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Can Music Therapy (Rhythmic Auditory Stimulations) Completely Replace the Conventional Medicine (Levodopa) Used to Treat All the Symptoms of Parkinson's Disease and Delay Its Deterioration?

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Abstract: ***There are various treatment options for Parkinson's which results in varying degrees of improvement depending on the subject. This dissertation contrasts and compares 2 such treatments, levodopa (a medicine) and RAS (a form of music therapy), that are widely and rarely used respectively. It examines the advantages, disadvantages and possible controversies in this area, exploring their effect on Parkinson's symptoms. This topic examines various case studies and research that showcases the role of RAS and levodopa, and how they distinctly yet similarly interact with the human body. It also intends to shed light on their function in treating both motor and non-motor symptoms, affecting patients' general health and quality of life.***

Keywords: Parkinson's disease, levodopa, rhythmic auditory stimulation, motor and non-motor symptoms, quality of life, Parkinson's treatment

1. Introduction

"Parkinson's disease is a progressive neurodegenerative disease" (Kouli et al. 2018) which is accompanied by a combination of motor and non-motor symptoms. Age being the leading factor, it has multiple causes with unfortunately no specific treatment that can bring about a measurable improvement in symptoms. This disease greatly inhibits the subject to perform their daily tasks, increases their dependency and could potentially put the body under a lot of stress as the stages progress (NHS, 2022).

However, meticulous use and combination of various drugs can support the management of the symptoms to a certain extent. The treatment plan generally revolves around levodopa, a chemical building block which has the ability to convert into dopamine (Parkinson's UK, n.d.) and replenish the low levels. Furthermore, while levodopa brings about a change in the symptoms of Parkinson's, it has its long-term issues including side effects, wearing off effect and toxicity to neurons. Therefore, while these drugs may play a role in managing this disease, an efficient treatment plan also requires alternative, non-pharmacological approaches including crucial lifestyle changes such as diet and exercise.

In addition to the drugs, an alternative pathway of expressive therapy can be adopted by patients which may potentially prove to be rewarding. Expressive therapy is an "integrative, multimodal technique" (Nash, 2022) which involves the combination of psychology and a creative process to achieve an individual's mental and personal growth (Psychology Today, 2022). It behaves as a restorative avenue, providing a pathway for self-discovery and achieving emotional release through a simplistic expressive approach (Nash, 2022). Overall, these therapies play a role in emotional, cognitive and physical well-being. Although this form of self-expression comes in a variety of forms including art, music and dance, they all tend to behave in a similar way, especially when it comes to treating symptoms of Parkinson's. RAS, in the form of music therapy, is unlikely to bring any major side effects, boost mental health and increase mindfulness (Blackburn et al. 2014), thus benefit a Parkinson's patient.

This dissertation delves into how RAS and levodopa interact with the brain, talking about the network involved, effect on the dopaminergic pathway and the body as a whole. It contributes to existing knowledge, and the findings could also potentially influence future treatment plans for Parkinson's. It evaluates that although RAS has significant impact on Parkinson's symptoms, it cannot completely replace levodopa nor delay the progression of the disease.

2. Literature Review

Overview on Parkinson's Disease

"Parkinson's disease is a progressive neurodegenerative disease" (Kouli et al, 2018) caused by the degeneration of 60-80% of dopamine releasing nerve cells in the ventral part of the pars compacta (Damier P. et al, 1999) which is found in the substantia nigra, the deep part of the brain (Cleveland Clinic, 2022). The substantia nigra pars compacta (SNpc) is a part of the basal ganglia- the area that controls voluntary movement of the body along with other functions such as emotions and motor learning (Lanciego, 2012). - and is made up of melanin rich cells, therefore appearing to be black. (Sonne et al, 2022; Cleveland Clinic 2022). These nerve cells are unable to produce the neurotransmitter dopamine, in the corpus striatum region of the brain (Thornton, 2023) hindering the fragile balance with other neurotransmitters, giving rise to the symptoms of Parkinson's disease such as rigidity, imbalance and poor posture, accompanied with psychological issues (UCSF health, n.d.).

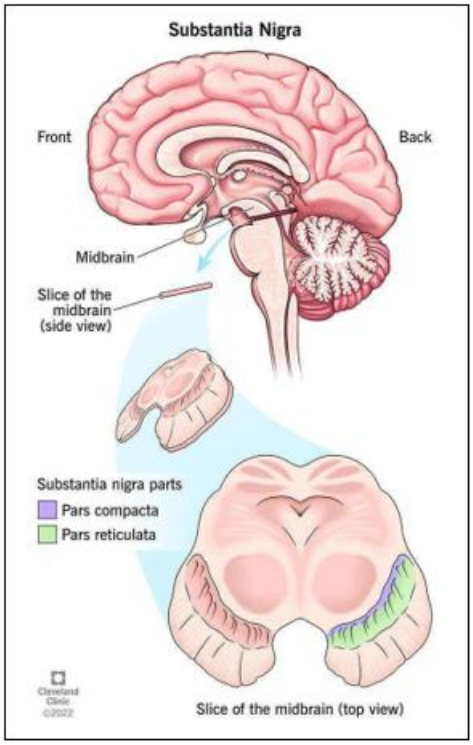
Furthermore, as the neurons are unable to produce the neurotransmitter dopamine, the dopaminergic pathway is affected. The dopaminergic pathway refers to the neural pathways that allow dopamine to travel across different areas of the brain and body to transmit crucial information, including functioning executively, memory, a perception of satisfaction, and voluntary motor actions. Out of the 4 major dopaminergic pathways- nigrostriatal, mesolimbic,

mesocortical, and tuberoinfundibular (Bridges, 2016) - the mesocortical and nigrostriatal pathway are particularly affected in which they cease to communicate with other neurons and parts of the brain. These pathways which are no longer connected results in a decline in this neurotransmitter.

