Music as treatment for Parkinson's disease

Premaster thesis
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University of Groningen, 24 May 2019

Abstract

Music is a diverse tool that uses words, rhythm, volume and key differences to stimulate the brain on many levels. It evokes emotions, pleasure feeling, increased heart rate and controlled movements like hand tapping or dancing. These areas are often affected in people with Parkinson's disease. Parkinson's disease arises from the degeneration of dopaminergic neurons and eventually causes problems in memory formation, emotional behaviour, motivation regulation, and motor movement. When the dopaminergic pathway is affected by dopamine loss, symptoms such as tremor, gait and balance dysfunctions occur. Many studies on rats and participants are conducted to examine the effect of music in affected areas of Parkinson's disease. Dopamine loss is associated with Parkinson disease and therefore it is interesting that scientists discovered that music can increase the dopamine levels in the forebrain structures of rats. Furthermore, music increases the speed processes and declarative memory performances of elder-aged participants, which are linked to motor areas. Freezing of gait is one of the symptoms of PD that can potentially be a serious problem because it increases the risk of falling. Though, several experiments show that music can improve gait performances of participants with Parkinson's disease. With these assumptions, it is explained how music contributes in attenuating movement and emotion dysfunctions in Parkinson's disease.

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Abbreviations

D1R	Dopamine receptor type 1
D2R	Dopamine receptor type 2
DA	Dopamine
Dopa	L -dihydroxyphenylalanine
GPi	Globus pallidus interna
GPe	Globus pallidus externa
IPL	Inferior parietal lobe
MCGT	Musically-cued gait training
PD	Parkinson's disease
PKA	Protein kinase A
SDMT	Symbol Digit Modality Test
SN	Substantia nigra
STN	Subthalamic nucleus
TH	Tyrosine hydroxylase
Vlo	Ventral lateral nucleus
5-HIAA	5- hydroxyindoleacetic acid

1. Introduction

1.1 What is Parkinson's Disease?

Parkinson's Disease (PD) is a neurodegenerative disorder that mainly affects the substantia nigra which leads to difficulty in initiating voluntary movement. In the Netherlands, more than 49.000 people are diagnosed with (Volksgezondheidenzorg, 2019). The common age at diagnosis is around 50-60 years and implies that symptoms are present around this age range. Around 10% of the patients with Parkinson's disease have symptoms that occur before their 40's. Symptoms of PD include bradykinesia, akinesia, hypokinesia, rigidity, and tremor. PD can also lead to sleep disorders, loss of smell, constipation, lack of motivation, and emotional disorders (Blonder & Slevin, 2011; Raglio, 2016). Many patients also suffer from cognitive deficits as the disease progresses (Parkinsonnet, n.d.). Every patient with PD experiences different sets of symptoms, but they all have a deficiency in dopaminergic neurons, due to dopaminergic degeneration. Moreover, the main symptom that occurs in PD is the difficulty of controlling the movement.

1.2 Function of dopamine in movement

Movement control is accomplished by complex interactions among various groups of nerve cells in the central nervous system. The basal ganglia are the main structure for controlling the movement. It relies on a specific amount of dopamine (DA) from the neurons surrounded, in order to function efficiently. Furthermore, nerve cells in the substantia nigra produce DA and when insufficient DA reaches the basal ganglia, voluntary movement may become delayed or uncoordinated. People with Parkinson's disease suffer from this unregulated mechanism. (Hussein, 2018).

DA is a neurotransmitter that arises from dopaminergic cells in the substantia nigra and the ventral tegmental area. Dopaminergic cells from the substantia nigra project axons to the striatum (the caudate nucleus and the putamen) and are able to facilitate the initiation of motor responses by environmental stimuli. This projection is regulated through the nigrostriatal pathway. DA is able to bind to multiple types of striatal DA receptors that mediate different effects. Behavioural aspects, such as emotion and reward-seeking behaviours, are regulated through the mesolimbic and mesocortical pathway (fig. 1) (Bear, Connors & Paradiso, 2016; Moraes et al., 2018). In the mesolimbic pathway, DA projects from the ventral tegmental area and spread to the amygdala, lateral septal nuclei and nucleus accumbens. Mesolimbic DA mediates pleasure in the brain and plays a role in controlling emotion, reward system and the processes related to addiction (Ayano, 2016). DA in the mesocortical pathway also arises from the ventral tegmental area and projects to the frontal cortex regions. Mesocortical DA mediates memory forming in the brain and plays a role in controlling emotion and the processes related to behaviour and attention (Gratton, Nomura, Perez, & D'Esposito, 2012; Puig, Rose, Schmidt, & Freund, 2014). The three dopaminergic pathways arise and project to different parts of the brain, but all are responsible for relaying messages that plan and control body movement.

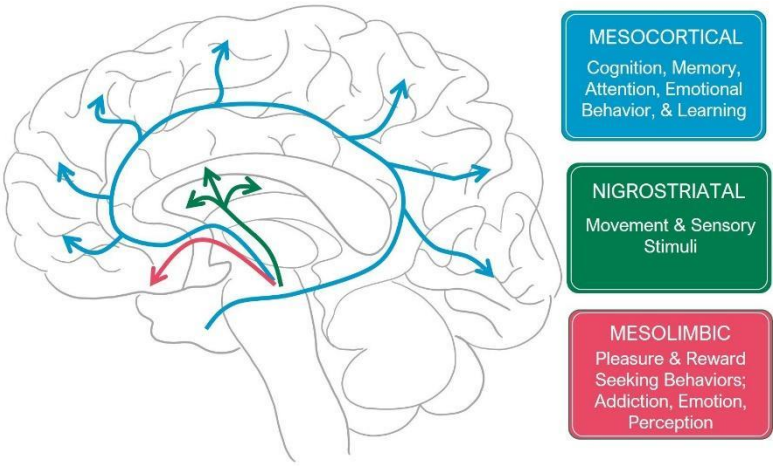

Figure 1 Three dopamine-related pathways and their cognitive functions. Dopamine pathways include mesocortical, nigrostriatal and mesolimbic areas. Each pathway arises and projects to different parts of the brain and has multiple functions (Harvard, 2018).

