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Using Music Therapy as a Rehabilitation for Parkinson's Disease

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Abstract

This paper aims to discover the neurochemical pathways underlying the therapeutic effects of music on the symptoms of patients with Parkinson's Disease. Since ancient times, music has been speculated to have healing properties. Music can evoke a wide range of emotions and has important functions including the regulation of mood, arousal, self-reflection, pleasure, and social bonding. Moreover, music can be applied as a therapeutic strategy to support development, health, and wellbeing. Music comprises numerous musical components, such as pitch, time information, timbre, emotion and meaning, giving it a complex multidimensionality. Thereby, listening to music affects the cerebral cortex and multisensory and motor integration regions in the frontal, parietal, and temporo-occipital brain regions. Research has demonstrated that music is a powerful stimulus for brain plasticity, implying it enhances learning and cognitive capabilities. Musical therapies can be positively applied to a broad range of diseases, including neurological disorders like aging, Alzheimer's Disease, stroke, Autism Spectrum Disorders, and Parkinson's Disease. Listening to music engages neurochemical systems for reward, motivation, and pleasure, stress and arousal, immunity, and social affiliation as it stimulates the release of dopamine, glucocorticoids and catecholamines, serotonin, and oxytocin. Rhythmic auditory stimulation and "relaxing" music (with a relatively low BPM) has been associated with improvements in gait in PD patients. Proposed mechanisms for music and rhythm-based interventions on PD involve the recruitment of alternative neural pathways, rhythmic entrainment, and enhanced motor learning. Moreover, it is suggested that the brainstem perceives music as a survival signal, which beholds that "stimulating" music may be interpreted as an alarm call leading to sympathetic arousal (respiration, heart rate and blood pressure), whereas "relaxing" music decreases sympathetic arousal as it mimics soothing sounds of nature. Yet, research has shown personality traits and temperament influence music-induced changes in neurochemistry, suggesting there is an individual variability in the response to music.

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Chapter 1: Introduction

Last year, my father told me a story about when he was working in an audio/video store. His job was to help customers and repair broken items. One day, a man wearing a set of headphones entered the shop. The man walked towards my father to ask him for help, and he apologized for not taking his headset off: "Sorry I am keeping my headphones on. I have Parkinson's Disease and I have noticed that when I listen to classical music, I can control myself better and I am less shaky". This happened almost 30 years ago.

I have always been intrigued by the effect that music has on people. Music is sounds that arouse strong emotions, resulting in joy, happiness, and sadness or even in overwhelming bodily reactions like tears in the eyes or shivers down the spine (Altenmüller and Schlaug, 2015). Music can set a mood, it can make you nostalgic and transport you back to a certain place in time, and it may connect you to other people, in the room, in your country, and all around the globe. But until my father told me the story about the man with the headphones, I had never thought of music being a strategy to directly reduce the symptoms of a neurodegenerative disease like Parkinson's.

Throughout human history, music has been speculated to have therapeutic value. Music has beneficial effects on cognitive, behavioural, motor, and psychosocial levels in injured, degenerating, and disordered brains. Therefore, music therapy can be positively applied to a broad range of diseases, including neurological disorders like Alzheimer's Disease (AD), Autism Spectrum Disorders (ASD), and Parkinson's Disease (PD). The beneficial impact of music therapy is often attributed to the structural and functional changes in brain regions (Speranza et al., 2022). It has been demonstrated that music is a potent stimulus for neuroplasticity, as it stimulates specific brain areas and affects processes responsible for memory, motor control, timing, and language (Demarin et al., 2016).

It is well documented that music positively affects neurodegenerative disorders in the long term. However, the anecdote from the beginning of this introduction suggests that (1) music has a direct influence on controlling the motor symptoms of PD, and (2) that the strength of motor improvements depends on the type of music. In absence of the music, the man probably would have started having a tremor, or had trouble maintaining his balance. Moreover, listening to a different type of music would have probably been less effective. Interestingly, the mechanisms of different music therapies on brain diseases remain less explored. Therefore, this report will aim to discover the neurochemical pathways that music enhances in patients with Parkinson's Disease. For this purpose, music will be discussed in sense of origin, function, therapy, neurological mechanisms, therapeutic effects, and acute effects. In addition, this investigation will explore the impact of different types of music on Parkinson's patients.

Chapter 2: Music

Archaeological Evidence of Music

Sometime between 50,000 and 100,000 years ago, the modern human mind came into being. These early humans with a similar mental architecture to ours were artistic, as archaeological findings have revealed that societal activities were intertwined with artistic behaviour. While paintings, sculptures, and literature are direct, tangible archaeological records, evidence for music is harder to find, because it consists of temporal sound patterns created by vibrated objects with resonance bodies (Thaut, 2015). Hence, the existence of complex musical instruments is universally accepted as an indication of music. The oldest musical instrument confirmed is a 45,000-year-old bone flute found near Geissenklößerle in Southwest Germany, which allows a musician to play modern scales (Conard et al., 2009).

Music is Complex

Music consists of complex sounds. A single melody even contains various dimensions of pitch (the individual intervals, and the overall pattern of 'ups and downs'), time (tempo, rhythm, metre), and the distinctive instrumental or human voices ('tone quality' or timbre) that carries the tune (Warren, 2008). Rhythm is defined as the time-based pattern of music or sound that consists of perceptible groupings of notes, beats, accents, and phrases (Ashoori et al., 2015). Moreover, musical elements include duration (the length of a musical note), dynamics (the variations in loudness of the musical composition or specific notes), harmony (the sound of multiple notes heard simultaneously), tonality, (the arrangement of pitches and/or chords), texture, musical structure, and pulse (musical beat) (Figure 1) (Dunnet, 2022).

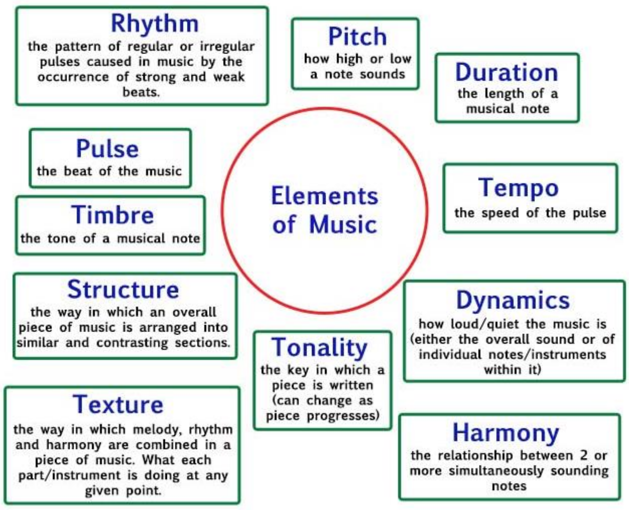

Figure 1: Schematic representation of the elements of music (Dunnet, 2022)

Music is defined as the art of combining vocal or instrumental sounds to produce beauty of form, harmony, and expression of emotion. It is found in every human society and lends itself easily to alliances with words, as in song, and with physical movement, as in dance. Despite its universality, the additional value of music has only been recently discussed (Epperson, 2022).

The Appearance of Music

In essence, music is an abstract auditory language. Music communicates emotions, concepts, or events symbolically, as humans have learned to assign expressive meaning to it. Since ancient times music has been used to support essential collective moments in society and to express rituals of life events such as birth, marriage, and death, and political values and norms (Speranza et al., 2022; Thaut, 2015). In this view, music may be considered an early biological language of the human brain that may have been fundamental to the emergence of the cognitive ability to construct symbols. Hence, music may be a prerequisite for developing verbal and numerical languages (Thaut, 2015). Yet, according to a study by Savage and colleagues, the cross-cultural universality of music and language suggests that music and language fulfil independent functions. (Harrison and Seale, 2021). While the function of language is to communicate, consisting of words used in a structured and conventional way, music is an arrangement of sounds consisting of previously mentioned musical components which appear to have a much deeper power over our emotions than does ordinary speech (Gonsior, 2011).

Studies have proposed that music evolved because it leads to social cohesion and thus increases the fitness of a group. It is speculated that music increases cooperation because it provokes similar emotional states among people (Snowdon et al., 2015). However, whether music is a domain-specific evolutionary adaptation for social bonding or a by-product of the evolution of other adaptations like vocal learning abilities remains debatable (Harrison and Seale, 2021). The theory of music-induced social bonding is in accordance with other views on the origin of music to contribute to human species survival via utilitarian functions, such as parental care and sexual selection (Thaut, 2015). The latter is a theory by Darwin, which describes music as a type of courtship behaviour that contributed to our species' sexual selection (Kleinman, 2015).

Functions of Music

Studies in music psychology have identified several functions music serves in daily life. The most important functions include the regulation of mood/emotions and the regulation of arousal/activations. Furthermore, functions of music cope with self-reflection, pleasure, entertainment, social bonding, and the expression of one's personal values and beliefs. A. study by Schäfer and colleagues showed that functions of music listening contribute to the development of music preference in western as well as eastern cultures. However, cultural differences may affect the predictive power of music function for the strength of the music preference (Schäfer et al., 2012). Beyond personal custom, the variety of different types of music (relaxing/stimulating) allows the application of music in a broad range of workplaces to enhance performance. Neurosurgeons use music to enhance concentration, armies to coordinate movements and increase cooperation, workers to improve attention and vigilance, and athletes to increase stamina and motivation (Chanda and Levitin, 2013). Through its variety of functions and mood-uplifting effects, music is considered to have therapeutic value. Therefore, another function of music is its healing effect by means of music therapy (Speranza et al., 2022).