About Music Therapy

This dissertation diverts its focus on music therapy, particularly rhythmic auditory stimulations (RAS) which will later be discussed in the EPQ.

Music therapy can be interpreted and defined in multiple ways. The American Music Therapy Association (AMTS) defines it as a "clinical & evidence-based use of music interventions to accomplish individualised goals within a therapeutic relationship by a credentialed professional" (AMTS, n.d.) while British Association for Music Therapy (BAMT) views it as "an established psychological clinical intervention… to help people whose lives have been affected by injury, illness or disability through supporting their psychological, emotional, cognitive, physical, communicative and social needs" (BAMT, n.d.). This EPQ will focus on the BAMT definition. These methods can either be active- patient performing an action in relation to the music- or receptive- listening to the music.



About Medications

Based on empirical evidence, pharmaceutics, surgical procedures and MRI guided focused ultrasound (MRgFUS) are the prominent treatment plans to Parkinson's, out of which medications are the most widely used (APDA, n.d.). Apart from levodopa, a combination of various other medicines is included in the treatment plan of patients with Parkinson's. This includes dopamine agonists which mimic dopamine affects; enzyme inhibitors such as monoamine oxidase B (MAO-B), ALDHD and Catechol O-methyltransferase (COMT); and Nuplazid (pimavanserin) (Mayoclinic, 2024). However, levodopa is one of the major pharmaceuticals that is present in a typical patient (with a few exceptions) irrespective of their stage or UPDRS score (Chou and Ferng, 2023; Parkinson's foundation n.d.).

3. Symptoms

Although the rate of aggravation may differ amongst individuals (Parkinson's Community Health, 2021), the various symptoms of Parkinson's disease develop as the individual progresses to the next stage of the disease. The condition presents multiple challenges for the affected individuals because of its symptoms, which are primarily a mix of motor and non-motor issues. The symptoms may be visible on one side of the body but as the disease progresses, both sides may be affected (National Institute on Aging, 2022).

Tremors or uncontrollably rhythmic movements of the jaw, hands, arms, and legs are among them. Furthermore, people frequently have muscular rigidity that primarily affects the arms, shoulders, or neck, which results in ligaments contracting for an extended period (Mayo Clinic, 2024).

As the disease advances, there is a progressive loss of spontaneity in movement, which often leads to changes in speech patterns, reduced cognitive response, and facial expressions, among other related symptoms. In addition, those who are impacted could assume a flexed posture, which is defined as bending the elbows, knees, and hips while leaning forward (NHS, 2022).

Unsteady gait or balance problems are another common symptom that can lead to a shaky walking pattern. Gait alterations can be viewed in 3 major parts: i) reduced asymmetry and variability, ii) slow gait, and iii) inadequate postural control (Peterson and Horak, 2016, Smulders et al., 2016). The gait is further accompanied by stride length, pace, and arm swing amplitude. Moreover, symptoms like drooling, loss of appetite, and irregular blinking may result from the increasing loss of reflex movements (NHS, 2022).

Apart from these symptoms, the loss of norepinephrine producing nerve endings, which is the "main chemical messenger of the sympathetic nervous system" (national institute on Aging, 2022), results in the non-motor symptoms and psychological impact. These include irregular blood pressure, fatigue, and gastroparesis (decreased movement of food through the digestive tract). Apart from this, individuals frequently experience skin-related issues and poor mental health such as stress and depression, a worry that is made worse by the side effects of the drugs used to treat it. Beyond these physical manifestations, these symptoms deeply affect the quality of life (national institute on Aging, 2022; Mayoclinic, 2024)

4. Stages

According to Parkinson's Foundation (no year) there are three dominant phases – preclinical, prodromal and clinal- in Parkinson's. Preclinical is categorised as the initial stage in which the symptoms haven't manifested but the "degeneration of dopamine producing neurons" has begun (Parkinson's Foundation, no year). In the prodromal stage, the

symptoms begin to emerge, but they aren't sufficient enough to be diagnosed. Finally, the symptoms of Parkinson's are clearly seen in the clinical phase.

Stage 1: The minor symptoms present in stage 1 of the disease do not considerably interfere with the individual's regular activities. Tremors and trouble moving that just affects one side of the body are some of these symptoms. At this point, people might exhibit changes in their posture, gait, and facial expressions.

The transition from stage 1 to stage 2 occurs over an unpredictable time span, lasting anywhere from months to years. Unfortunately, there are no proven, trustworthy techniques to forecast the precise course of the condition's development.

Stage 2: Stage 2 of the illness is quite moderate in which people have more trouble completing everyday tasks due to muscle stiffness, thus taking longer to complete. At this point, people can usually continue to live independently despite these obstacles. There are considerable stiffness, trembling, and trembling on both sides of the body, including the midline. There are also noticeable alterations in facial expressions. Moreover, people usually do not have problems with balance, however they may have trouble speaking and walking. Postural adjustments made during this phase may result in neck and back pain.

Stage 3: This is the mid stage of the pathology, marking a critical turning point in the course of the illness. At this point, people have the same symptoms as in Stage 2, but their motor symptoms are noticeably worse. The probability of suffering unbalance, impaired reflexes, and a general slowing down of movement is significantly increased. As a result, problems with reflexes and balance lead to an increased risk of falls.

Even though people are still capable of completing tasks, Parkinson's disease greatly reduces the pace and efficiency at which these tasks may be finished. Occupational therapy and medicine have been recognized as potential therapies to address these issues, with the goal of improving functional abilities and symptom relief at this time.

Stage 4: Stage 4 denotes the full development of Parkinson's disease symptoms, which leads to a high degree of disability. Deep brain stimulation methods are considerably less successful due to the severe impairment of motor functions. Independence is undermined when people need help for safety and support, which might come from other people or from using a walker or cane. Even though people can stand on their own, they greatly depend on assistance in order to move. One cannot live alone if they have a discernible decline in their ability to move and react.