1.3 Direct and indirect pathways through the Basal Ganglia

The initiation of voluntary movement is regulated by a motor loop which consists of the cerebral cortex, basal ganglia, thalamus, and spinal cord. The motor loop controls the motor movement through a direct pathway and an indirect pathway, also known as the salience network (fig. 2.) (Macpherson, Morita, & Hikida, 2014).

In general, the direct pathway allows the basal ganglia to enhance the initiation of the desired movement. The cerebral cortex excites signals to the striatum. Putamen and the caudate are parts of the striatum and this complex inhibits the globus pallidus interna (GPi). The thalamus is inhibited through Gpi and activated through inputs towards the thalamus and inhibition of GPi from the striatum. Activation of the thalamus leads to excitatory signals back to the cerebral cortex, which then will stimulate the spinal cord for movement. Information from the cortex flows through the direct and indirect pathways in parallel, and the outputs of both pathways ultimately regulate the motor thalamus.

The indirect pathway consists of the complex of direct pathway together with the substantia nigra (SN), globus pallidus externa (GPe) and the subthalamic nucleus (STN). The substantia nigra contains dopaminergic neurons that can modulate the putamen and caudate nucleus. When the GPe receives an excitatory signal from the striatum, it will, in turn, inhibit the GPi and the STN. Furthermore, the subthalamic nucleus is excited by axons from the cortex. Its projections excite the neurons of the GPi, which then inhibit thalamic neurons.

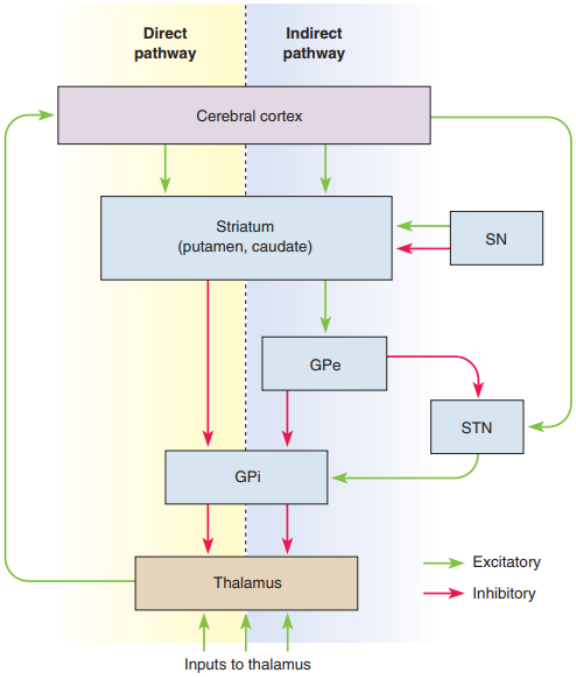

Figure 2 An overview of the direct and indirect pathway in the basal ganglia. Green represents the excitatory stimulus and red inhibitory stimulus (Bear, Connors & Paradiso, 2016).

Dopamine is needed for neurons of the substantia nigra to communicate with neurons in the basal ganglia. The interaction at the biochemical level is responsible for the regulation of movements. Moreover, due to neurodegeneration and imbalance of dopamine levels, characteristic symptoms such as poor balance, dysfunctions in motor coordination and freezing of gait occurs in PD (Pal et al., 2016; Raglio, 2016).

1.4 DA metabolizers and synthesis

Amino acid tyrosine is the precursor of the catecholaminergic neurotransmitter DA. All catecholaminergic neurons contain the enzyme tyrosine hydroxylase (TH), which catalyses the conversion of tyrosine to L-dihydroxyphenylalanine (L-dopa). In turn, L-dopa is converted to DA by dopa decarboxylase. In other words, TH is activated to increase the L-dopa concentration. After decarboxylation of L-dopa into DA, transportation of DA in the synaptic vesicle by vesicular monoamine transporter occurs. Additionally, catecholaminergic synthesis continues in vesicles via actions of dopamine-β-hydroxylase and phenylethanolamine-N-methyltransferase. The increase of calcium in the cell causes emptying of the vesicle into the synaptic cleft, followed up by a nervous signal. The activity of TH is continued till the need for neurotransmitter is fulfilled and a signal is processed (Daubner, Le, & Wang, 2012). Moreover, DA that excites from the axon terminal of presynaptic dopaminergic neurons is able to bind to DA receptors on the postsynaptic neuron. Binding of DA to D1R leads to the activation of adenylate cyclase. The activation results in an increase of cAMP followed by a decrease of calcium concentrations and an increase of protein kinase A (PKA) activity in the cell. The drop in calcium level and increase of PKA activity triggers the muscle to relax. However, binding of DA to D2R leads to an inhibition of adenylate cyclase. This inhibition eventually leads to muscle contraction (Ayano, 2016; Korchounov, 2008). Movement control is dependent on DA release and interaction of dopaminergic neurons. Unfortunately, this regulation is disrupted by the degeneration of dopaminergic neurons in the brain of people with Parkinson's disease (Duke, 2016).

