofield, 2010), suggesting that auditory stimuli activating the primary auditory cortex may be able to affect the activity in the PPN and thereby influence the BGTC motor pathway.

At the cortical level, the acoustic information is further processed along the temporal lobe from the Heschl gyrus to the superior temporal gyrus (STG) as well as to the frontal, cingulate, anterior and posterior parietal, occipital cortices, amygdala and the striatum. These

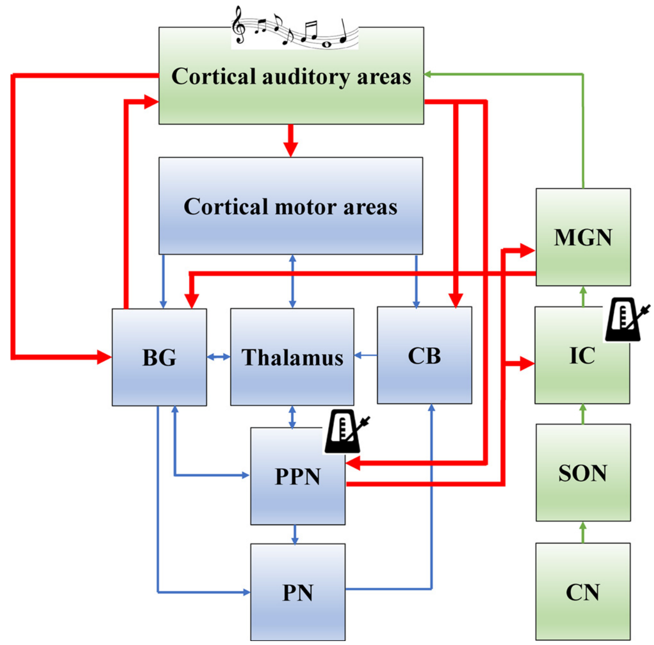

Fig. 2. Simplified illustration of auditory-motor connectivity. Green boxes and lines indicate auditory structures and pathways. Blue boxes and lines indicate motor structures and pathways. Red lines indicate connections between auditory and motor structures in which rhythm and music can modulate activities in motor pathways. BG: basal ganglia; CB: cerebellum; CN: cochlear nucleus; SON: superior olivary nucleus; IC: inferior colliculus; MGN: medial geniculate nucleus; PN: pontine nucleus; PPN: penduculopontine nucleus.

connections are topographically organized (Hackett, 2015; Yeterian and Pandya, 1998), suggesting that different auditory input may be able to modulate brain activity in other non-auditory areas (Thaut et al., 2014) and facilitate distinct functions. For example, lack of connections from the primary auditory areas to the striatum suggests that more complex auditory processing such as music perception may have greater impact on the striatal activity.

In addition to these anatomical connections, a resting-state functional MRI (rs-fMRI) study also showed that the STG (BA22) and the posterior putamen were functionally connected in both people with PD and healthy older adults (Helmich et al., 2010). Furthermore, functional MRI studies showed that passive listening to auditory rhythms or music activated motor areas such as the BG, cerebellum, premotor cortex and supplementary motor area (SMA) (Chen et al., 2009, 2008; Fujioka et al., 2012, 2010; Grahn and Brett, 2007; Grahn and Rowe, 2009; Seger et al., 2013; Thaut et al., 2014).

To summarize, the functional and anatomically connectivity data suggest that (1) auditory stimuli can influence the motor pathways/networks associated with rhythmic movement such as gait (Fig. 2), (2) these motor pathways/networks may coordinate with one another to generate auditory-motor entrainment, and (3) pathological brains such as PD may show differential use of the pathways/networks in response to external cueing (e.g., more reliance on external cueing) during motor behavior.

4. Neuroimaging studies on auditory-motor entrainment in Parkinson’s disease

Functional neuroimaging studies can reveal changes in brain activity during auditory-motor entrainment by employing a simple repetitive motor task (e.g., a finger tapping task) synchronized to RAS (e.g., isochronous metronome clicks). This task is commonly referred to as a synchronization (SYNC) task. The changes in brain activity during the SYNC task can be contrasted to those during a compatible control task such as a continuation (CONT) task in which participants perform the same motor task but without RAS to elucidate the role of RAS. Alternatively, brain activities are compared before and after the motor training using RAS in both people with PD and healthy controls (HC).

One study reported that people with PD in the ON state (PD-ON) showed significantly reduced variabilities of both finger tapping and gait, which became compatible to those for HCs after the motor training using RAS (one hour/day, five days/week for four weeks) (del Olmo et al., 2006). These patients also showed significantly increased activity in the right anterior cerebellum and the right parietal and temporal lobes (BA 22, 42, 43) after the training compared to before the training. These findings suggest that strengthened right-lateralized auditory and corticocerebellar activity may present compensatory/adaptive responses that emerged after the training using RAS in PD. However, whether the neural plasticity observed in PD would differ from the one in HCs is unknown as HCs did not have the training.