Daily tasks become extremely difficult, if not impossible, to complete on one's own. This presents risks because, at this stage of the disease, these tasks are dangerous to conduct independently.

Stage 5: Parkinson's disease reaches its most advanced stage in stage 5. People in this stage have significant difficulties in walking and standing because of their extreme leg stiffness, which might eventually cause them to become bedridden or require constant use of a wheelchair.

Without assistance, carrying out daily tasks becomes impossible and dangerous, always necessitating constant care and support for the person. Particularly, in up to 50% of patients, confusion, hallucinations, and delusions are among the extra difficulties in stages 4 and 5, which increases the complexity and care requirements related to this last stage of the disease

(Parkinson's Foundation, n.d.; Cherney, 2021; Dementech Neurosciences, 2022; Braak and Ghebremedhin, 2004)

MDS-UPDRS Scale

The MDS-UPDRS scale is used to determine the severity of the symptoms of Parkinson's and evaluate the effectiveness of different treatments. This widely used scale due to its reliability, validity and sensitivity to change, adopts a 5 point like system in which higher scores naturally indicate an increased severity. It has been further divided into 4 sections, each showing a distinct aspect of Parkinson's such as mentation, behaviour and mood in part 1 while complications of therapy in part 4 (Holden S.K. et al, 2018). This is then extended and modified by the Hoehn and Yahr scale and Schwab and England ADL scale (Physiopedia contributors, 2021). The Hoehn and the Yahr scale consist of stages 1 (unilateral) to 5 (bed ridden) to help determine the severity and the progression of the disease with time as it "evaluates clinical function combining disability and impairment" García-Casares et al., 2018).

Existing Debate

The integration of music therapy in the treatment of Parkinson's remains controversial. Proponents strongly favour the inclusion of RAS, stating its role in improving cognitive performance (Mahendran et al, 2018), alleviating the psychological symptoms of Parkinson's - such as relieving anxiety and depression- and therefore, improving the overall quality of life for the individuals. Various research led by many prominent institutions such as Abertay University (2023), NHS and University of Toronto (2018) suggest the importance of incorporating expressive therapy and RAS because it enhances motor function with inventive and rhythmic motions. Levodopa brings about a series of side effects and raises controversies over appropriate dosage and safety. (Parkinson's UK, n.d.)

On the other hand, critics raise doubts about the validity of the empirical data and scientific methodology underlying these treatments. Although RAS comes with numerous benefits, multiple drawbacks and issues shadow it. In addition, due to the lack of empirical data, standardised protocols and financial constraints, there are disagreements over whether it is feasible and accessible to incorporate these therapies into the treatment plan. The curation of the treatment plan must also consider the patient's preferences and the stage they are in. This further complicates the treatment plan as it must be changed constantly. On the other hand, levodopa is a targeted medicine towards Parkinson's, meaning that it can certainly improve the symptoms, but it includes multiple challenges and its side effects can drastically impact the subject.

5. Discussion

Music Therapy

Interaction between the parts of the brain and music therapy

It is vital to know how music affects different parts of the brain and its interaction in the world of neurology. This would help the reader understand how music therapy works in patients with Parkinson's Disease (can also be written as PD) and its effect on symptoms of Parkinson's.

The two regions- basal ganglia-thalamo motor cortices and the cerebellar-thalamo motor cortices- near the basal ganglion are networks that are responsible for movement, but interestingly, are also connected with the auditory cortex. These two regions work simultaneously to coordinate movement and focus on time intervals. The basal ganglia-thalamo motor cortices (consists of the basal ganglia, premotor cortex, supplementary motor cortex and cerebellum (Nombela et al., 2013) is the explicit neural circuit and it is dependent on the internal perception of time. The internal perception of time refers to the comparison made between a previously memorised standard time and intervals between events. In simpler words, this allows the subject to roughly estimate the current time based on the duration of events that previously took place. The cerebellar-thalamo motor cortices (majorly sustained by the cerebellum), however, is an intrinsic neural circuit, in which time is tracked based on external stimuli and coordinating movement to sound. (Herbst, Obleser and Vassenhove, 2022). This dissertation focuses on RAS which is significantly involved with the cerebellar-thalmo-motor-cortices.

With music therapy, the sensorimotor network is also involved. The sensorimotor network is the integration of motor signals with sensory information such as music to generate accurate and coordinated motions (Lynne, 2023). Thanks to the basal ganglia, it allows one to internally create a beat and sequence rhythmic events (Grahn 2011) which is otherwise dysfunctional in PD. Additionally connected to sensorimotor linkages, the cerebellum may regulate rhythmic auditory-motor synchronisation by keeping an eye out for patterns and modifying behaviour in response to tempo changes (Nozaradan, et al., 2017). Evidence revealed using "functional magnetic resonance imaging" shows the involvement of several areas of the sensorimotor network (examples are the basal ganglia, supplementary motor areas, and parts of the cerebellum) in auditory rhythm perception which leads to the effect of auditory cueing in movement (Schaefer, 2014).

In Parkinson's, both implicit and explicit timings are compromised to a certain extent, resulting in a range of symptoms including gait issues and imbalance. So, the "internal cue" that coordinates the "loop" cycle between the basal ganglia and supplementary motor area (SMA) is impaired, missing or delayed (Nombela et al., 2013).

What is Rhythmic Auditory Stimulation (RAS) and how does it work?

Music therapy consists of different forms such as rhythmic auditory simulations, vibroacoustic therapy, and melodic intonation therapy. Out of these forms, Rhythmic Auditory Stimulations (RAS) is widely used by therapists and doctors to specifically enhance gait related symptoms or other aspects of movement related to Parkinson's. It can be practised in several different ways including metronome, music and counting (Erra et al., 2019).