1.5 Dopaminergic neurodegeneration in PD

Parkinson's disease arises from the degeneration of certain neurons in the substantia nigra and the inputs towards the striatum. This degeneration leads to a reduction of DA concentrations in the brain. As a result, a blockade of the channel that usually feeds the activity to the supplementary motor area (SMA) via the basal ganglia and VLo (Ventral lateral nucleus) occurs. Moreover, the decrease of DA concentration also leads to constitutively inhibitory outputs from the striatum to the GPe, via the indirect pathway, since DA usually inhibits this pathway. Researchers are trying to discover why dopaminergic neurons degenerate in Parkinson diseases. One assumption is that patients with Parkinson disease include mutations in genes that result in misfolded proteins that aggregate and accumulate in neurons. This triggers or facilitates the death of dopaminergic neurons (Song & Kim, 2016). Overall, people with PD suffer from degeneration of dopaminergic neurons and a deficiency of dopamine, which causes the unbalanced and unregulated movements.

1.6 Treatments of PD and its limitations

The main strategy of most therapies for Parkinson's disease is to enhance the levels of DA delivered to the caudate nucleus and putamen. The therapy includes L-dopa together with peripheral decarboxylase inhibitor that is induced to the patients. This combination is being used, because L-dopa is able to cross the blood-brain barrier while DA lacks this function. However, L-dopa easily gets converted to DA in the peripheral by decarboxylase. A peripheral decarboxylase inhibitor is also being used in order to inhibit the conversion before the drug enters the brain barrier. This strategy is only helpful in the early phase of Parkinson, but the effects of the drug usually diminish in later phases of the disease (Cilia et al., 2014). New types of movement disorders such as dyskinesia may appear in the later phases (Bear, Connors & Paradiso, 2016). Another strategy to boost the DA concentration is by inducing DA agonists to the patients. However, treatments with L-dopa or DA agonists do not alter the progressive development of the disease. They also do not alter the rate at which substantia nigra neurons degenerate. Additionally, many significant side effects occur with time (Bear, Connors & Paradiso, 2016). The symptoms of some PD patients can also be improved with brain surgery or with deep brain stimulation, but significant risks such as stroke and sensory loss may occur (Michael S. Okun, Hubert H. Fernande, & Kelly D. Foote, 2019).

The limitations of the current strategies to ease the symptoms of PD have led researchers to develop alternative methods to treat PD. An interesting therapy to increase the DA level in Parkinson patients is by stimulating the brain with music (Raglio, 2016; Thaut, 2005). Music is a diverse tool that consists of words, rhythm, volume, and key differences to stimulate the brain on many levels. It evokes emotions, pleasure feeling, increased heart rate, and controlled movements like hand tapping or dancing (Blood, 2001; Fernández-Sotos, Fernández-Caballero, & Latorre, 2016; Raglio, 2017; Stegemöller et al., 2017). Given these assumptions, it is interesting to investigate how music contributes in attenuating symptoms of Parkinson's disease. This review will highlight the effect of music on the brain and whether it is possible to normalize the movement of PD by music stimulation. Different studies will show the effect of music on dopamine levels, mainly because all PD patients suffer from dopamine deficiency. Additionally, dysfunction in emotion, memory, and movement processes also occurs in PD patients. Therefore, insights regarding the effect of music on these impairments will be discussed. Freezing of gait is one of the symptoms of PD that can potentially be a serious problem because it increases the risk of falling (Okuma, 2014; Shine et al., 2013). Thus, it shall also be discussed whether music can potentially attenuate gait problems in PD.

2. Effect of music to the brain

2.1 Classical music changes DA level in forebrain structures of Wistar rats

Music has a lot of benefits to brain activity. It can evoke emotions, heart rate, motor movements, and reward mechanisms (Fernández-Sotos, Fernández-Caballero, & Latorre, 2016; Koelsch, 2009; Raglio, 2016; Song & Kim, 2016). Furthermore, melodic music evokes the processes involving in the brain dopaminergic systems, which are associated with pleasure, reward and movement mechanism (Túnez et al., 2012). Haloperidol is a drug that is known to inhibit DA receptor type 2. Scientists treated Wistar rats with haloperidol and investigated the DA concentrations differences in musical conditions and in no music conditions. The rats that were only treated with haloperidol had decreased DA levels in the prefrontal cortex, striatal nucleus, and mesencephalon compared to the control rats (table 1). However, results showed that music prevented the decline of DA levels from haloperidol treatment. Interestingly, the rats with haloperidol had higher DA levels in the striatal nucleus and the mesencephalon after stimulation with music, compared to rats without haloperidol. Overall, this experiment indicated that classical music has a positive influence on the DA level in the prefrontal cortex, striatal nucleus, and mesencephalon of Wistar rats. These three areas are dependent on DA in order to have a balanced regulation of the dopaminergic system.

Table 1 Dopamine concentration in the prefrontal cortex, striatal nucleus, and mesencephalon of Wistar rats changes in control, music conditions, haloperidol conditions or combined conditions.

	Dopamine (ng/g tissue)			
	Prefrontal cortex	Striatal nucleus	Mesencephalon	Animals per group (n)
Control	73.01±2.02	60.15±2.84	58.59±2.20	5
Music	96.00±3.75**	69.70±2.08***	71.60±1.75*	6
Haloperidol	57.23±5.74*	42.06±1.98*	50.25±2.15***	5
Haloperidol + music	87.75±4.15***,****	71.50±1.97**,****	117.58±4.87****	6

Another recent study showed that music-associated benefits are associated with the activation of brain dopaminergic mechanisms in the forebrain structures from Wistar rats (Moraes et al., 2018). The rats were randomly assigned to a control group without music stimulation and an experimental group that was exposed to music. The music stimulation consisted of 8 sessions of Mozart's sonata and the rats were decapitated after the last music exposure. Concentrations of DA and 3,4-dihydroxyphenylacetic (DOPAC) were then analysed.