Chapter 3: Music as Therapy

Early Uses of Music and Healing

Cross-cultural investigations emphasize that people have perpetually believed that music exerts a “healing” effect on the mind and body (Chanda and Levitin, 2013). In pre-literate cultures, music was habitually employed during rituals to communicate with magic forces to petition for healing. Structures in music (rhythm and frequencies) could create specific physical responses (e.g. wailing sounds to express grief), and different classes of healing songs and dances were associated with different types of illnesses. With the rise of early civilizations, new rational medicine superseded the ancient magical, spiritual, and physical components of medicine. However, music is still applied today as therapy in rational medicine, and physiological and psychological healing (Thaut, 2015).

Music Therapies

Music therapy refers to the clinical approach of employing music interventions with therapeutic relationships to support development, health, and wellbeing (Brault and Vaillancourt et al., 2022). Thereby, it aims to maintain, and restore mental, physical, emotional, cognitive, and social individual needs (Speranza et al., 2021). Music therapy is suitable for people of any age and with any musical experience, as it can be highly personalized (Wong, 2021). It can be an active process in which clients play musical instruments or a passive process that involves listening and responding to music. An advantage of receptive methods is that the therapist may ‘prescribe’ music medicine that a client can listen to outside the therapy room (Craig, 2019). Furthermore, music interventions may vary in type of music (usually only two broad types, stimulating vs relaxing), locus of control (experimenter-selected vs participant-selected music), and social context (e.g. individual activity, recreational group activity, or dyadic therapist-guided intervention) (Chanda and Levitin, 2013).

Music therapists often work in hospitals, substance abuse treatment centres, or private practices. Therapists may use one or a combination of approaches. Examples of active music therapies that encourage clients to play an instrument are *Analytical*, *Benenzon*, and *Nordoff-Robbins music therapy*. The goal of these therapies is to incite the expression of unconscious thought and enable self-expression. Another active approach is *vocal psychotherapy*, which uses vocal exercises, natural sounds, and breathing techniques to connect an individual with his/her emotions and impulses (Wong, 2021). An example of receptive music therapy is the *Bonny method of guided imagery and music*. This type of therapy exposes clients to images to open a conversation, and classical music is used as a so-called ‘co-therapist’ (Craig, 2019). *Cognitive behavioural music therapy* combines both passive and active methods, including listening to music, dancing, singing, or playing an instrument, to reinforce and modify behaviours. While most therapies occur one-on-one, *Community music therapy* uses musical rituals to acquire a communal change in group sessions (Wong, 2021). Besides these general forms of music therapy, neurologic music therapists use forms of Neurologic Music Therapies, which refers to a research-based system of standardized clinical techniques for sensorimotor, speech/language, and cognitive training (Table 1) (Devlin et al., 2019).

Table 1: Neurologic music therapy interventions. (Devlin et al., 2019)

Sensorimotor training	
Rhythmic auditory stimulation (RAS)	Application of auditory entrainment stimulus to intrinsically rhythmic movements, such as gait, to achieve more functional movement patterns
Patterned sensory enhancement (PSE)	Application of rhythmic, melodic, harmonic, and dynamic-acoustical elements of music to provide temporal, spatial, and force cues for non-rhythmic movements (e.g., functional exercises, activities of daily living)
Therapeutic instrumental music performance (TIMP)	Playing of musical instruments to exercise and stimulate functional movement patterns
Speech and language training	
Melodic intonation therapy (MIT)	Technique for expressive aphasia utilizing a patient's unimpaired ability to sing to facilitate speech through sung and chanted melodies resembling natural speech intonation patterns
Musical speech stimulation (MUSTIM)	Use of familiar music materials (songs, phrases, chants) to stimulate non-propositional speech
Rhythmic speech cueing (RSC)	Application of rhythmic cueing via metronome, drum, or moving the client's hand to prime and control initiation and rate of speech
Vocal intonation therapy (VIT)	Application of vocal exercises simulating normal speech patterns to train all aspects of voice control (i.e., inflection, pitch, breath control, timbre, dynamics)
Therapeutic singing (TS)	Use of singing activities to facilitate speech initiation, development, articulation, and respiration
Oral motor and respiratory exercises (OMREX)	Use of music materials, such as vocalization and wind instrument play, to support articulation and respiration as related to speech
Developmental speech and language training through music (DSLM)	Application of developmental appropriate music experiences (i.e., singing, instrument play, movement) targeting speech and language development
Symbolic communication training through music (SYCOM)	Use of vocal or instrumental improvisation to simulate social interaction and train elements of communication including behavior, language pragmatics, speech gestures, and nonverbal emotional communication
Cognitive training	
Musical sensory orientation training (MSOT)	Application of live or recorded music to stimulate arousal and emphasize orientation to time, place, and person
Musical neglect training (MNT)	Active structured performance of exercises on musical instruments with appropriate spatial instrument placement to focus attention to a neglected visual field.
Auditory perception training (APT)	Use of tactile, visual, and kinesthetic musical exercises to emphasize sound discrimination, including time, tempo, duration, pitch, timbre, rhythmic patterns, and speech sounds.
Musical attention control training (MACT)	Application of active or receptive musical experiences involving pre-composed songs or improvisation during which musical elements cue specific attentional responses (e.g., sustained, selective, divided, alternating attention functions)
Musical mnemonics training (MMT)	Facilitation of memory encoding and recall functions through the use of musical stimuli and exercises, often involving the organization of non-musical information into musical contexts (i.e., songs, rhymes, chants)
Associative mood and memory training (AMMT)	Use of musical mood induction techniques to facilitate memory recall or to access associative mood and memory functions through the induction of positive emotional states during the learning and recall process
Musical executive function training (MEFT)	Use of improvisation and music composition exercises to practice executive function skills within a social context

Effectiveness of Music Therapy

For decades, researchers have studied the uses and benefits of music therapy. Research has shown that music-based interventions can improve expression, communication, and social interaction, and reduce anxiety and agitation (Speranza et al., 2021). Music's anxiety-reducing effect can be helpful in the treatment of depression, anxiety, sleep disorders, and even cancer (Wong, 2021). Furthermore, music therapy can be used as a beneficial concomitant therapy for neurological disorders (García-Casares et al., 2018). As music exerts such a broad range of effects, it highly suggests that music influences the brain in a complex manner (Speranza et al., 2022).

Chapter 4: Music in the Human Brain

The Musical Brain

How does the brain process music? For decades, researchers have tried to establish the mechanisms of the musical brain. Studies on patients with acquired brain defects of music processing or 'amusias' and no other neurological dysfunctions have implied musical deficits are functionally and anatomically specific. Through the application of brain imaging techniques, positron emission tomography (PET) and functional MRI (fMRI), the organization of the musical brain has been assessed (Warren, 2008)

Any type of conscious perception of sensory information is processed through the primary and secondary regions in the cerebral cortex. However, music also affects multisensory and motor integration regions in frontal, parietal, and temporo-occipital brain regions (Altenmüller and Schlaug, 2015). This is due to music's complex multidimensionality, derived from its variety of musical components like pitch, time information, timbre, meaning, and emotion (Warren, 2008). Thereby, music involves listening, watching, feeling, moving and coordinating, remembering, and expecting musical elements (Altenmüller and Schlaug, 2015). The general roles of different brain areas involved in music listening and playing have been visualized in figure 2 (Speranza et al., 2022). Some of these brain regions will be discussed further throughout the following paragraphs on the auditory encoding and cognitive and emotional processing of music.

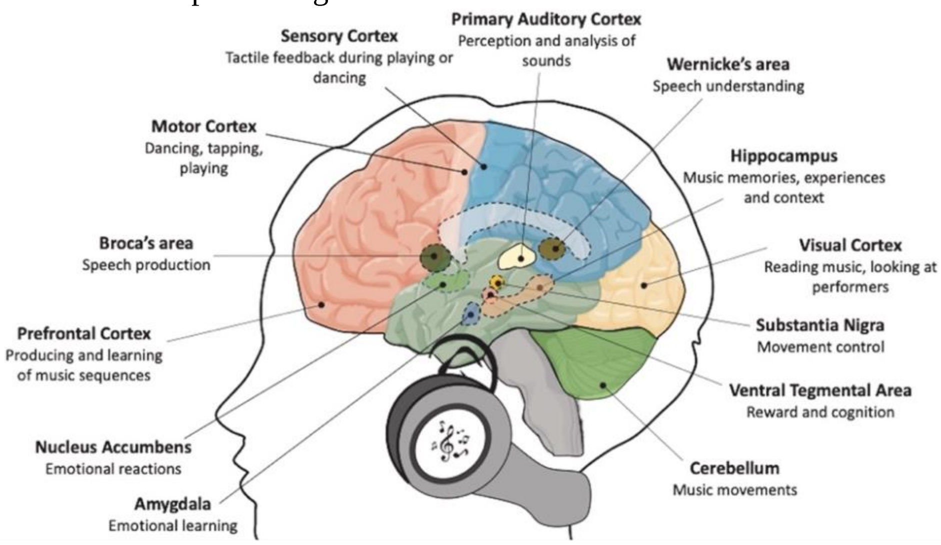

Figure 2: Schematic representation of different brain areas implicated in listening and playing music. (Speranza et al., 2022)

Auditory Encoding of Music

Like any sound, music is first processed in the ascending auditory pathways to the primary auditory cortex, located in the medial part of the Heschl's gyrus (HG) in the superior temporal lobe. The acoustic dimensions of music are encoded as particular patterns by the primary and higher auditory cortices and areas surrounding the HG. Pitch perception occurs in the lateral HG (Patternson et al., 2002). The planum temporale (PT), which corresponds to Wernicke's area in the left hemisphere, plays a role in the analysis of complex sound sources, including their spatial location, identifying features (timbre and acoustic patterns), and pitch patterns. The superior temporal gyrus (STG) analyses streams of auditory information, including spoken sentences and musical melodies (Warren, 2008).