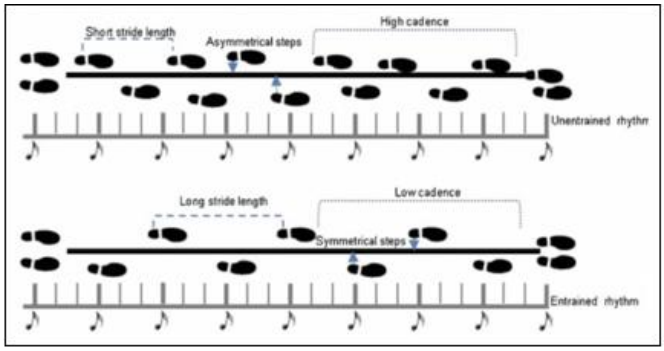
RAS is a therapeutic use of pulsating rhythmic or melodic stimulations that requires the synchronisation of footstep (Mainka et al., 2014), supporting gait initiation and continuation (Bella et al., 2017). There is also a clear connection between auditory signals and motility as mentioned in (Scataglini et al., 2023). According to (Calabrò et al., 2019), giving someone an external rhythmic signal usually makes up for their inability to generate rhythm internally, serving as a replacement. Alternatively, these auditory cues behave as a "pacemaker" and can "recalibrate timing mechanisms and access motor programs" (García-Casares et al., 2018). Overall, this method is deeply dependent on a mechanism called "entrainment", a process of synchronising an external movement rhythm with endogenous beat feelings (Nombela C. et al 2013).

In addition, auditory cues appear to be more effective on motor symptoms of Parkinson's than any other cues like olfactory and visual. Auditory cues have a much shorter reaction time of around 8-10 mm to reach the brain (Jain et al., 2015) because sounds "can directly increase the excitability of the spinal motor neurons, thereby reducing the time required for the muscle to respond to a given motor command" (Nombela et al., 2013). This suggests that the subject will be able to quickly react to the auditory cue and should ideally be able to synchronise their gait as well. Furthermore, unlike other sensory systems, the auditory system is predisposed to identify "temporal periodicity" and "structural patterns", therefore the incorporation of RAS has a greater effect on gait (Nombela et al., 2013; García-Casares et al., 2018; and Erra et al., 2019)

Advantages of RAS

RAS mainly works with the intrinsic neural circuit and gait which is one of the prominent symptoms of Parkinson's that is also considered to be intrinsically rhythmical (Nombela C. et al 2013).

Benoit et al. (2014), wang et al. (2022) and Bella et al. (2017) proposes that auditory simulations might improve motor difficulties by reinforcing the remaining activity of the two areas (basal ganglia-thalamo motor cortices and the cerebellar-thalamo motor cortices) and strengthening the cortical basal ganglia network. This then potentially aids to reestablish the dopaminergic stimulation that has been lost (Cock et al., 2018) Rhythmic music also "increases the connectivity between premotor and auditory areas", stimulating the sensorimotor network activity and enhancing gait (Grahn and Rowe, 2009). According to (Nombela et al., 2013), they achieve gait improvements by reducing the fluctuations in neurological functions over time (also known as temporal variability) and enhancing the symmetry of muscle activation in the arms and legs, which then leads to more steady walking (Chu et al., 2023).



As mentioned before, RAS is said to significantly improve gait related symptoms. The beats produced by the music provide temporal information, resulting in temporal processing. The "entrainment of gait to the rhythmic beat" (Nombela et al., 2013) improves gait related symptoms including lower cadence, symmetrical steps and longer stride length.

This dissertation will examine one of the clinical trials conducted to test the patient outcome of RAS. According to Benoit et al (2014), RAS has effects beyond motor symptoms, affecting the perceptual timings of the 15 IPD (idiopathic parkinson's disease) patients over the course of a 1-month training program. Through training, patients have the capacity to adapt to durational variations in a sequence during hand tapping activities and perform better on tasks requiring synchronisation with isochronous sequences. This suggests that RAS has the ability to enhance motor timing skills in several non-gait tasks evaluated by the UPDRS scale, concluding that Parkinson's patients depend on a brain network which is involved in both perceptual and motor timings.

Eventually, even though the beat is first produced by the auditory input, rhythm may also cause an internally created sensation of beat as it coordinates with the basal ganglia. Once the pattern is formed, the listener can continue to perceive it even after the rhythm stops, and their gait may restabilize (Nombela et al., 2013). This results in RAS having long lasting effects on the gait, even when it has been stopped.

Furthermore, correlation of psychology with music advocates satisfaction and motivation derived from actions stimulates the mesolimbic dopaminergic pathway (García-Casares et al., 2018). Therefore, an emotional response to music therapy activates this brain network (cortex and basal ganglia), leading to improved mental health and motivation. However, other expressive treatments such as dance and music and certain lifestyle activities such as exercise can also stimulate an emotional response, activating the cortical-basal ganglia network. This suggests that RAS is not the only alternative to stimulate an emotional response in the subject.

Disadvantages of RAS

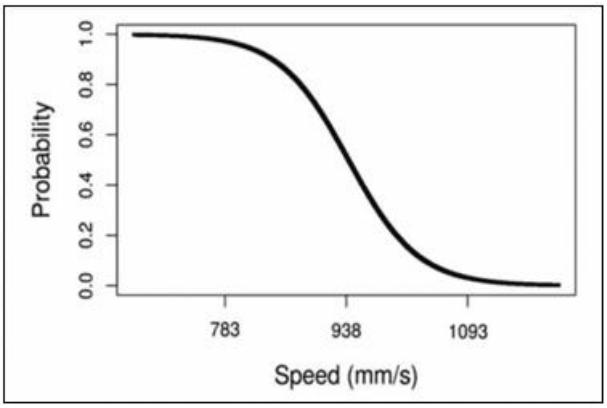
Although RAS serves to be extremely beneficial in improving gait kinematics and related symptoms, it must be implemented with precision and care.