Their results indicated that music influences the dopaminergic systems in the caudate-putamen (which is involved in the movement regulation) and in the Nucleus accumbens (which is involved in the reward mechanism) of the rats. DA concentrations were significantly increased in the caudate-putamen (CPu) after stimulation with music. However, music did not change the DA concentrations in the nucleus accumbens (NAcc) (fig. 3). Though, the auditory stimuli increased the DOPAC and DA ratio in the NAcc. The ratio represented the neurotransmitter-turnover. The results of this study suggested that melodic music influences both DA and DA synthesis in rats. (Moraes et al., 2018).

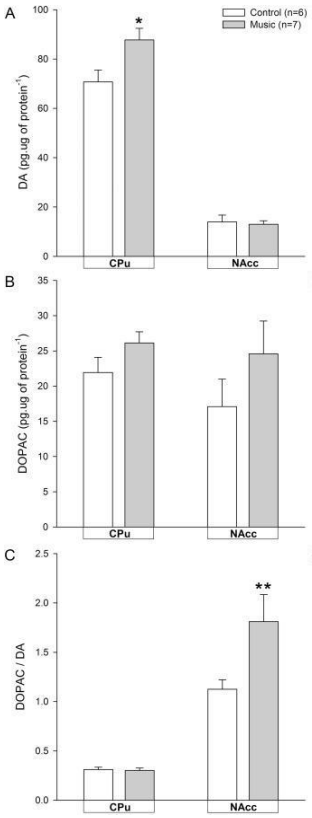

Figure 3 Dopaminergic variables concentrations in the caudate-putamen and nucleus accumbens of rats that were exposed to classical music. A) DA, B) DOPAC, C) DOPAC/DA ratio (Moraes et al., 2018).

2.2 Classical music enhances speed processing and declarative memory performances

PD patients with dopaminergic neurodegeneration often have problems with emotional and speed processes and declarative memory performances (Blonder & Slevin, 2011; Pal et al., 2016; Stefanova et al., 2010). These problems likely arise from dopamine deficiency and previous results showed that music has a positive influence on dopamine levels. Scientists stimulated participants with several types of music and analysed the emotional processing, speed processes and declarative memory performances (Vecchi, Bottiroli, Cavallini, Russo, & Rosi, 2014). In this study, they used two types of music. The first type, Mozart's Eine Kleine Nachtmusik, had a fast tempo and was in the major mode, while the other type, Mahler's 5th Symphony Adagietto, had a slow tempo and was in a minor mode. Experimental group with an age range of 60-84 years were exposed with Mozart's Eine Kleine Nachtmusik, Mahler's 5th Symphony Adiagetto, white noise, and no background noise or music. The white noise refers to environmental stimulation consisting of exposure of a continuous auditory signal. To ensure whether the two classical music induced differences in emotions, a mood questionnaire for Mozart, Mahler and white noise background were obtained and analysed.

The questionnaire showed that Mozart's music was experienced happier than Mahler's music and the white noise condition. Moreover, participants rated Mahler's music as equal to the white background noise. Furthermore, the white noise condition was rated sadder than Mozart's music. Overall, the results of the mood questionnaire showed that Mozart's music induces greater emotions than Mahler and white noise conditions. This experiment indicated that the music written in a fast tempo and in major key evoked a happier and more intense emotion than music with a slower tempo and in a minor key. Music is often associated with the right hemisphere of the brain. It has been shown that the right hemisphere is preferentially activated when listening to music that is correlated

with emotional experiences (Trimble & Hesdorffer, 2017). In general, music that is written in the major key often provokes a happy emotion. While music that is written in the minor key is experienced as a sad emotion. Besides differences in key modes, experiences of music can also differentiate by tempo and volume. Slower rhythms tend to be less joyful than faster rhythms (Fernández-Sotos et al., 2016). These assumptions indicated that music evokes a certain movement that can be associated with an emotional experience.

Using previous information, the declarative memory and emotions of the participants were observed and analysed while different background music and noises were induced. The declarative memory test consisted of an episodic memory task and a semantic memory task. The episodic memory is a type of long-term memory that is involved in the conscious recollection of previous experiences, together with their context in terms of time and place. Overall, episodic memory is associated with processing emotions. The semantic memory is also a type of long-term memory but involving in the capacity to recall words, concepts or numbers. This is essential for the use and understanding of language (Manuscript & Memory, 2009).

Participants of the experiment had to memorize four parallel versions of words-list and each episodic memory task was performed in different background sound conditions. The episodic memory task score was obtained by subtracting intrusion words from the number of correctly answered words. The semantic memory task was obtained by a fluency test but in four different background music conditions. Results of the episodic and semantic memory showed that classical music stimulation leads to better performances than stimulation with white noise or no noise (table 2). Furthermore, no significant difference between both memory tasks occurred between the two classical music conditions respectively between the two non-music conditions. Overall, this experiment showed that classical music provokes higher declarative memory performances than white noise and no noise. Though, Mozart's music did not particularly provoke a better declarative memory performance than Mahler's music.

Table 2 means value and standard deviations of cognitive tasks in different background conditions. Episodic memory, semantic memory, and speed processing values were measured while Mozart's Mahler's, White noise or no music was induced to participants.