Cognitive and Emotional Processing

Beyond the auditory cortex, distributed brain areas link perception with meaning and memory and regulate behavioural responses to music. The limbic circuitry (LC) is responsible for the primitive emotional responses to music, which are fundamental to the quality of musical experiences (Warren, 2008). Therefore, the emotional network is crucial for an individual's motivation to listen to or engage in any musical activity (Altenmüller and Schlaug, 2015). Nonverbal sounds and familiar music are identified in the anterior temporal lobe (TP) and insula (INS) (Warren, 2008). Interestingly, a study by Groussard and colleagues compared fMRIs during a musical familiarity task between musicians (22.85±3.05 years; years of uninterrupted music practice: 15.3±3.67) and nonmusicians (24.55±3.80 years; no musical performance or received musical lessons (except for basic music education at secondary school 1h/week)). The study revealed that familiar music induces supplementary activations in the hippocampus, medial frontal gyrus, and superior temporal areas on both sides of musicians (Figures 3A and 3B). This suggests musical expertise induces a constant interaction between episodic and semantic memory (Groussard et al., 2010).

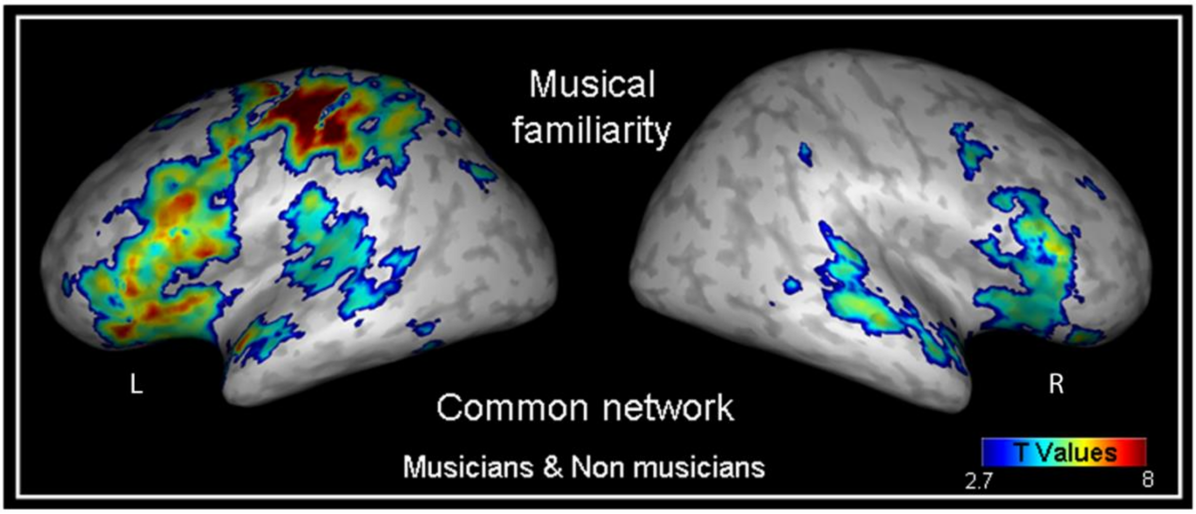

Figure 3A: Common network musicians & nonmusicians.
This network was composed of a left extensive cluster including motor, and inferior frontal areas, the bilateral superior temporal gyri, the right cerebellum and the inferior frontal gyrus. Abbreviations: L =left hemisphere, R = right hemisphere. (Groussard et al., 2010)

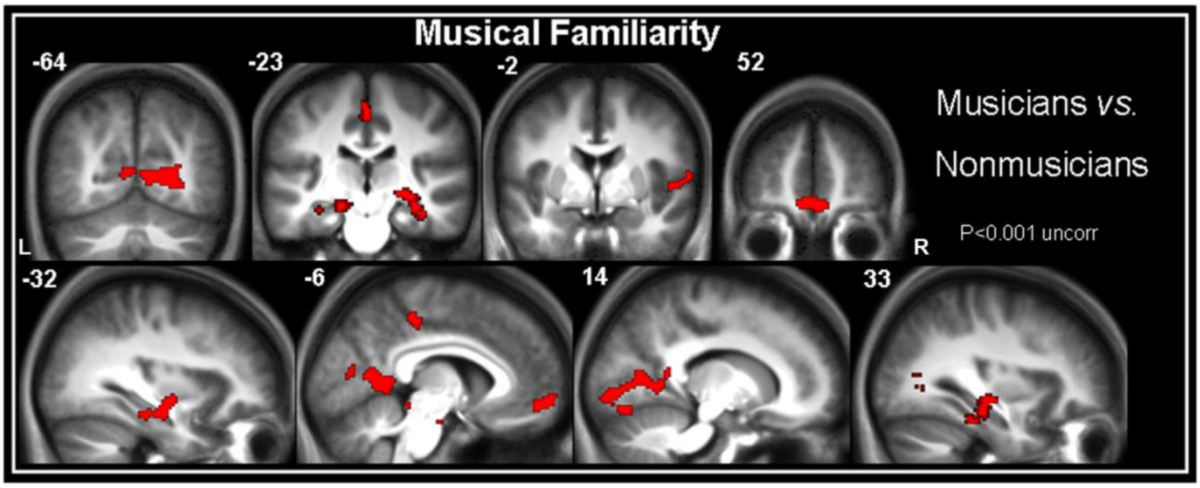

Figure 3B: Higher Activations in musicians vs nonmusicians during musical familiarity task
Areas of significantly stronger in musicians compared with nonmusicians during the musical familiarity task. The bilateral anterior portion of the hippocampus, the bilateral calcarine, and oribitomedial frontal gyri, the middle cingulate cortex and the bilateral superior temporal areas, including Heschl's gyri, were associated with increased familiarity for the musicians. Contrasts are displayed at p<0.001 (uncorrected) and superimposed onto the average of normalized brains using MRIcron software. Abbreviations: L = left hemisphere, R = right hemisphere. (Groussard et al., 2010)

Auditory information is linked to other sensory input (especially vision) by the lateral temporal or temporal pole (TP), and parietal lobes (PL). Behavioural responses to sound and working memory for music and sounds are mediated in the parietal and frontal lobes (FL) (Warren, 2008). Moreover, the cerebellum is involved in rhythm processing, and tapping in synchrony with an external pacemaker (Altenmüller and Schlaug, 2015). Thereby, it regulates musical movements (Speranza et al., 2022). Figure 4 shows a schematic representation of the organization of the musical brain (Altenmüller and Schlaug, 2015).

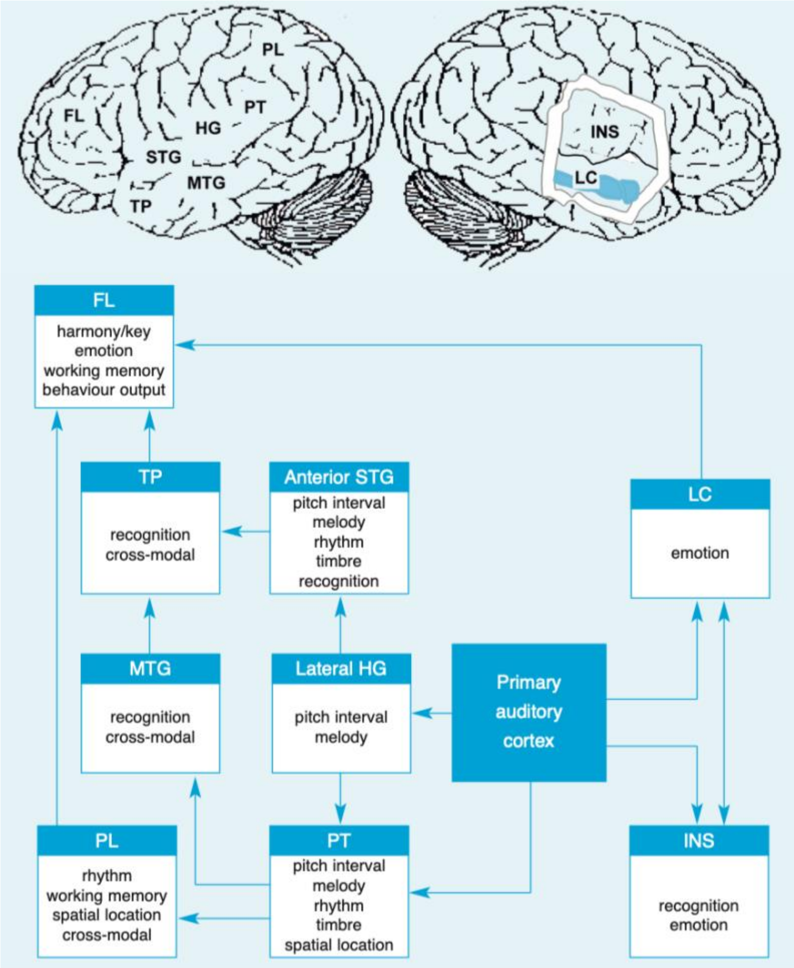

Figure 4: A scheme for the organization of the musical brain.
Arrows indicate predominant flow of information between cortical areas. The scheme indicates the broadly hierarchical nature of music processing with more complex and abstract properties represented by areas further beyond the primary auditory cortex. FL= frontal lobe; HG= Heschl's gyrus; IN= insula (shown with overlying cortex removed); LC= limbic circuit. (showed with overlying cortex removed); LC= limbic circuit (showed with overlying cortex removed); MTG= middle tempora; gyrus; PL= parietal lobe; PT= planum temporale; STG= super temporal gyrus; TP= temporal pole. (Altenmüller and Schlaug, 2015)