Having perceptual skills and some musical experience, which is either self-assessed or musically trained, may be beneficial as it serves to be a neuroprotector. But this leaves out the vulnerable patients who are unable to appreciate music or haven't received music in the past. Also, poor motivation and mental health can hinder the beneficial impact, diluting the effectiveness of RAS. Although music is a stimulant that motivates people as it activates the dopaminergic system, engages emotions, and stimulates the reward system, it may not apply to all individuals (Bella et al., 2017)

Bella et al. (2017) and Nombela et al. (2013) states that the degree to which RAS enhances or deteriorates motor function may differ depending on the person's rhythmic aptitude and their emotional state. These factors are further emphasised by the variation of sensorimotor skills within the individuals of the population, explaining why ultimately only a small group can benefit from RAS (Bella et al., 2017). The subject must synchronise their gait with the rhythmic beat to mitigate the increased probability of negative consequences (Ashoori et al., 2015). Failure to do so due to several reasons including struggle with beat perception or lack of instructions can result in adverse effects such as decreased gait speed and stride length, and increased risk of dependence and falls (Bella et al., 2017). Other reasons for synchronisation failure may be due to increased cognitive workload as their attention is severely diverted by external tactile stimuli or the subjects are listening to music with no fixed metre, rhythm or rate (Brown et al., 2009), making it hard to focus.

For example, 4 various studies conducted by Olmo et al (2005), Bella et al (2015), Brown et al (2010) and Hwang et al (2009) have explored that following music therapy, participants either did not improve or performed worse with reference to gait. This could be due to reduced temporal stability when walking, inaccurate finger tapping along with isochronous sequence to test motor timings, reduced speeds when crossing obstacles while enjoying music, and decrease in upper limb functional task performance respectively- all these tests are accompanied with auditory cues. Furthermore, Bella et al. (2017) concludes that although people who benefitted from RAS showed an improvement in gait, they eventually demonstrated a lower cognitive flexibility compared to the control group and other patients with PD.

Also, patients with more severe symptoms may benefit more from RAS as they experience an extensive stride length decrease (Willems et al., 2006). This is further backed up by studies conducted by Aries and Cudeiro in 2010 and 2008 in which patients who were on stage 3 of the H&Y scale performed better - showing fewer and shorter freezing episodes post simulations - than subjects with a lower UPDRS score. It ultimately suggests that practising RAS at early stages have minimal effects as opposed to later stages. It indicates that RAS doesn't serve as a preventative measure in delaying deterioration in early stages, rather lingers the subject at stage 3 or 4, making it an unideal practice. Bella et al. (2017), however, contradicts with the idea that patients with greater impairments have a greater scope for improvement and exhibit greater progress because the ones at an earlier stage were able to demonstrate greater accuracy from the very beginning.



In addition, auditory cues/ metronome beats must be catered to the subject's baseline cadency. For example, auditory cues that were presented to be 20% slower than the preferred gait resulted in reduced "temporal stability" in both control and PD (Nombela et al., 2013). Also, extreme ends of the beat - being too low at around 60 bpm or too high at 150 bpm - can potentially decrease stride length and gait cadency. This claim is further emphasised by the graph from (Bella et al., 2017) in which increasing speed resulted in decreased probability of success because these weren't suitable walking speeds.

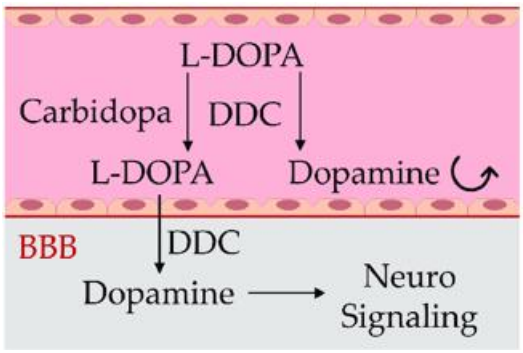
Overall, RAS can only improve gait kinematics and related symptoms. It has little or no effect on other prominent symptoms of Parkinson's such as muscle stiffness, tremors, speech and poor cognitivity. A combination of other alternatives of music therapy such as melodic intonation therapy or therapies from a different domain such as dance or ozone can have a greater impact on the symptoms of Parkinson's (Jola et al., 2022 and Algin et al., 2023).

Medication

What is Levodopa and how does it work?

This chemical building block, levodopa, (Parkinson's UK n.d.), is a naturally occurring amino acid (ACS, 2009) that belongs to the class of large neutral amino acids (LNAA) (Contin and Martinelli, 2010). Therefore, it competes with other protein molecules for absorption into the small intestine (The Michael J. Fox Foundation, n.d.). This is commonly used as a "metabolic precursor of dopamine" and is a "derivative of phenylalanine" (LiverTox, 2012) to treat "bradykinetic" levodopa symptoms or related symptoms of Parkinson's.

Its dosage is generally increased when it becomes too "difficult to control with other antiparkinsonism drugs" (Gandhi and Saadabadi, 2023) but it's also dependent on clinical response and tolerance (LiverTox, 2012) Also, it can be administered in several ways such as oral inhalation and oral infusion- each type having its own benefits and limitations (Thirunavukarasu et al., 2023).



As an overview, according to NHS (2022), levodopa can be converted into the neurotransmitter dopamine in both the CNS (brain and spinal cord) and peripheral organs (Bandopadhyay et al., 2022) after being absorbed by the nerve cells (Gandhi and Saadabadi, 2023). Metabolization takes place with the aid of aromatic L-amino-acid decarboxylase (also known as DDC) which is present in the peripheral blood stream and the brain. However, it is vital for metabolization to occur in the brain to maximise dopamine yield in the substantia nigra and reduce symptoms of Parkinson's. Therefore, carbidopa, an enzyme inhibitor, is additionally administered with levodopa to minimise peripheral metabolization.