	Background condition			
	Mozart	**Mahler**	**White noise**	**No-music**
Cognitive tasks				
Episodic memory	9.82 (2.41)^{ab*}	9.92 (2.38)^{cd}	9.11 (2.32)^{bd}	8.71 (2.45)^{ac}
Semantic memory	41.61 (11.55)^{ab}	39.80 (9.78)^{c}	36.39 (11.42)^{bc}	38.34 (9.22)^{a}
Processing speed	38.89 (10.31)$^{abc+}$	35.51 (9.45)^{b}	34.65 (11.17)^{a}	36.76 (11.63)$^{c+}$

The declarative memory is not the only cognitive ability that is mostly affected by aging. Speed processing tends to decline within age too (Salthouse, 2004). Furthermore, processing speed is one of those abilities that is sensitive to the tempo and mode of music (Schellenberg, 2011). Thus, it was interesting to evaluate whether background music evokes a negative or positive effect regarding speed processing. Speed processing was assessed by the Symbol Digit Modality Test (SDMT), which consists of geometric shapes that were associated with digits. Participants had to write the right association as quickly as possible and the test was performed in the four different conditions. Their results showed that speed processing was performed the highest in the Mozart condition compared to the other three conditions (table 2). This may be associated with arousal and mood hypothesis, which include that the speed performance is correlated with positive mood and arousal conditions. These results show the that different types of music cause differences in emotion processing and stimulate cognitive abilities, that are usually affected in PD. Overall, these studies concluded that

classical music is a promising tool to attenuate PD because music enhances speed processing and declarative memory performances.

2.3 Rhythm improves gait movement in PD

Poor declarative memory performances are also associated with the deactivation of motor areas which could potentially lead to freezing of gait in PD (Pal et al., 2016; Vikene, Skeie, & Specht, 2019). Freezing of gait can be a serious problem because it increases the risk of falling. An interesting study indicated that the rhythms of music can improve the gait movement of patients with PD (Bella et al., 2017). In this study, 14 patients with PD were trained with a rhythm program using musically-cued gait training (MCGT). Their ability to synchronize movements (steps and hand taps) to sounds was measured before and after the gait training. Gait kinematics were recorded with a Motion Capture System using Nexus software at a sampling frequency of 200Hz. Sensorimotor timing skills were measured using the Battery for the Assessment of Auditory Sensorimotor and Timing Abilities (BAASTA). Their results showed that the gait cadence, gait speed, stride length and stride time were significantly increased from 50 percent of the PD participants, after the training program based on rhythm. The improved performance of the speed and stride of the participants remained after one month in the follow-up conditions (table 3).

Table 3 Performances of gait task from idiopathic PD patients obtained pre-, post-training and at the follow-up conditions.

	Controls	Patients		
		Pre	*Post*	*Follow-up*
	Mean (SEM)	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*
Cadence (step/min)	100.5 (*1.8*)	106.3 (*2.3*)	108.0 (*2.2*)	109.5 (*2.2*)
Speed (mm/sec)	964.4 (*25.9*)	898.9 (*48.1*)	952.7 (*37.0*)	961.5 (*39.3*)
Stride length (mm)	1152.0 (*22.3*)	1011.7 (*44.8*)	1057.5 (*37.8*)	1053.7 (*38.7*)
Stride length variability	10.4 (*0.7*)	10.8 (*0.9*)	10.4 (*0.9*)	10.8 (*0.6*)
Stride time (sec)	1.2 (*0.02*)	1.1 (*0.03*)	1.1 (*0.02*)	1.1 (*0.02*)

The training program based on rhythm stimulation overall improved gait movement such as speed and stride length of patients with PD. Since these results maintained after one month of the training program, it is promising to use rhythms as a tool to attenuate movement symptoms of people with PD.

Other studies showed that the motor area and the caudate nucleus were highly activated by rhythm in PD participants (Vikene, Skeie, & Specht, 2019). For this experiment, 15 PD participants and 15 healthy control participants were stimulated with two different rhythms. The motor area and the caudate nucleus activity were then measured and analysed from fMRI scans.

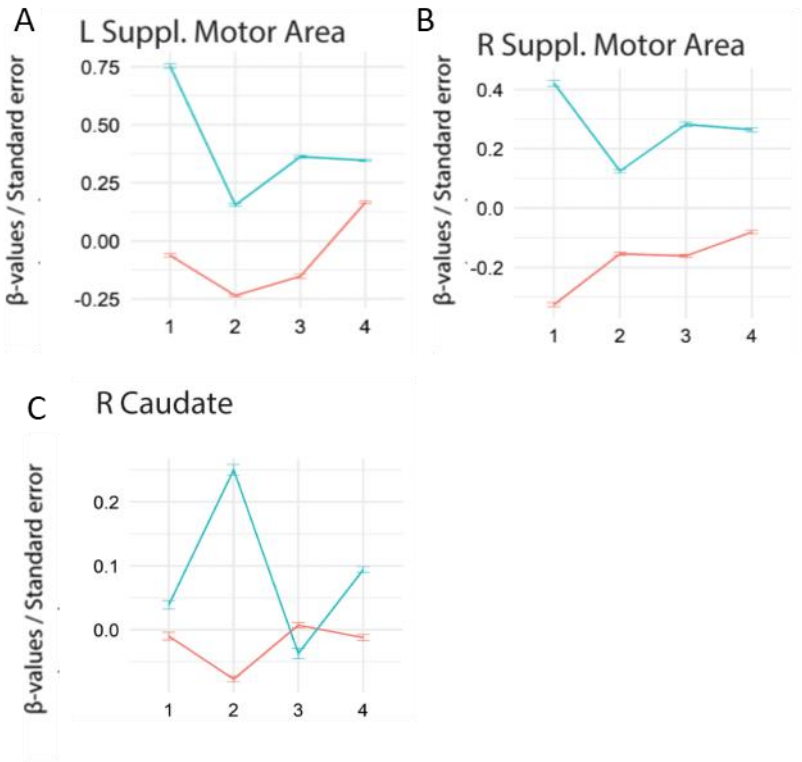

Figure 4 ß-values (brain activity) for PD (blue) and healthy control (red) over four-time rhythm stimulation (0–4, 4–8, 8–12, 12–16 s). A) Left Motor Area, B) Right Motor Area, C) Caudate (Vikene et al., 2019).