Music as a Driver of Brain plasticity

Neuroplasticity is the brain's ability to change and adapt as a consequence of environmental experiences. Thereby, brain plasticity enhances learning and cognitive capabilities. It has been demonstrated that musical activity is a powerful stimulus for brain plasticity (Altenmüller and Schlaug, 2015). The previously mentioned study of Groussard and colleagues that compared the brains of young musicians to that of non-musicians, revealed that musicians have increased amounts of gray matter in the hippocampus, as a result of brain plasticity attributed to continuous learning and practice of musical instruments (Groussard et al., 2010). Professional musicians also show a reorganization of the motor and auditory cortex. Furthermore, music alters neurotransmitter and hormone serum levels. Studies showed the most prominent correlation between music and neuropsychological activity and performance enhancement involves Mozart's music, implying it has a strong impact on the brain (Demarin et al., 2016). EEG recordings by Verrusio and colleagues show that Mozart Sonata K448 increases the alpha band (Figure 5A) and median frequency index (MF)(Figure 5B) of background alpha rhythm activity (brain wave activity linked to memory, cognition and open mind to problem-solving), while Beethoven's "Fur Elise" does not (Verrusio et al., 2015).

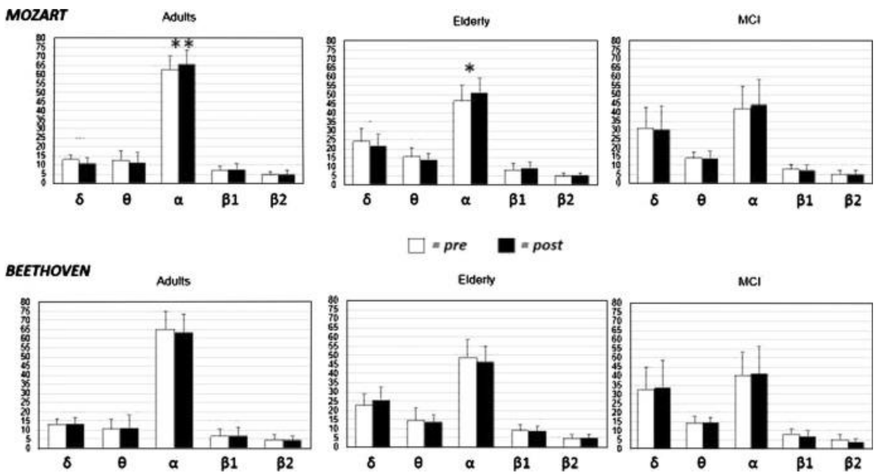

Figure 5A: Relative (%) power of EEG bands (mean ± SD) at basal rest condition (pre) and after Mozart K448 and "Fur Elise" Beethoven's sonates listening (post). (*p<0.05; **p<0.001). White bars = pre; Black bars = post. (Verrusio et al., 2015)

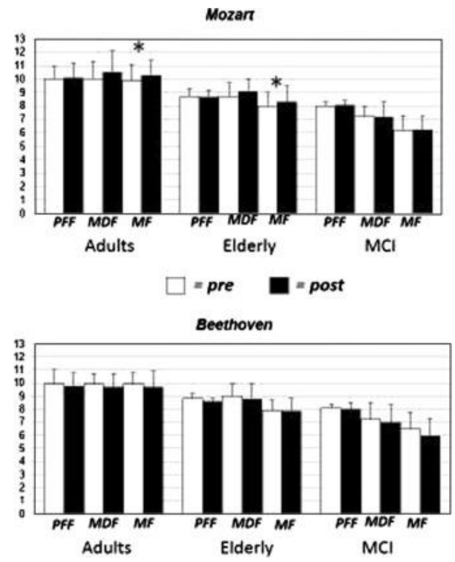

Figure 5B: Frequency indexes of background EEG activity at basal rest condition (pre) and after Mozart K448 and "Fur Elise" Beethoven's sonatas listening (post). PFF = peak power frequency, MDF = main dominant frequency, MF= median frequency; values expressed in Hz (mean± SD); (*p<0.05; **p<0.001). White bars = pre; Black bars = post. (Verrusio et al., 2015)

Interestingly, music-induced neuroplasticity may lead to improvements in cognition, motor skills and recovery after brain injury, as new synapses can remodel damaged neural connections (Demarin et al., 2016; Speranza et al.,2022). Therefore, music-supported therapies can be used as a non-invasive therapeutic tool to manipulate brain rewiring in neurological disorders (Altenmüller and Schlaug, 2015; Speranza et al., 2022).

Chapter 5: Music Therapy on the Diseased Brain

…there's something about the temporal structure of the music, the emotional content of the music, that arouses areas of the brain that are still functioning and allows a lost ability to become present as they participate in the music. – Dr. Concetta Tomaino, Executive Director/Co-Founder, Institute for Music and Neurologic Function (Ashoori et al., 2015).

Clinical tests have demonstrated that music benefits cognitive, behavioural, motor, and psychosocial levels in injured, degenerating, and disordered brains. Therefore, music-based interventions can be used to slow down the physiological cognitive decline during aging, or as a therapeutic adjuvant in neurodegenerative and neurodevelopmental disorders, or after injuries (stroke) (Figure 6) (Speranza et al., 2022). In this chapter, the effects of music therapy on the degenerating and diseased brain will be discussed.

Figure 6: Schematic representation of beneficial effects of music therapy on neurological disorders (Speranza et al., 2022)

Aging

Aging declines attention, memory, processing speed, executive functions, cognitive flexibility, logical thinking, and auditory selective attention due to age-dependent microstructural and physiological changes in the brain. Listening to music is an intellectually, emotionally, and socially stimulating activity that can delay aging and cognitive decline (Hsu et al., 2021; Speranza et al., 2022). Moreover, music has been utilized as a strategy for motor relearning and shaping (Hsu et al., 2021). The following paragraphs show the effects of music in neurological disorders in more detail.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive age-related neurogenerative disorder and the leading cause of dementia (Ortí Casañ et al., 2019). The disease is characterized by progressive memory loss and functional impairment, which impacts the daily life of an individual (Yu et al., 2021). Despite Alzheimer patients having severe impairment of episodic (and moderate impairment of semantic) memory, the memory of musical information may remain nearly preserved, even in the advanced stages of the disease. (Flo et al., 2022). A study by Jacobsen has found that the musical memory retrieval is possible due to the relatively long perseverance of the pre-supplementary motor area (Jacobsen et al., 2015). Research has shown that brief music exposure can induce episodic memory retrieval unrelated to the music itself, suggesting that music can benefit the domains of episodic and semantic memory retrieval in AD patients. Besides, music programs have been proven effective for reducing stress, and the symptoms of depression and improving the emotional well-being of people with Alzheimer's disease (Flo et al., 2022; Gulliver et al., 2021). A study by Guétin showed that 16 weeks of receptive music therapy reduced anxiety and depression scores of patients with mild to moderate AD (Guétin et al., 2009). Active forms of music therapy have a strong effect on brain plasticity and global cognition in AD patients. More beneficial effects are observed when familiar and personalized music was used compared to unfamiliar music (Flo et al., 2022).

Stroke

Ischemic stroke is the second leading cause of both disability and death worldwide (Saini et al., 2021). Music-based interventions can improve language, motor, and cognitive functions in stroke patients, as music promotes the structural reorganization of frontal (superior frontal gyrus) and limbic areas (anterior cingulate cortex and ventral striatum) with an increment of volume and connectivity (Speranza et al., 2022). Lyrics, rhythm, and melody are considered to play an important role in changing neuroplasticity. One of the most common symptoms after stroke is aphasia, which is characterized by impaired language expression and comprehension (Liu et al., 2021). There are two types of aphasia: fluent/Wernicke aphasia, which is caused by a lesion involving Wernicke's area, and non-fluent/Broca aphasia, which is caused by a stroke involving Broca's area. Wernicke aphasia is characterized by impaired language comprehension and intact speech production, while Broca's aphasia encompasses impairments in speech production and articulation and intact speech comprehension (Acharya & Wroten, 2022). Musical therapies can improve functional communication, repetition, and naming in patients with post-stroke aphasia (Liu et al., 2021). An effective form of output-focused language therapy for Broca aphasia is *Melody Intonation Therapy (MIT). MIT* treated non-fluent aphasia patients show a reorganization of right-hemisphere vocal-motor network brain function and improvements in speech output. Interestingly, the patients are better at singing lyrics than speaking the same words (Schlaug et al., 2010; Tabei et al., 2016; Wan et al., 2014). Other studies show that *rhythmic auditory stimulation (RAS)*, a music invention that uses a strong beat, induces temporal stability and enhances motor control in walking. Therefore, rhythmic stimulation improves gait after stroke. In addition, music therapies may be beneficial for improving the speed of repetitive arm movements in people with a stroke (Magee et al., 2017).