Numerous studies have been biassed towards the effectiveness of levodopa, taking a strong stance either against or for it.

Advantages of Levodopa

Unlike RAS, levodopa has been clinically tested and has empirical data, making it one of the most reliable medications to be used to treat symptoms of Parkinson's. The human body naturally produces dopamine and taking it as medication increases the amount available to the nerve cells, prompting them to produce more of it.

For instance, a clinical study conducted by Fahn et al. (2005) accounts for the effectiveness of levodopa. This investigation demonstrated that levodopa at all dosages showed clinical improvements in the UPDRS score. In the end, levodopa not only successfully and dose-dependently improved the symptoms of PD, but the results also lend credence to the theory that the medication may slow down the illness's progression rather than accelerate it. Therefore, many doctors strongly prescribe levodopa to their patients with Parkinson's, irrespective of the stage they are in. An example of this was Dr Arun Saroha, a neurologist in Medanta Hospital in New Delhi, and his strong opinion towards RAS and levodopa. Upon asking him the EPQ question, "Can music therapy (Rhythmic Auditory Stimulations) completely replace the conventional medicine (Levodopa) used to treat all the symptoms of Parkinson's disease and delay its deterioration?", Dr Saroha strongly opposed RAS and stated that this method is only suitable for a very small group of people. He affirmed that as a doctor, you can't pressure your patients to do something they don't like considering that they are already sick. "We need to prescribe levodopa because it has been clinically tested over several phases and approximately 95% of the time, it relieves Parkinson's symptoms", he added. He also expressed his sheer opposition

to RAS, suggesting that it leads to a higher frequency of falls and always requires assistance.

Furthermore, a common notion rises in terms of the body's ability to become resistant to levodopa, thereby reducing its effect. However, according to (Parkinson's UK n.d.), the brain won't become resistant to this drug due to its composition so it can be administered for a long time and still be effective. Other studies, for instance (Shaw et al. 1980), mentions the effect of levodopa to diminish over time in some patients, particularly after 6 years, but at the same time, this medication has significantly decreased mortality rate in those who were able to sustain its effect for a longer period.

Disadvantages of Levodopa

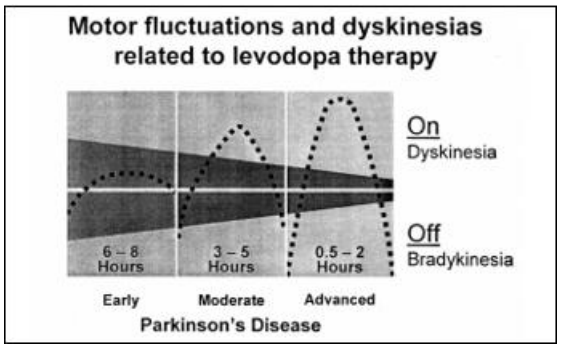
Although levodopa is a targeted drug towards solely reducing the symptoms of Parkisnon's to allow the subject to carry out daily tasks with minimum difficulties, it comes with numerous challenges. In fact, its side effects may be more problematic than the symptoms of PD itself, it may be toxic to aminergic neurons and aren't suitable for all patients

The side effects of levodopa to the human body could be acute which is peripheral such as nausea and tachycardia or it could be chronic which is central such as hallucination, psychiatric problems and involuntary movements like dyskinesia (NHS, 2022 and Jankovic 2002). Apart from this, there is also a risk for the development of melanoma, but many studies oppose this statement which will later be discussed in this dissertation. There are also gastrointestinal issues, but this could be controlled by "titrating the dose" (Jankovic 2002). Furthermore, occurrence of somnolence as a side effect requires levodopa to be discontinued in patients who already experience excessive sleepiness (Gandhi and Saadabadi, 2023). Some individuals may also develop sensorimotor peripheral neuropathy, which manifests as distal weakness or numbness in the fingers and feet (Mascarenhas and Jude, 2013).

Dyskinesia is one of the major side effects of levodopa. These involuntary movements cause uncontrollable, strange, jerky movements like twisting, twitching, or head bobbing (Rath 2024). These, however, aren't the same as tremors caused by Parkinson's (Parkinson's Foundation, n.d.). In this, either a single body part or the entire body may be affected, causing a continuous sense of restlessness (Rath 2024). The degree of intensity depends on the levodopa dosage and its concentration in blood plasma (Contin and Martinelli, 2010). in which it may vary from almost imperceptible to obvious. Though dyskinesia doesn't develop for everyone who receives levodopa, it's very likely to develop if used for longer than five years (Rath 2024). It can be categorised into 3 major sections: peak dose dyskinesias which happens in 80% of the patients for 20 to 90 minutes post dosage, end of dose dystonia in 20%, and biphasic dyskinesia which consists of two separate bouts of uncontrollable movement in 3% of the patients (Shaw et al. 1980).

Levodopa results in changes in the blood composition while RAS has minimal interaction with the human body, apart from the brain and muscles. Blood reports of patients who consume levodopa show alleviated levels of dopamine, norepinephrine and epinephrine because some levodopa can potentially decarboxylase in the periphery. Moreover, this drug can reduce vitamin B12, alleviate methylmalonic acid levels and increase homocysteine levels which could cause hip fractures (Gandhi and Saadabadi, 2023).

One of the prominent motor fluctuations related to levodopa is called the "wearing off effect". This is associated with the recurrence of Parkinson's symptoms post levodopa consumption, typically 3-4 hours (Liang, 2024), due to end of dose deterioration (Jankovic 2002). To elaborate, this is due to the shortening of levodopa's half-life in the striatum and low levels of levodopa in blood plasma (Contin and Martinelli, 2010).