The bilateral supplementary motor areas (SMA) and caudate nucleus were highly activated in the PD group but not in the healthy control group after the stimulation with rhythm (figure 4). The SMA activity was downregulated after the second time-bin but upregulated in the third and fourth time-bin. Interestingly, the caudate nucleus activity was upregulated in the second time-bin in the PD group, followed by deactivation in the third time-bin and upregulation in the fourth time-bin. These activation patterns did not occur in the healthy control group. Overall, this data shows that music improves motor areas and the caudate nucleus, which are areas that are often affected in PD patients.

3. Discussion and conclusion

Parkinson's disease arises from the degeneration of dopaminergic neurons. Consequences from the dopaminergic neuron degeneration lead to a decrease of dopamine levels in the brain, followed up by an unbalanced regulation of the dopaminergic system. Three pathways that get affected by the mechanism are the mesocortical pathway, the nigrostriatal pathway, and the mesolimbic pathway. The dopaminergic pathway is responsible for memory formation, emotional behaviour and perception, motivation regulation and motor movement. When the dopaminergic pathway is unregulated, symptoms such as tremor, muscular rigidity, bradykinesia and gait, and balance dysfunctions occur. Alternative therapies to attenuate the symptoms of Parkinson's disease are currently being explored by researchers. Music is a diverse tool that includes words, rhythm, volume and key differences that stimulate the brain on many levels (Lu et al., 2010; Margulis, 2017; Raglio, 2017). It evokes emotions, pleasure feeling, increased heart rate and controlled movements like hand tapping or dancing. Given these assumptions, it is interesting to investigate how music therapy contributes in improving symptoms of Parkinson's disease.

Different studies showed that classical music increases DA levels of monoaminergic areas in the brain of Wistar rats. Though, the exact mechanisms where DA levels increase through music stimulation remains unknown. Evidence suggested that music stimulation increases DA concentration through a calcium/calmodulin cell pathway (Sutoo & Akiyama, 2004). Studies indicated that peripheral calcium is transported to the brain via blood and thereby enhances the calmodulin activity. Subsequently, calmodulin-dependent systems increase DA synthesis in dopaminergic brain regions such as neostriatum and nucleus accumbens, through the phosphorylation of TH. Other studies suggested that music directly increases the turnover of L-DOPA to DA and is associated with emotional processing (Moraes et al., 2018). Another aspect of the experiment we can speculate on is that rats that were treated with haloperidol do not represent directly to the situation of dopaminergic neurodegeneration in people with PD. The data does not directly show what the effect of music on DA levels will be in PD. Thus, it is interesting to investigate the association of these different findings of via which mechanism music increases DA in PD.

Studies also confirmed that Mozart's music that is written with a fast tempo and in a major key evokes a happier and more intense emotion than Mahler's music which is written with a slow tempo and written in a minor key. This is in concordance with other studies that concluded that the tempo modulates the arousal value of the emotions and that music that evokes happiness is associated with high-arousal emotions. However, other studies showed that happy music that is associated with high-arousal increased the strength of mind-wandering. (Franklin, Smallwood, & Schooler, 2011; Smallwood, Ruby, & Singer, 2013). Mind-wandering is involved in delaying gratification and in disrupting ongoing task performances. Unfortunately, these disadvantages also occur in PD patients. Thus, music with high-arousal does not always have a positive influence on attenuating all symptoms of PD. Interestingly, results of the speed processing tasks were performed greater in Mozart's condition in comparison with Mahler's, white-noise and no noise. This result indicates that not all happy music disrupts ongoing task performances and can interestingly increase speed processing tasks. Studies showed that the type of music influence positively and negatively on different symptoms of PD. However, PD consists of a group of symptoms. Thus, it is necessary to understand which music type is associated with what type of PD symptoms and how those types of music can attenuate the correlated symptoms.

Results of declarative memory tasks showed that classical music provokes higher declarative memory performances than white noise and no noise. Declarative memory forming is important for recalling previous memories together with the context, time and place. However, the results of the declarative performances were just obtained via word-memorizing tests and fluency tests. There is still some speculation whether the results are reliable for all declarative memory forming and processes because the declarative memory depends on more than just memorizing words. Other studies showed that declarative memory forming plays a role in regulating the gait movement. Moreover, the decline of the declarative memory forming is likely to be associated with the freezing of gait in PD. Therefore, it is interesting to investigate further on how music exactly provokes higher declarative memory forming in PD and thereby attenuating correlated movement symptoms.

Results showed that the rhythm of music can attenuate gait problems in PD. Furthermore, rhythm improved the gait speed and stride length for one month. These results are in concordance with previous studies, which they conclude that gait kinematics are regulated by a stimulus-driven allocation of attention. The rhythm causes a stimulus that enhances the temporal prediction and initially facilitates movement planning and initiation (Obrig et al., 2014). However, there are still some speculations whether the rhythm training program is suitable for all PD patients since only 50 percent of the PD participants of the experiment gained gait benefits from the rhythm. It is interesting to investigate further why the rhythm program did not improve the gait performances of the other 50 percent of PD participants. It is also interesting to explore how long the improved performances of the gait speed and stride length in the PD participants will last. Thereby, scientists need to optimize the rhythm training program in order to attenuate gait movements in more PD patients and for maintained results. First, more PD participants and non-PD participants are needed for the experiment. Second, the progression of the participants needs to be tracked through a longer period than one month.

Another interesting approach to explore further is the salience network of PD patients and the effect of music towards it. The salience network is responsible for the processing of the reward, emotion and movement system. These three systems are all affected in PD. FMRI scans showed that the bilateral supplementary motor areas (SMA) and caudate nucleus were highly activated in the PD participants but not in the healthy control participants, after the stimulation with rhythm. This result is in concordance with neuro-images of previous studies that showed that rhythm induces reinforcement of dorsal anterior cingulate cortex connectivity within the salience network (Ros et al., 2012). Though, the caudate nucleus activity was decreased after the third music stimulation. The caudate nucleus is involved in preparation, production and motor imaging response processing (Vikene et al., 2019). Which could explain why the rhythm stimulation of the second time-bin caused a stronger activation than stimulation from the third and fourth time-bin. Overall, rhythm did increase the activity of both areas in PD patients, which is promising since both areas are often affected in PD patients.