Autism Spectrum Disorders

Autism spectrum disorders (ASD) refers to complex neurodevelopment conditions characterized by some degree of impairments in behaviour, communication, and social functioning (Applewhite et al., 2022). Despite children with ASD show problems with identifying emotional faces, the processing of musical cues seems intact. Music-based interventions are beneficial in improving the social, emotional, and behavioural problems of patients with ASD. Studies show that congruent emotional music can boost facial emotion recognition in children with ASD (Speranza et al, 2022; Wagener et al., 2020). Furthermore, *RAS* may benefit motor areas and improve movement and sensory abnormalities in patients with ASD (Hardy et al., 2013). A study by Sharda and colleagues shows that children (6-12 years) with ASD who participate in music-based interventions, have increased functional connectivity between the bilateral primary auditory cortex and sub-cortical and motor regions, contributing to sustained attention, memory, and enhanced verbal communication (Sharda et al, 2018)(Figure 7).

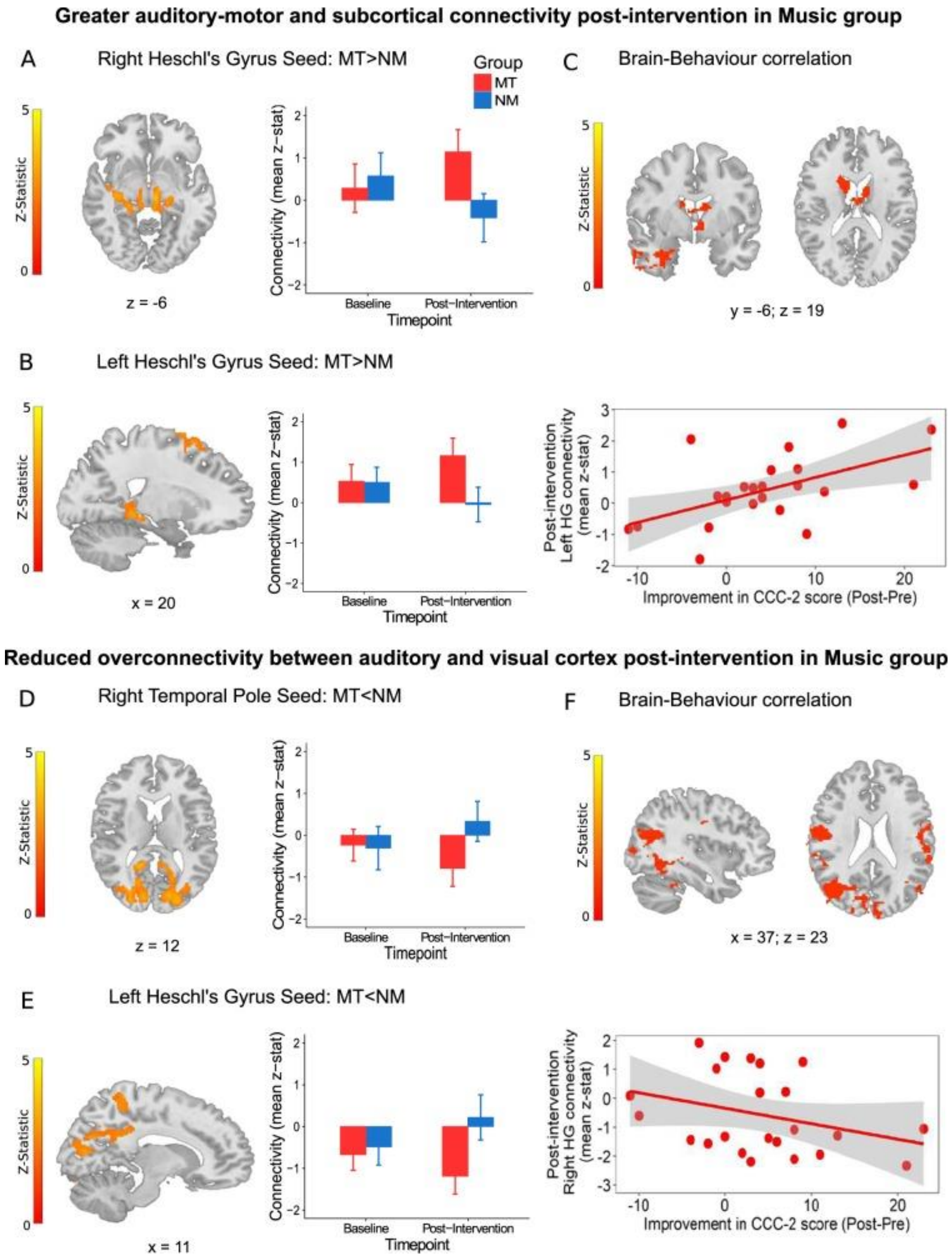

Figure 7: Brain functional connectivity outcomes and correlation with behavioural improvement
The top panel shows regions of increased resting-state functional connectivity (RSFC) post-intervention in the Music (MT) vs. Non-music (NM) groups between **a** Right Heschl's gyrus seed and subcortical regions (hippocampus and thalamus) (z=3.94, P<0.0001) and **b** left Heschl's gyrus seed and fronto-motor regions (z=3.16, P<0.0001). **c** Connectivity between auditory and subcortical thalamic and striatal regions post-intervention is directly related to improvements in communication using the change in CCC-2 composite score in MT (z=3.57, P<0.0001). The bottom panel shows regions of decreased RSFC post-intervention in MT vs. NM groups between **d** right temporal pole seed and occipital regions (z=4.01, P<0.0001) and **e** left Heschl's gyrus seed and bilateral calcarine and cuneus regions (z=3.39, P<0.0001). **f** Connectivity between auditory and visual sensory cortices post-intervention is inversely related to improvements in communication measured using the change in CCC-2 composite score in MT (z=3.64, P<0.0001). MT = red, NM = blue. Error bars represent standard error (SE). all. Brain images are presented in radiological convention and coordinates are in MNI space.

Parkinson's Disease

Since this report aims to reveal the mechanisms of music therapy on patients with Parkinson's disease, this section will discuss the background of PD and the general effects of music therapy on PD patients.

Background

Parkinson's disease (PD) is the second most frequent chronic neurodegenerative disease after Alzheimer's disease. The neurological disorder is characterized by bradykinesia, resting tremor, rigidity, and postural instability (Riederer et al., 2019). The intellectual abilities of patients with PD remain relatively preserved (Machado Sotomayor et al., 2021). In addition to the motor symptoms, nonmotor symptoms involve hyposmia, sleep disturbances, depression, constipation, and other dysautonomic symptoms (Antony et al., 2013). The motor symptoms are the result of the loss of dopaminergic (DA) neurons and iron overload within the substantia nigra (SN), which is a brain structure that is part of the basal ganglia (Bae et al., 2021). The dopaminergic neuronal loss is caused by an accumulation of intraneural protein inclusions, known as Lewy bodies, which are composed mainly of misfolded α-synuclein aggregates (Vascellari and Manzin, 2021). Furthermore, nonmotor symptoms can develop through other neurotransmitter systems, among which glutamatergic, cholinergic, tryptaminergic, noradrenergic, adrenergic, serotoninergic, and peptidegic systems (Antony et al., 2013; Bae et al., 2021). Studies show that pathological changes may be the result of genetic as well as non-genetic factors like aging, environmental components, and oxidative stress (Vascellari and Manzin, 2021). Current drugs used to control the worsening symptoms of PD include levodopa, dopamine agonists, monoamine oxidase inhibitors, peripheral dopa-decarboxylase inhibitors, and catechol-O-methyltransferase inhibitors. However, PD treatment also increasingly uses other alternative and nonpharmacologic therapies such as music therapy (García-Casares et al., 2018).

General Effects of Music Therapy on Patients with PD

PD patients have impairments in the timing and size of repetitive, internally generated automatic sequences of movement, resulting in altered and frozen gait patterns, accommodated with a loss of rhythmicity, shorter steps, slower walking, and trunk instability (De Bartolo et al., 2020). Similar to other movement disorders, music therapy and rhythm-based interventions offer various symptomatic benefits for patients with PD. Therapies that involve listening to music, dancing, and *RAS* improve gait and motor performance in PD (Machado Sotomayor et al., 2021). Studies have shown that five days of intensive modern dance training leads to increased functional connectivity between the basal ganglia and premotor cortex, and 3 weeks of Tango classes improves muscle synergy during balance and walking tests. It has been documented that physical activity promotes DA release and neuroprotection (Speranza et al., 2022). Furthermore, external sound rhythms can evoke internal rhythm information related to gait in the brain, resulting in improvements in walking. A study by Gondo and colleagues investigated gait disturbance in PD, using gait training with and without *RAS*. Subjects were to perform walking tasks on a music intervention that gradually increased in tempo from 90 to 120 beats per minute (BPM). Changes in the walking trajectory of the centre of the body were evaluated by a portable gait rhythmogram (PGR). Post-music therapy values showed improvements in acceleration, gait speed, cadence, and step length were recognized, even in absence of music (Figure 8). Moreover, regarding the trajectory of the centre of the body, the mediolateral (ML) amplitude, which is typically large in patients with PD, decreased significantly (Gondo et al., 2021).