As seen in the diagram, advanced stages of levodopa result in increased unpredictable "on-off" effect, narrowing the therapeutic window, and resulting in enhanced Parkinson's symptoms plus involuntary movements (ex dyskinesia) (Contin and Martinelli, 2010 and Jankovic 2002)

However, this could be overcome by administering levodopa frequently as suggested by the doctor to give a continuous simulation (Jankovic 2002). Another alternative could be consuming a low protein diet or managing the time of protein intake since levodopa is also an amino acid. This is evident in a study conducted by (Nutt et al., 1984) in which a high protein meal that goes up to 104g paired with levodopa leads to twice the "plasma concentration of LNAAs" (Contin and Martinelli, 2010) and deteriorates levodopa's effect. This eventually reveals "competition at the blood-brain barrier" (Leenders et al., 1986) and prevents maximum levodopa from metabolising in the brain. A high protein meal would also hinder its absorption due increased competition with amino acid transporters whilst causing GI issues (Gandhi and Saadabadi, 2023). Other patients who suffer from unpredictable "off" periods can also adopt a rescue therapy in which subcutaneous injections, inhaled levodopa or sublingual apomorphine are used (Liang, 2024).

Several debates have arisen upon levodopa being either neurotoxic or neuroprotective to the neurons. There have also been varying results in in-vivo (done in living organisms) and in-vitro (done in lab conditions) studies (Eldridge, 2024). While no direct evidence is seen in the neurodegeneration of neurons in in-vivo studies, in vitro studies show the contrary (Jankovic 2002). The in vitro studies are flawed due to reduced levodopa concentration used and the absence of a substantial number of potentially neuroprotective glial cells in comparison to in vivo studies (Simuni and Stern, 1999). Glial cells help neurons communicate between one another, establish the blood brain barrier and regulate inflammation

(Sherrell, 2023). Therefore, it is not possible to apply similar circumstances to three-dimensional brain regions in which protective interactions with the cellular environment aren't prevalent (Agid, 1998). Furthermore, even non-PD individuals who take large doses of levodopa regularly don't exhibit any evidence of neurodegeneration or the development of parkinsonian symptoms. Therefore, clinically or experimentally, levodopa has not demonstrated to hasten neurodegeneration or damage cell function permanently in a way that would have irreversible destructive effects (Agid, 1998). On the other hand, the oxidative process involved in the metabolization of levodopa is affiliated with cell destruction in which the nigrostriatal pathway is damaged, resulting in neurotoxicity (Jenner and Brin, 1998). This is backed by the study (Fahn, 1996). Furthermore, levodopa can produce free radicals of oxygen (Simuni and Stern, 1999) which are reactive species (Jenner and Brin, 1998) that contribute to cell toxicity. Since the dopaminergic neurons in patients are already under oxidative stress as part of PD's degenerative process, additional oxygen radicals would enhance the death of these neurons (Jenner and Brin, 1998).

Apart from this, the subject's medical history can have significant impacts on them as they consume levodopa. Therefore, a large group of patients must consume levodopa with caution and care. For instance, ocular pressure, GI bleeds and psychosis risk increases with patients who suffer from narrow-angle glaucoma, history of peptic ulcer disease and psychotic disorders respectively. Extreme care must also be taken by individuals who already suffer from atrial nodal or ventricular arrhythmias (Gandhi and Saadabadi, 2023). Furthermore, it is believed that patients with a history of malignant melanoma have a positive correlation with the risk of activating melanoma. However, studies like (UCLAHealth, 2021). shows that PD itself is positively correlated with melanoma - further studies, however, remains lacking.

RAS and Levodopa- a summary

The next 2 parts would compare RAS and levodopa, emphasising on how they are so different yet similar.

Differences

Overall, RAS employs the intrinsic neural system (Herbst, 2022) to synchronise the subject's footfall with the beat. It achieves its purpose by activating muscles and boosting the dopaminergic pathway (Bella et al., 2017), whilst levodopa works by passing through the blood-brain barrier, going through decarboxylation and maximising dopamine levels in the brain with the help of COMT/MAO (LiverTox, 2012).

Levodopa dose is determined by clinical response and tolerance (LiverTox, 2012), whereas RAS is mostly reliant on the entrainment mechanism (Nombela et al., 2013). Furthermore, while RAS appears to be more beneficial at later stages, levodopa is effective throughout.

In terms of symptoms, RAS appears to have a significant impact on motor symptoms, particularly balance and gait with reference to stride length, pace, cadence and stability (Erra et al., 2019). Levodopa, meanwhile, takes a holistic approach and helps with tremors and stiffness in the muscles. Therefore, while RAS just focuses on gait, levodopa's overall aim is to allow individuals to carry out daily tasks with minimum hindrance.

However, levodopa has much more adverse effects than RAS, including dyskinesia, nausea, changes in blood composition, and the possibility of neurotoxicity (Medlineplus, 2022). It can also instil psychiatric issues like psychosis, impulsivity and rapid fluctuations between mood states (Taylor et al., 2016). Meanwhile, RAS has a contrasting effect, in which it can elicit an emotional response to enhance mental health. Although RAS has better side effects, it is a much more intensive process as it can induce exhaustion and potentially diminish cognitive thinking skills (Gonzalez-Hoelling et al., 2021).

Levodopa has sufficient scientific evidence supported by empirical data to back up its efficacy while RAS is still under research and doesn't assure symptom relief. Evidently, levodopa has higher chances of showing improvements in subjects than RAS.

Similarities

Although levodopa and RAS are extremely distinct, they share some similarities.