There is one preliminary functional MRI study that directly contrasted brain activity during the SYNC and CONT tasks between PD-ON and HCs, and demonstrated that PD-ON showed greater activity in a large neural network including the anterior cingulate and medial frontal regions, bilateral middle frontal gyri, bilateral parietal lobe, insular cortices, cerebellum, and the body of the caudate nucleus (Thaut et al., 2015a). A graph theoretical analysis further revealed that PD-ON had a greater functional connectivity within sensorimotor areas consisting of the left pre- and postcentral gyri and SMA, and between these motor regions and the auditory cortex in the SYNC condition. These findings suggest that the SYNC task activated both CTC and BGTC networks by consolidating the cortical auditory-motor interactions. The role of dopaminergic medication on RAS-induced enhanced BGTC needs to be elucidated.

Other studies suggest that the SYNC task enhance the activity in cortical regions in PD. In one study, PD showed a wide distributed cortical activation, but not either striatum or cerebellum during the SNYC task compared to the CONT task (Jahanshahi et al., 2010). In another study, PD showed that enhanced activation in the right insula and left inferior parietal cortex (BA40) during the OFF state, and in the left superior frontal gyrus (BA9) and left subcallosal gyrus (BA34) during the ON state compared to HCs (Elsinger et al., 2003). In either study, the results of direct contrast of SYNC > CONT between PD and HC groups are not reported.

In another study, when the activity in the sub-putaminal regions were specifically analyzed during auditory-cueing ankle movement in PD-ON group compared to HC group, there was no group differences in the putaminal activation (Nieuwhof et al., 2017). In both group, the dorso-posterior putamen showed significantly greater activity than the rest of the putaminal subregions (ventro-posterior, sorso-anterior, ventro-anterior regions).

These few published studies vary in the experimental method (e.g., types and frequencies of RAS presentation or motor responses, types of control task and image contrasts, clinical characteristics of PD and medication state), which makes it challenging to draw a conclusion. To date, there is only one preliminary study that specifically address the neural underpinning for auditory-motor entrainment in PD-ON. There has been no study to address it in the OFF state and therefore, the interaction between medication and external auditory cueing on motor behavior is unknown. Moreover, there has been no study to interrogate the PPN-BG activity during auditory-motor entrainment. Thus, further studies are warranted. Pertinent investigations are needed contrasting brain activation during SYNC and CONT tasks and during ON and OFF states. To elucidate the effects of RAS on BG activity, it may also be useful to contrast dopaminergic responses during the SNYC task to those during the CONT task using DA PET radioligands such as [^{11}C] raclopride and [^{11}C]-(+)-PHNO. The latter radioligand may be advantageous as it shows higher sensitivity in detecting changes in extracellular DA induced by external stimuli (Narendran et al., 2010) and shows stronger binding signals in more brain structures associated with the BGTC motor network including the striatum, globus pallidus, and substantia nigra (Freedman et al., 1994; Graff-Guerrero et al., 2008; Narendran et al., 2006; Willeit et al., 2006).

It is also crucial to determine the neural basis of the optimal auditory stimuli for rhythmic entrainment that will maximize the therapeutic effects targeted for PD. In healthy adults, some studies showed that rhythmic music appears to be more effective than metronome tones to improve gait performance in both younger (Leman et al., 2013; Styns et al., 2007) and older (Wittwer et al., 2013) healthy adults. Another study showed that metronome cues and music with high beat salience (high–groove music) elicited similar effects and better effects compared to music with low beat salience (low-groove music) on gait parameters in young healthy adults (Leow et al., 2014). Furthermore, metronome cues were equally effective in improving gait behavior as high-groove familiar music in young healthy adults (Leow et al., 2015). On the contrary, patients with Huntington's disease walked faster with the metronome cues compared to with rhythmic music (Thaut et al., 1999b).

The inconsistent findings may be partly due to individual differences in beat perception associated with cognitive ability (Leow et al., 2014) and cognitive or attentional demands of auditory stimuli (Ashoori et al., 2015; Leow et al., 2015; Thaut et al., 1999b). Thus, simple isochronous metronome cueing may elicit greater therapeutic effects than rhythmic music in patients who are likely to have cognitive impairment (Thaut et al., 1999b). People with PD who showed cognitive impairment measured by MMSE (scores ranging from 22.5 to 25) were able to improve gait behavior with metronome cues (Rochester et al., 2009). More studies are needed to determine the effects of different forms of rhythmic entrainment on brain activity and motor behaviors in PD with different cognitive profiles.