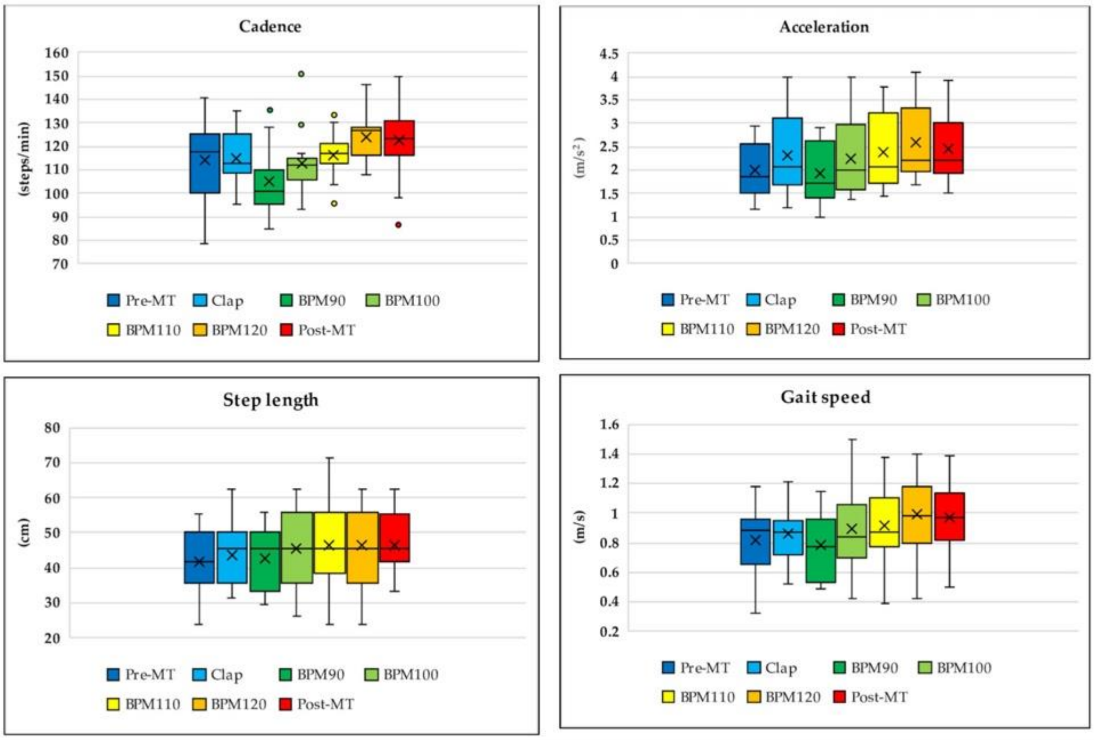

Figure 8: Transition throughout the entire walking task for acceleration, gait speed, cadence, and step length.
During transitions in the walking tasks with music (from Tasks 3 to 6) values of acceleration, gait speed, cadence and step length increased gradually. The best improvement was observed in Task 6 (120 BPM) and remained in Task 7 even without music. Walking speed in Task 3 (90 BPM) was slightly slower than that in Task 2 (hand clapping while walking at subjects' own pace). (Gondo et al., 2021)

Other studies have demonstrated that musical programs that involve singing with deep breathing training and song learning benefit the treatment of nonmotor symptoms of PD patients (Machado Sotomayor et al., 2021; Speranza et al., 2022). The mechanisms of speech and singing share considerable similarities, which clarifies why voice-related music therapies ameliorate memory, language, speech information processing, executive function, and respiratory muscle strength (Han et al., 2018). Moreover, musical group sessions, like choir singing, can improve the mental health of PD patients, as it counteracts social isolation and low morale. Altogether, musical therapies improve the well-being of those with PD, making it a suitable non-pharmaceutical treatment (Machado Sotomayor et al., 2021; Speranza et al., 2022).

Despite musical processing and the general effect of musical therapy in PD patients have been described, the neurochemical mechanisms of how music therapy may improve the motor symptoms in Parkinson's disease remains unexplored. In order to answer this question, music-induced neurotransmitter release will be explored.

Chapter 6: Music as Neurotransmitter

Music is able to change the neurochemistry in the brain, by inducing the secretion of neurotransmitters and hormones. Studies have revealed that music engages neurochemical systems for reward, motivation and pleasure, stress and arousal, immunity, and social affiliation, as it respectively stimulates the release of dopamine (DA), glucocorticoids and catecholamines, serotonin (5-HT), and oxytocin (Chanda and Levitin, 2013).

Dopamine – Reward, Motivation, and Pleasure

Dopamine is a neurotransmitter that affects movement, behaviour, motivation, punishment, learning, reward, cognition, attention, dreaming, working memory, mood, and sleep. It influences the brain via nigrostriatal, mesocortical, tuberoinfundibular, and mesolimbic pathways. The production of DA occurs in the substantia nigra (SN), ventral tegmental area (VTA), and hypothalamus. The dopaminergic neurons originating from the SN project to the striatum, and are involved in the control of body movements and muscle tone. DA also plays a role in the reward pathway and induces subjective feelings of pleasure, when it is released from the VTA, into the prefrontal cortex and nucleus accumbens (NAcc) (Chanda and Levitin, 2013; Latif et al., 2021). Reward-related signals, like music, food, and sex, can be powerful enhancers of learning and memory (Ferreri et al., 2021).

Music activates dopaminergic neurons. Ligand-based positron emission tomography (PET) studies have documented that emotional arousal peaks during music increase DA release in the ventral striatum or NAcc and caudate putamen, suggesting that musical pleasure is closely related to the intensity of emotional arousal. In addition, an increase in connectivity between the Nacc and the auditory, amygdala, and ventromedial prefrontal cortex can be observed (Chanda and Levitin, 2013; Salimpoor et al., 2011). Another study by Moraes and colleagues has shown that melodic music (Mozart's sonata for two pianos (K.488)) increases DA levels and 5-HT release in the caudate putamen (CPu) and increased DA turnover in the NAcc in rats (Figure 9). This implies that music directly regulates monoamine activity in forebrain areas linked to reward and motor control (Moraes et al., 2018).

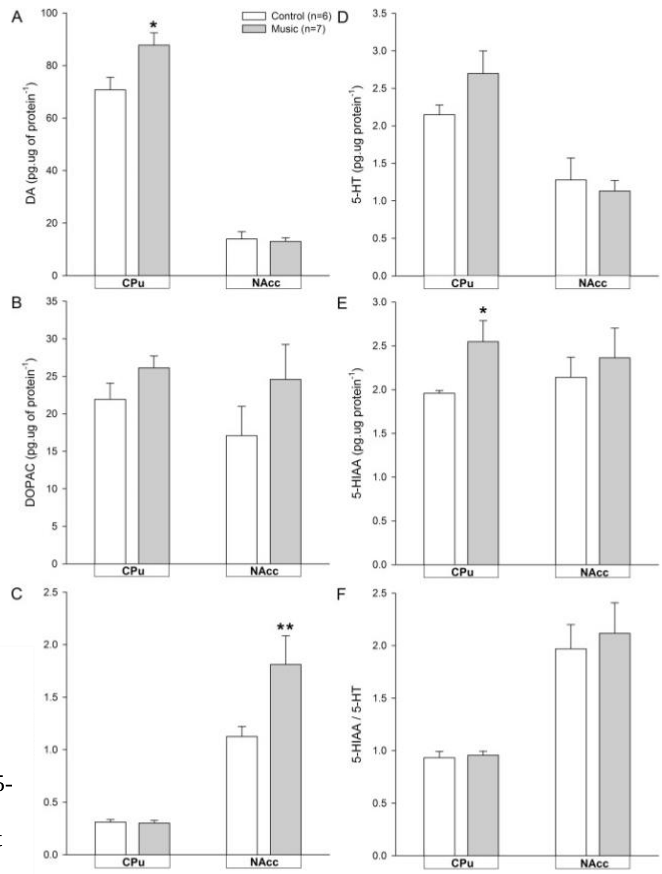

Figure 9: Concentrations of dopaminergic and serotonic variables in the coudate-putamen (CPu), and nucleus accumbens (NAcc) of rats exposed to classical music.
A) Dopamine (DA), B) 3,4-dihyrdoxyphenylacetic acid (DOPAC), C) the DOPAC/DA ratio, D) Serotonin (5-HT), E) 5-hydroxyindolecacetic acid (5-HIAA) and F) the 5-HIAA/5-HT ratio. Values are shown as the means ± S.E.M. *Different from the control group (*P<0.05, **P<0.01). (Moraes et al., 2018)

Serotonin – Mood

As mentioned previously, music listening increases 5-HT release (Moraes et al., 2018)(Figure 9). Serotonin is a monoamine neurotransmitter found in the cell lining of the gastrointestinal tract. Similar to dopamine, serotonin plays a role in positive mood and emotion. However, while 5-HT is associated with feelings of satisfaction and expected outcome, DA is related to pleasure based on novelty (Zald and Zattorre, 2011). Studies have investigated the neurochemical pathways in the perception of pleasant and unpleasant music. Using the platelet model for central neurotransmission of 5-HT, Evers and Suhr demonstrated that pleasant music increases the 5-HT content of platelets compared to unpleasant music (Figure 10). The findings suggest that unpleasant music perception induces emotional stress with the activation of the prefrontal cortex and subsequent 5-HT release, and decreased intracellular 5-HT content of the serotonergic neurons (reflected by the 5-HT content of the platelets) (Evers and Suhr, 2000).