They both have certain requirements to create maximum benefit on the subject. RAS, for instance, requires the subject to appreciate music, be determined, successfully synchronise their footsteps and the cadence of the beat must be catered to the subject's walking speed (Bella et al., 2017). Levodopa, like any other drug, needs to be administered whilst considering the subject's medical history, protein intake and lifestyle (Gandhi and Saadabadi, 2023 and Contin and Martinelli, 2010). Therefore, they are both not suitable for all patients.

In addition, although they both interact in different ways, they both include the involvement of the sensorimotor network.

Research has also shown that both levodopa and RAS cannot possibly slow the progression of Parkinson's, they can only reduce the intensity of the symptoms (Parkinson's UK, n.d.)

6. Conclusion

In conclusion, the best patient outcome emerges with a multidisciplinary approach in which both RAS and levodopa are implemented together.

Levodopa is a necessary component of the treatment plan because it addresses a large spectrum of symptoms - both motor and non-motor - while RAS primarily targets gait-related aspects. It is a clinically endorsed medication with well-established efficacy and therefore is administered to 94.2% of Parkinson's patients (Mitkova et al., 2021). Exceptions, however, can be made based on a patient's medical history such as psychiatric conditions and skin lesions which can activate melanoma. If levodopa is being administered, it is imperative to also include COMT or MAO-B into the treatment regime to optimise its efficacy.

This dissertation also proposes that RAS should be included in the treatment plan due to its minimal side effects and potential to improve gait related symptoms if implemented

correctly. Otherwise, discontinuation is necessary as it can induce counterproductive outcomes. Even though there is limited information on how RAS works, several studies have demonstrated positive results. However, Parkinson's stage, individual preferences and consistency need to be considered which may limit the appliance of RAS.

Further areas of research for this dissertation involve the implementation of a large-scale clinical trial to examine the long-term effects of RAS and levodopa. Now, there is minimal information on the effect of levodopa and RAS on the rate of progression of the disease. Specific clinical trials are also necessary to determine whether levodopa is neurotoxic, but it remains unconfirmed. Additionally, RAS require relatively intact sensorimotor timing skills and the optimal conditions for maximum efficacy hasn't been studied much yet either.

Overall, this dissertation suggests that though levodopa is associated with a wide range of adverse effects, RAS is inadequate in substituting levodopa to treat all the Parkinson's symptoms.

7. Evaluation

The aim of this project was to determine the efficacy of Rhythmic Auditory Stimulations (RAS) and evaluate its potential to completely substitute levodopa. This was achieved by examining the respective advantages and the disadvantages of both the treatment options. Upon finishing this dissertation, I am content with the outcome; nevertheless, I believe my question is still partially open due to the lack of information about RAS's and levodopa's ability to delay the disease's deterioration.

I am pleased that I was able to find many sources which spoke about RAS, levodopa and Parkinson's, ensuring accurate and reliable information in my dissertation. Since a lot of the information in these sources were identical, I decided not to spend extensive time in each source, instead, adopt a methodology of skim reading and highlighting otherwise helpful information. Additionally, the main sources I used were mainly written or reviewed by MD's and were well-cited, allowing extensive cross-referencing and adding to the validity of the information presented. However, determining and using the most relevant sources in context for my EPQ posed to be extremely challenging because many either weren't specific or too detailed. In addition, as I reviewed through multiple sources over time, I was able to eventually successfully evaluate the most reliable sources through CRAAP analysis, thus strengthening my critical thinking skills and the ability to find the most relevant sources. Another significant weakness was the synthesis of information across the three different domains (neurology, pharmaceutics and music) in my own words and minimise the reliance on quotation marks as the information presented in many sources were extremely detailed, complicated and full of jargon.

During the research process, although I spent a lot of time formulating a research question which I'm deeply motivated about, it significantly compromised my commitment in following the time management plan. This further aggravated as I underestimated the complexity of the topic, after all, I am only a sixth form student, and I was dealing with information which was targeted towards undergraduates and educators. Therefore, I spent a significantly large proportion of my time reading widely about my question. Though this wasn't unproductive, I could have spent a lot of my time looking for sources on levodopa and reading more books which is otherwise a very time-consuming process. I also managed to extensively conduct secondary research, encompassing a variety of sources including books, journal articles and websites, thereby enhancing my research and critical thinking skills. However, a heavy reliance on secondary sources may have resulted in unreliability and the sources may not capture the complexity of my EPQ. Furthermore, I gathered some primary information through an interview with a neurologist, getting an insight regarding his opinion towards RAS and Levodopa for Parkinson's. Since my consultation was limited to a single neurologist, it may have introduced bias toward levodopa. To mitigate this, I could have also spoken to more neurologists, institutions specialising in RAS and care homes for Parkinson's patients to get a comprehensive understanding into patient lifestyles. However, even if I was able to do this given that I had a wider time frame and resources, my lack of experience and expertise may have resulted in inaccurate answers.

Time management emerged as a notable weakness for me. I would frequently set unrealistic and ambitious deadlines without considering external commitments beyond EPQ, leading to disappointment as I failed to meet them. Given that this was my first, independently led project, this issue can be attributed due to my inability to accurately predict the duration of certain activities such as reading a source or writing a paragraph on a subtopic. Eventually, these missed deadlines accumulated towards the end of the first draft, resulting in insufficient time and substantial amount of work. Consequently, I adopted a strategy to set smaller, incremental deadlines that would collectively add up to a larger goal. Post Easter, I effectively distributed my time, mindfully planning, considering all future commitments and ensuring that I have extra time ahead for potential contingencies. If I were to repeat the process, I would also make a risk assessment to identify potential setbacks such as missed deadlines, unable to find a source, or comprehending complex information. In this risk assessment, I would also incorporate the underlying reasons, strategies to mitigate this and a plan of action if these issues arise.

After finishing this research project, I am more certain about the treatment plans and the potential to incorporate RAS. Scientific information is extremely dynamic due to continual technological advancement and emergence of new findings; therefore, I am extremely curious to know how the research changes.

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