5. Music based interventions for non-motor symptoms of Parkinson's disease

Music as a highly complex stimulus (Thaut, 2015) may be able to be applied to alleviate non-motor symptoms of PD. For example, cognitive impairment is prevalent in people with PD, particularly executive dysfunctions associated with frontal regions and DA (Schapira et al., 2017). A recent pilot study including 25 people with PD without dementia or depression demonstrated that a six-week active music interventions consisting of production of music, singing, and dancing improved frontal lobe function as well as memory function (Spina et al., 2016).

To date, there is no neuroimaging study addressing the brain changes induced by music based interventions in cognitive impairment of PD. However, a randomized controlled study in patients with stroke showed that daily listening of favorite music resulted in significant increase in gray matter (GM) volume in wide areas of brain compared to listening to an audio book and no intervention (Särkämö et al., 2014). The cortical GM increase was apparent particularly in the right frontal regions including the superior, middle, and inferior frontal gyri, orbitofrontal cortex, and superior medial frontal gyrus, in addition to the left SMA and left ventral/subgenual anterior cingulate cortex (ACC) as well as the right precuneus and posterior cingulate cortex in the parietal region and the right fusiform gyrus in the temporal region. Subcortically, the volume increase occurred in the right ventral striatum and ventral GP. Furthermore, the increased GM volume in the SFG was associated with better cognitive performance. Cortical thinning in the SFG was associated with executive dysfunction and general cognitive impairment in people with PD (Koshimori et al., 2015). These results suggest that music based interventions may be able to counteract the cortical thinning and cognitive impairment of PD.

Depression and anxiety are also part of common non-motor symptoms of PD (Schapira et al., 2017). In the study by Särkämö et al. (2014), the increased GM volume in the subgenual ACC was associated with reduced negative mood including depression, tension, fatigue, forgetfulness and irritability. Furthermore, a meta-analysis of functional neuroimaging studies suggests that music in general can modulate brain activity in various brain regions that are implicated in psychiatric disturbances such as amygdala, hippocampal formation, ventral striatum including the ventral pallidum, the head of the caudate nucleus, the pre-SMA, cingulate cortex, and orbitofrontal cortex (Koelsch, 2014). Moreover, highly pleasant music induced DA release in the ventral and dorsal striatum, which was positively correlated with degree of pleasure felt in young healthy adults (Salimpoor et al., 2011). Taken together, listening to music, particularly favorite or pleasant music may contribute to psychological well-being in PD, which is also accompanied with structural and functional brain changes.

Rhythm and music can also alleviate some of the impairment associated with speech in PD (Thaut, 2015). One study investigated the effectiveness of different types of rhythmic components to improve speech intelligibility in people with PD who had hypokinetic dysarthria (Thaut et al., 2001). Both metered and patterned rhythmic cueing led to significant improvement in speech intelligibility rates in these patients. In addition, there was a case study in PD demonstrating that the presence of march that is more congruent with the predominant meter of the language, but not waltz that is not congruent with that, improved speech perception. This was also accompanied with a robust evoked potential response demonstrated using EEG (Kotz and Gunter, 2015).

In summary, the brain regions whose activity modulated by music well overlap with those in the cortico-striatal circuits, suggesting the potential therapeutic effects of music to partially alleviate non-motor symptoms of PD such as cognitive impairment and psychological disturbances. Interestingly, the results reported by Särkämö et al. (2014) were only present in the stroke patients with left hemispheric damage. This may be related to the right hemisphere dominance of music processing (Zatorre et al., 2007). It may be interesting to investigate the relationship between the laterality of music processing and the side of symptom dominance in people with PD. In addition, future research is needed to uncover the specific neural mechanisms underlying how rhythm and music improve speech impairment in PD.

6. Conclusion and future directions

At present, due to a paucity of literature specifically investigating the effects of RAS and music on brain dysfunction underlying motor and non-motor symptoms in PD, a full understanding of the neural substrates underlying the therapeutic effects await further research. However, important key findings in the literature shows already that rhythm and music modulate the brain activity in the DA pathways and DA release in the striatum, as well as the brain activity in the associated regions/network such as the cerebellum possibly as a compensatory/adaptive mechanism, amygdala, parietal regions and PPN. Therefore, rhythm and music based interventions have promises for complementary therapy for PD, by likely inducing positive effects on disease associated regions and/or facilitating compensatory mechanisms. The literature also suggests that different auditory stimuli may vary in their therapeutic effects. However, the consistent point in the research literature in this respect seems to be the emphasis on an isochronous rhythmic stimulus structure to optimally facilitate the effects. Further neuroimaging studies, especially with an emphasis on functional connectivity and neurotransmitter functions, are needed to elucidate the relationship between rhythm and music based interventions and their therapeutic effects on motor and non-motor symptoms of PD.

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