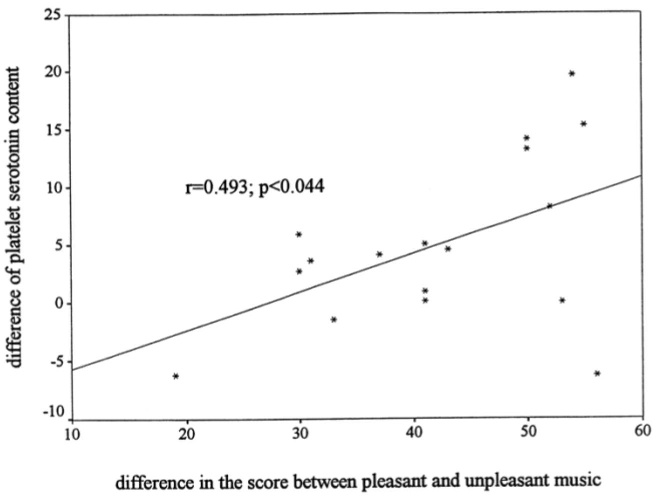

Figure 10: Scatter plot of the score difference between pleasant and unpleasant music perception (x-axis) and of the different of the corresponding 5-HT content of platelets (y-axis). Statistical analysis by Pearson's product-moment correlation coefficient. (Evers and Suhr, 2000)

Furthermore, serotonin regulates body functions such as sleep, digestion, nausea, wound healing, bone health, blood clotting, and sexual behaviour. Low levels of serotonin have been associated with mood disorders like depression, anxiety and mania (Cleveland Clinic, 2022).

Glucocorticoids & Catecholamines – Stress and Arousal

Stress refers to the neurochemical response to the loss of homeostatic equilibrium, motivating the individual to engage in activities that will restore it. The response involves multiple feedback loops at the levels of the central and peripheral nervous systems, triggering short-term adaptive behaviours, including arousal, and temporarily inhibiting functions that are nonessential during a crisis, such as eating and digestion. Glucocorticoids (e.g. cortisol), secreted by the HPA stress axis, and catecholamines (norepinephrine and epinephrine), regulated by the brainstem locus coeruleus and central and peripheral autonomic nervous system, are key neurochemicals that mediate the stress response. Other neurotransmitters involved are 5-HT, CRH, ACTH, and POMC. Studies have shown that listening to relaxing music (slow tempo, low pitch, and no lyrics) reduces plasma cortisol and noradrenaline and thus stress and arousal in healthy subjects and in patients undergoing invasive medical procedures (e.g. surgery, colonoscopy, and dental procedures). On the contrary, stimulating music increases cortisol and arousal (Chanda and Levitin, 2013). Excessive cortisol levels can inhibit the immune system, resulting in decreased immunoglobulin A (IgA) levels, whereas low levels of cortisol are related with increased levels. A study by Nilsson and colleagues has demonstrated that postoperative music decreases cortisol levels compared to control (206 and 72 mmol L^{-1} decreases, respectively) after 2h in the post-anaesthesia care unit (PACU). The postoperative music group experienced less anxiety and pain and required significantly less morphine than the control group. Moreover, the intraoperative music reported less pain after 1h in the PACU (Figure 11). The data suggests that postoperative music may decrease pain, morphine consumption, and stress response to surgery, and intraoperative music may reduce postoperative pain (Nilsson et al., 2005).

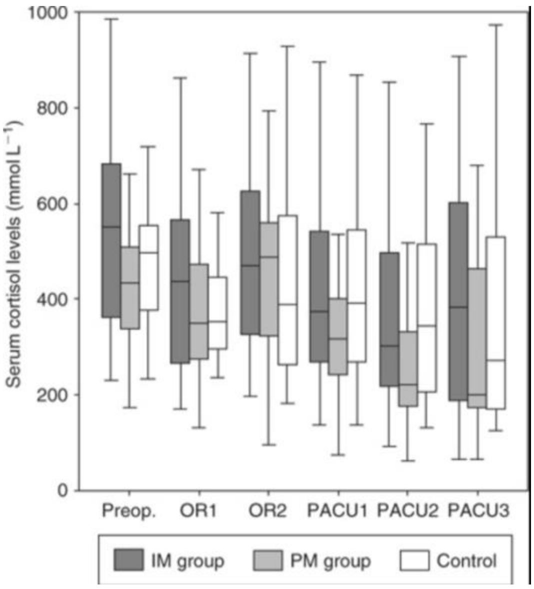

Figure 11: Box and whisker plots of serum cortisol levels
Preoperatively (Preop.), at the end of surgery (OR1), after wound dressing (OR2) and 1, 2, 3h after arrival at the PACU in patients exposed to music intraoperatively (IM group), postoperatively (PM group) or control (sham CD player).
P<0.001 in variation over time within groups compared with baseline level i.e. preoperative value. (Nilsson et al., 2015)

In addition to this, studies have shown that self-selected music decreases cortisol levels significantly compared to experimenter-selected music in post-operative conditions (Chanda and Levitin, 2013).

Oxytocin – Social Affiliation

Oxytocin is a hormone produced by the hypothalamus and secreted into the bloodstream by the posterior pituitary gland to control key aspects of the reproductive system, including childbirth and lactation, and aspects of human behaviour. Human behaviours include sexual arousal, recognition, trust, romantic attachment and mother-infant bonding (You andyour Hormones, 2020). Research has shown that group music and singing increases the production of oxytocin in the brain, promoting prosocial systems (Speranza et al., 2022). Interestingly a study by Campbell and colleagues has shown that two species of ‘singing mice’, ecologically specialized Central American rodents with a highly developed form of vocal communication, exhibit high oxytocin receptor binding within brain areas associated with social memory (hippocampus and medial amygdala)(Figure 12)(Campbell et al., 2009).

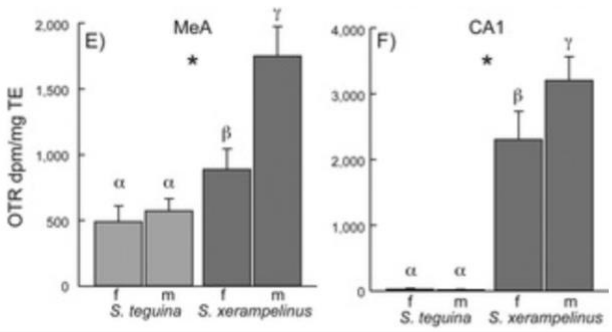

Figure 12: OTR binding in singing mice in structures implicated in social memory
Binding in the medial amygdala (MeA) and CA1 was significantly higher in *S. xerampelinus* (dark grey). Within *S. xerampelinus* OTR binding in MeA and CA1 was significantly higher in males (m) compared to females (f). (Campbell et al., 2009)

Chapter 7: Music in Parkinson's Disease

Previous chapters have elucidated the pathological hallmarks of PD, the influence of music on PD patients, and the neurochemical basis of music. Throughout this paper, music, and rhythm has shown to improve the motor and nonmotor symptoms in patients with PD (Devlin et al., 2019). Various mechanisms have been proposed to explain these therapeutic effects. This chapter will explore the neurochemical and physiological pathways that are responsible for the improvements in controlling the symptoms of patients with PD.

Proposed Mechanisms for Music and Rhythm-Based Interventions on PD

<u>Recruitment of alternative neural pathways</u>
The first potential mechanism involves the recruitment of alternative neural pathways that are relatively spared in PD. PD is characterized by impairments in basal ganglia function causing deficiencies in internal timing, which is a neural mechanism that precisely times and coordinates body movements. Loss of rhythmicity for timed movements results in gait abnormalities (Devlin et al., 2019; Waerden et al., 2008). Potentially, the recruitment of relatively spared cerebellar networks, which rely on external (auditory/visual) cues, may help compensate for the motor symptoms in PD. Studies have demonstrated that music, dance, and *RAS* increase functional neural connectivity between the auditory cortex and executive control network, between the executive control network and cerebellum, and between the basal ganglia and premotor cortex. The latter in particular may lead to symptomatic improvements in PD, as PD patients have a loss of dopaminergic neurons in the basal ganglia (Devlin et al., 2019).