Taken together, music may represent a promising strategy towards attenuating movement and emotional symptoms of PD by increasing the dopamine levels and thereby stimulating the dopaminergic pathway. Since music is such a diverse tool, it is still a challenge to understand how music exactly attenuates PD symptoms. In order to understand how music attenuates PD symptoms, we have to understand how music processing works in the brain of healthy and PD participants. Therefore, we can analyse the differences or the similarity and improve the music therapy for long-lasting attenuation of PD symptoms. Further studies regarding the effects of music as treatment could focus on 1) determining the effect of music and rhythm towards the reward system 2) the association of improved reward, emotion and movement mechanism by music stimulation 3) the duration of the maintained and improved movement in PD.

4. Literature

Ayano, G. (2016). Dopamine: Receptors, Functions, Synthesis, Pathways, Locations and Mental Disorders: Review of Literatures. *Journal of Mental Disorders and Treatment*, *2*(2), 2–5. https://doi.org/10.4172/2471-271x.1000120

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2016). Neuroscience: Exploring the brain. Philadelphia: Wolters Kluwer. doi:10.1111/j.1944-9720.2011.01128.x

Bella, S. D., Benoit, C., Farrugia, N., Keller, P. E., Obrig, H., Mainka, S., & Kotz, S. A. (2017). Gait improvement via rhythmic stimulation in Parkinson ' s disease is linked to rhythmic skills. *Nature Publishing Group*, (January), 1–11. https://doi.org/10.1038/srep42005

Blood, A. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences*, *98*(20), 11818–11823. https://doi.org/10.1073/pnas.191355898

Blonder, L. X., & Slevin, J. T. (2011). Emotional dysfunction in Parkinson's disease. *Behavioural Neurology*, *24*(3), 201–217. https://doi.org/10.3233/BEN-2011-0329

Cilia, R., Akpalu, A., Sarfo, F. S., Cham, M., Amboni, M., Cereda, E., … Pezzoli, G. (2014). The modern pre-levodopa era of Parkinson's disease: Insights into motor complications from sub-Saharan Africa. *Brain*, *137*(10), 2731–2742. https://doi.org/10.1093/brain/awu195

Daubner, S. C., Le, T., & Wang, S. (2012). NIH Public Access, *508*(1), 1–12. https://doi.org/10.1016/j.abb.2010.12.017.Tyrosine

Duke (2016). Content Background: Anatomy of the Dopamine Neuron. sites.duke. Retrieved from https://sites.duke.edu/thepepproject/module-3-how-do-drugs-damage-neurons-its-radical/content-background-anatomy-of-the-dopamine-neuron/

Fernández-Sotos, A., Fernández-Caballero, A., & Latorre, J. M. (2016). Influence of Tempo and Rhythmic Unit in Musical Emotion Regulation. *Frontiers in Computational Neuroscience*, *10*(August). https://doi.org/10.3389/fncom.2016.00080

Franklin, M. S., Smallwood, J., & Schooler, J. W. (2011). Catching the mind in flight: Using behavioral indices to detect mindless reading in real time. *Psychonomic Bulletin and Review*, *18*(5), 992–997. https://doi.org/10.3758/s13423-011-0109-6

Gratton, C., Nomura, E. M., Perez, F., & D'Esposito, M. (2012). NIH Public Access. *Journal of Cognitive Neuroscience*, *24*(6), 1275–1285. https://doi.org/10.1162/jocn

Haynes T. (2018). Dopamine, Smartphones & You: A battle for your time. Harvard. Retrieved from http://sitn.hms.harvard.edu/flash/2018/dopamine-smartphones-battle-time/

Hussein, R. (2018, January 2). Functions of Dopamine: What is Dopamine and How Does It Affect you? Retrieved from https://blog.cognifit.com/functions-of-dopamine-serve-you/

Koelsch, S. (2009). A neuroscientific perspective on music therapy. *Annals of the New York Academy of Sciences*, *1169*, 374–384. https://doi.org/10.1111/j.1749-6632.2009.04592.x

Korchounov, A. M. (2008). Role of D1 and D2 receptors in the regulation of voluntary movements. *Bulletin of Experimental Biology and Medicine*, *146*(1), 14–17. https://doi.org/10.1007/s10517-008-0197-0

Lu, Y., Liu, M., Shi, S., Jiang, H., Yang, L., Liu, X., … Pan, F. (2010). Effects of stress in early life on immune functions in rats with asthma and the effects of music therapy. *Journal of Asthma*,

47(5), 526–531. https://doi.org/10.3109/02770901003801964

Macpherson, T., Morita, M., & Hikida, T. (2014). Striatal direct and indirect pathways control decision-making behavior. *Frontiers in Psychology*, *5*(NOV), 1–7. https://doi.org/10.3389/fpsyg.2014.01301

Manuscript, A., & Memory, D. (2009). NIH Public Access, *17*(2), 112–118. https://doi.org/10.1111/j.1467-8721.2008.00559.x.Declarative

Margulis, E. H. (2017). How music meets mind. *Nature*, *546*, 351. Retrieved from ehm@uark.edu

Michael S. Okun, Hubert H. Fernande, & Kelly D. Foote (2019). What are the Risks of DBS? Movementdisorders.ufhealth. Retrieved from https://movementdisorders.ufhealth.org/for-patients/deep-brain-stimulation-information/what-are-the-risks-of-dbs/