<u>Motor system- Rhythmic entrainment, Anticipation, and Motivation</u>
Another suggested mechanism is rhythmic entrainment. This process refers to internal body patterning to external rhythms, which means that the auditory system synchronizes with the motor system resulting in facilitated movement. Music therapy has shown to PD patients induce synergistic activation of auditory and motor cortices. This was shown in a study by Buard and colleagues, that administered 15 sessions of somatosensory-related neurologic music therapy (NMT) techniques 3 times per week for 5 weeks. Fine motor changes were assessed and quantified before and after NMT within 2 days from the first and last NMT session. The results show increased simultaneous beta power increase in auditory and motor areas, suggesting increased connectivity between the auditory and motor cortices (Figure 13)(Buard et al., 2019).

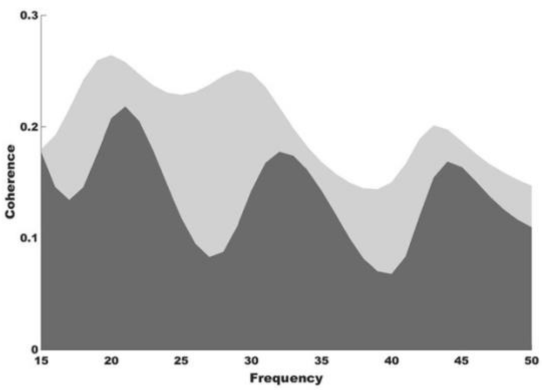

Figure 13: Coherence results.
Coherence spectra show increased functional connectivity between the auditory and motor cortices after (light grey shade) compared to before NMT (dark grey shade). (Buard et al., 2019)

Furthermore, the provision of rhythmic timed cues, like music, allows the brain to anticipate movement, leading to improvement in movement synchronization. Thereby, music activates dopaminergic pathways, which increases motivation (which is affected in PD due to dopaminergic deficits), resulting in accelerated motor learning (Devlin et al., 2019).

Music as a survival signal

Lastly, an interesting, proposed mechanism for the therapeutic effects of music in PD includes the perception of music as a survival signal. As mentioned before, music induces a broad range of physiological effects, including autonomic responses of respiration, heart rate, and blood pressure regulated by noradrenergic neurons in the brainstem. Besides, music-induced brainstem activation mediates cholinergic and dopaminergic neurotransmission and sensory and motor function through epinephrine, norepinephrine, and serotonin. Hence, simple musical properties like tempo may influence central neurotransmission affecting cardiovascular and respiratory control, motor function and even cognitive functions. In this perspective, music is translated as a signal related to survival and nature, causing the brainstem to initiate corresponding physiological responses. For example, “stimulating” music may be interpreted as an alarm call, positive affect, or reward anticipation, which leads to sympathetic arousal. In contrast, “relaxing” music decreases sympathetic arousal as it mimics soothing sounds, like maternal vocalizations, purring, and cooing (soft, low-pitched sounds) (Chanda and Levitin, 2013).

Different Types of Music in PD

The last proposed mechanism emphasizes that different types of music (relaxing vs stimulating) may exert different effects on patients with PD. A study by De Bartolo and colleagues investigated the effect of different types of music on modifications of spatiotemporal parameters and trunk oscillations during walking. The experiment included three groups: healthy young adults (32.3±5.93 years; 8M, 12F), healthy elderly (72.1±5.6 years; 8 M, 12 F), and PD patients (72.5±9.2years; 14M, 6F). Subjects were provided with a wireless headset and inertial measurement unit at pelvis level to assess their walking patterns and asked to walk while listening to one of six different music tracks (related to four different musical genres)(Table 3). The study found that music influences walking manner depending on its genre/BPM. The effects resulted similarly in all the subjects, implying that music can counteract some specific deficits of PD. Classical, relaxing tracks (andante = slow), reduced walking speed and anteroposterior trunk tilt range of motion, and increased stride duration, suggesting it could be helpful for improving festinating gait in PD patients (Figure 14) (De Bartolo et al., 2020).

Table 3: List of musical tracks used for the study
Beats per minute (BPM) were estimated using a metronome

Artist and song	Musical tracks	BPM
Chopin—Prelude op 28 n 4	Classical *Andante*	92
Beethoven—Ninth Symphony	Classical *Allegro*	126
The Beatles—Yellow submarine	Pop	118
Survivor—Eye of the tiger	Motivational Hard Rock	120
Queen—We will rock you	Rock Arena	148
Metallica—Master of puppets	Heavy Metal	120

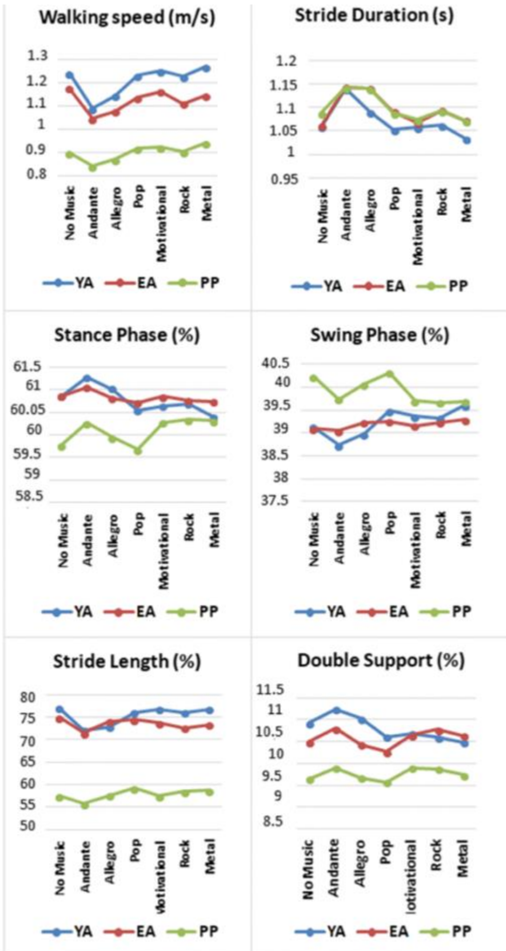

Figure 14: Graphic Representation of Spatiotemporal Gait Parameters During Walking Conditions.
Data are summarized in mean value and divided for groups (YA, young adults; EA: elderly adults; PP, Parkinson patients). (De Bartolo et al., 2020)

The Man with the Headphones…

The findings from this study and the proposed mechanisms for the therapeutic effect of music on PD bring me back to the man with the headphones from the beginning of this paper.

… was listening to Classical *Andante*?

The man with the headphones had mentioned that "classical music" in particular helps him control his motor symptoms. When considering the data from De Bartolo, one can now hypothesize that the man was probably listening to a Classical *Andante* musical track, which was found most effective in improving gait in PD patients. According to the proposed mechanisms, the relaxing music likely enhanced the brainstem to decrease sympathetic arousal, resulting in decreases in heart rate, respiration and blood pressure, and the slow external rhythms may have stimulated his internal rhythmicity and movements.

… enjoyed listening to Classical music?

However, it is important to note that music induces changes in neurotransmitters, peptides, and hormonal reactions, related to mental state and personal involvement. A study by Gerra and colleagues suggest that personality traits and temperament affect the wide inter-individual variability in response to music (Gerra et al., 1998). This suggests that people may have an individual perception of what is pleasant and unpleasant music. For example, while heavy metal is commonly interpreted as an "extreme" form of music that enhances anger and restlessness, some people who like it may experience it as calming and soothing (The Guardian, 2015). Therefore, the man with the headphones probably enjoyed listening to classical music, leading to the enhancement of monoaminergic pathways. This is in accordance with studies that show that patient-selected music is more effective than experimenter-selected music. Hence, the locus of control influences the physiological impact of music as well. However, one should keep in mind that studies on locus control elude a trivial or illusory sense of choice, which enhances motivation and thus may contribute to the difference in outcome. (Chanda and Levitin, 2013). Yet, the effect of personal music implies that the man with the headphones, as well as other patients and healthy people, know themselves well and thus know what type of music they like and need to hear to feel better.

… needed the direct stimuli of music?

While the proposed mechanisms regarding the motor system (rhythmic entrainment, preparation, and motivation), and music as a survival signal, explain the processes underlying the direct influence of music on PD patients, the suggestion that music may help recruit alternative neuronal pathways may explain how the brain compensates for the dopaminergic neuronal loss in the long term. However, how long these effects remain remains unclear. Hence, future research should investigate the neurology of PD patients in periods of music therapy vs. periods of no musical therapy. The case of the man with the headphones suggests that the direct neurochemical effects of music are critical for improving his motor control, as he did not want to put his headset off. This implies that the man may not have followed any music therapy, but used music as a means of self-medication, where he profited of the direct impact of music on his brain.

Chapter 8: Epilogue

Writing this paper allowed me to increase my understanding of how music may have affected the man with the headphones. Music has unique properties, allowing the brain to rewire at degenerating conditions through complex mechanisms involving various neurological pathways. Personally, I find the manner in which different types of music can enhance the brainstem in specific ways resulting in physiological changes in the body very intriguing. The implementation of 'relaxing' music, be it in stressful situations, during intra- and postoperative care, or as a receptive therapy for patients with neurodegenerative diseases is proven to be beneficial in infinite ways, yet so simple, inexpensive, and non-invasive. Hence, the therapeutic value of music should not be underestimated, and music should be applied whenever the opportunity arises. Maybe then, in the future, when the benefits that music and its variety of therapies offer are recognized throughout society, we will all be singing:
"I don't need no doctor, 'cause I know what's ailing me" – Ray Charles.

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