Moraes, M. M., Rabelo, P. C. R., Pinto, V. A., Pires, W., Wanner, S. P., Szawka, R. E., & Soares, D. D. (2018). Auditory stimulation by exposure to melodic music increases dopamine and serotonin activities in rat forebrain areas linked to reward and motor control. *Neuroscience Letters*, *673*(February), 73–78. https://doi.org/10.1016/j.neulet.2018.02.058

Obrig, H., Benoit, C.-E., Kotz, S. A., Dalla Bella, S., Farrugia, N., & Mainka, S. (2014). Musically Cued Gait-Training Improves Both Perceptual and Motor Timing in Parkinsonâ€™s Disease. *Frontiers in Human Neuroscience*, *8*(July), 1–11. https://doi.org/10.3389/fnhum.2014.00494

Okuma, Y. (2014). Freezing of Gait and Falls in Parkinson ' s Disease, *4*, 255–260. https://doi.org/10.3233/JPD-130282

Pal, G., O'Keefe, J., Robertson-Dick, E., Bernard, B., Anderson, S., & Hall, D. (2016). Global cognitive function and processing speed are associated with gait and balance dysfunction in Parkinson's disease. *Journal of NeuroEngineering and Rehabilitation*, *13*(1), 1–8. https://doi.org/10.1186/s12984-016-0205-y

Parkinsonnet (n.d). parkinson. Parkinsonnet. Retrieved from https://www.parkinsonnet.nl/parkinson

Puig, M. V., Rose, J., Schmidt, R., & Freund, N. (2014). Dopamine modulation of learning and memory in the prefrontal cortex: insights from studies in primates, rodents, and birds. *Frontiers in Neural Circuits*, *8*(August), 1–15. https://doi.org/10.3389/fncir.2014.00093

Raglio, A. (2016). Music therapy interventions in Parkinson's disease: the state-of-the-art. *Nursing Older People*, *28*(9), 12. https://doi.org/10.7748/nop.28.9.12.s15

Ros, T., Frewen, P. A., Calhoun, V. D., Densmore, M., Lanius, R. A., Kluetsch, R., & Théberge, J. (2012). Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. *NeuroImage*, *65*, 324–335. https://doi.org/10.1016/j.neuroimage.2012.09.046

Salthouse, T. A. (2004). What and When of Cognitive Aging, *13*(4), 140–144.

Schellenberg, E. G. (2011). Examining the association between music lessons and intelligence, *6*, 283–302. https://doi.org/10.1111/j.2044-8295.2010.02000.x

Shine, J. M., Matar, E., Ward, P. B., Frank, M. J., Moustafa, A. A., Pearson, M., … Lewis, S. J. G. (2013). Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. *Brain*, *136*(12), 3671–3681. https://doi.org/10.1093/brain/awt272

Smallwood, J., Ruby, F. J. M., & Singer, T. (2013). Letting go of the present: Mind-wandering is associated with reduced delay discounting. *Consciousness and Cognition*, *22*(1), 1–7. https://doi.org/10.1016/j.concog.2012.10.007

Song, J., & Kim, J. (2016). Degeneration of dopaminergic neurons due to metabolic alterations and Parkinson's disease. *Frontiers in Aging Neuroscience*, *8*(MAR), 1–11. https://doi.org/10.3389/fnagi.2016.00065

Stefanova, E. D., Kostic, V. S., Ziropadja, L., Ocic, G. G., Markovic, M., Kostic, V. S., … Markovic, M. (2010). Declarative Memory in Early Parkinsons Disease : Serial Position Learning Effects Declarative Memory in Early Parkinson ' s Disease : Serial Position Learning Effects, *3395*. https://doi.org/10.1076/jcen.23.5.581.1239

Stegemöller, E. L., Hurt, T. R., O'Connor, M. C., Camp, R. D., Green, C. W., Pattee, J. C., & Williams, E. K. (2017). Experiences of persons with Parkinson's disease engaged in group therapeutic singing. *Journal of Music Therapy*, *54*(4), 405–431. https://doi.org/10.1093/jmt/thx012

Thaut, M. H. (2005). The future of music in therapy and medicine. *Annals of the New York Academy of Sciences*, *1060*, 303–308. https://doi.org/10.1196/annals.1360.023

Trimble, M., & Hesdorffer, D. (2017). Music and the brain: the neuroscience of music and musical appreciation. *BJPsych International*, *14*(2), 28–31. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29093933%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5618809

Túnez, I., Montilla, P., García-Mayórgaz, Á. D., del Río, M. C., Tasset, I., & Quero, I. (2012). Changes caused by haloperidol are blocked by music in Wistar rat. *Journal of Physiology and Biochemistry*, *68*(2), 175–179. https://doi.org/10.1007/s13105-011-0129-8

Vecchi, T., Bottiroli, S., Cavallini, E., Russo, R., & Rosi, A. (2014). The cognitive effects of listening to background music on older adults: processing speed improves with upbeat music, while memory seems to benefit from both upbeat and downbeat music. *Frontiers in Aging Neuroscience*, *6*(October), 1–6. https://doi.org/10.3389/fnagi.2014.00284

Vikene, K., Skeie, G. O., & Specht, K. (2019). Abnormal phasic activity in saliency network, motor areas, and basal ganglia in Parkinson's disease during rhythm perception. *Human Brain Mapping*, *40*(3), 916–927. https://doi.org/10.1002/hbm.24421

Volksgezondheidenzorg (2019). Ziekte van Parkinson. Volksgezondheidenzorg. Retrieved from https://www.volksgezondheidenzorg.info/onderwerp/ziekte-van-parkinson/cijfers-context/huidige-situatie

Wessel, J. R., Aron, A. R., City, I., Sciences, B., City, I., & Jolla, L. (2018). HHS Public Access, *93*(2), 259–280. https://doi.org/10.1016/j.neuron.2016.12.013.On