Deep Brain Stimulation, physical activity, and exercise as viable interventions for the motor symptoms of Parkinson's disease patients

In what way are Deep Brain Stimulation, exercise, and physical activity viable interventions for Parkinson's disease?

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Summary

The main cause of neurodegenerative disorders, such as Parkinson's disease, is ageing. It is known the quality of life of Parkinson's patients' decreases, among others because of the displayed motor symptoms. The reduction of dopaminergic neurons and the growth of intracellular inclusions are pathological characteristics of the disease. Neuroinflammation is among other things a contributor to the development of those characteristics, with α-synuclein having an important role. The displayed symptoms are not consistent for all individuals leading to irregular treatment patterns. To improve the health-related quality of life different interventions, pharmacological as well as non-pharmacological, are applicable. The influence of different interventions varies. For that reason, this research paper focuses on Deep Brain Stimulation, exercise, and physical activity specifically as interventions for motor symptoms of Parkinson's disease. Deep Brain Stimulation is the stimulation of deep brain nuclei with the use of electrodes. Performing this surgery on the subthalamic nucleus and the globus pallidus internus illustrates the improvement of the overall motor function and thereby an improvement in the quality of life. Stimulation of the globus pallidus internus indicates improvements for the motor symptom dyskinesia in particular. The concept of exercise falls within the definition of physical activity. It is important to prevent adjusting to a sedentary lifestyle since this contributes to a decreased quality of life. The synthesis of dopamine by neurons is stimulated by exercise, consecutively this delays the progressive nature of the neurodegenerative disease. Additionally, neuroinflammation can be repressed by exercise and treadmill training is applicable as an intervention for the disruption of gait. Altogether, the mentioned interventions can be applied to diminish the motor symptoms of Parkinson's patients improving the health-related quality of life.

Preface

In general, neurodegenerative disorders have my interest since I find it intriguing how the brain is affected during the process of ageing. Although the precise cause of the majority of neurodegenerative disorders is generally not known, the effects are clearly visible over time. During the second year of my studies, I followed the courses 'Neurobiology of Aging' and 'Integrative Neurobiology'. These two courses were the main reason to spark my interest in ageing and associated neurodegenerative disorders since the lectures were very intriguing. Because of the course 'Medical Cell Biology', which I followed only a few months ago, my interest in neurodegenerative disorders was encouraged again and thereby my interest increased even more. Fancying a topic considerably makes studying easier. Learning more about these disorders made me find out that Parkinson's disease was my main interest as this disease runs in the family as well. Therefore, after discussing possible topics with my thesis supervisor, Eddy van der Zee, we decided that Parkinson's disease would be the appropriate topic for my thesis. I am eager to learn more about the mechanisms behind the disease, what medicines can be applied, and how to prevent Parkinson's disease. To be more specific, learning what interventions can be applied to Parkinson's diseases sparks my interest and I am enthusiastic about researching this topic.

I wish you a good and educational time reading this thesis!

18 June 2021, Groningen

Marlin Leemhuis

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1. Introduction

1.1. Parkinson's disease

The most frequently occurring neurodegenerative diseases are Parkinson's disease and Alzheimer’s disease, with the latter being the most prevalent (Hou et al., 2019). In general, neurodegenerative diseases affect the quality of life. The symptoms of both Parkinson's and Alzheimer’s disease progressively worsen over time and the prevalence of both diseases grows with age. Consequently, the incidence of the disorders is higher in the elderly compared to the younger part of society. Ageing is known to be a risk factor in the development of neurodegenerative diseases. The intriguing thing about ageing is that individuals age differently, both within species as between different species (Carmona & Michan, 2016). Brain tissues of the human elderly contain aggregates of certain proteins, like misfolded and damaged proteins.

This research paper focuses on the diminishing of the motor symptoms caused by Parkinson's disease. Parkinson's disease is the second most common neurodegenerative disorder, with intracellular inclusions including α-synuclein aggregates as one of the hallmarks (Hou et al., 2019). Another hallmark is a neuronal loss in, amongst others, the substantia nigra. Additionally, the neuromuscular dysfunction that influences the motor system belongs to the diagnostic characteristics. In particular, the motor systems of patients with Parkinson's disease can be affected concerning the patient’s rest tremor, rigidness, and/or the amplitude and the speed of movement. Symptoms that are non-motor related may vary, from cognitive dysfunction to depression (Speelman et al., 2011). Taking both motor and non-motor abnormalities into consideration, patients show a variety of progressive symptoms. Consequently, the symptoms contribute to patients adapting to a sedentary lifestyle, which is plausibly a reaction to prevent additional difficulties. A sedentary lifestyle, however, is comprehensively one of the foremost causes of deaths (Marcus et al., 2006). Accordingly, it is of importance to intervene in the symptoms patients with Parkinson's disease display.

Different types of interventions, both pharmacological as well as non-pharmacological, are meant to stabilize the displayed symptoms and thereby improve the patients’ quality of life (Speelman et al., 2011). In particular, the interventions aim to treat the symptoms, but not to counter neurodegeneration (Balestrino & Schapira, 2019). Sufficient control of symptoms by means of pharmacological treatments is observed in the initial stages of the disease. The most effective drug for treating the decreased motor function in Parkinson’s disease is levodopa (Fox et al., 2018). The effects of the drug on motor symptoms are substantial compared to the placebo group. Notwithstanding, the probability of developing resistance to levodopa exists. Given the resistance development, the dysfunction of the patients’ increases in later stages (Balestrino & Schapira, 2019). Considering the functioning of pharmacological treatments for Parkinson's disease in the long term is limited, this thesis discusses several interventions. In particular, interventions focusing on the lessening of the displayed motor symptoms by Parkinson's patients since the outcome of these intercessions is substantial. Specifically, the benefits of the interventions Deep Brain Stimulation, physical activity, and exercise on motor symptoms will be discussed.

1.2. Deep Brain Stimulation

Deep Brain Stimulation is an intervention that can be used for diminishing the motor symptoms of Parkinson's disease (Balestrino & Schapira, 2019). The intervention is used to treat advanced Parkinson's disease by supplying electrical impulses to particular brain areas. This is specifically done bilaterally to the subthalamic nucleus, the thalamus, or the globus pallidus internus.

The procedure proficiently controls motor symptoms of Parkinson's disease patients. Therefore, a reduction in drug intake is possible.

The procedure is performed via surgery, at which the patients are usually awake to map the anatomical target (Kochanski & Sani, 2018). Microelectrode recording is used to visualize the borders of the deep brain nuclei. Side effects can arise during the surgery which can cause psychiatric symptoms and cognitive deterioration but also demolishes the ability to respond to medicine like levodopa (Balestrino & Schapira, 2019). To determine what kind of intervention is best, the Deep Brain Stimulation of different brain areas will be discussed.

1.3. Physical activity and exercise

In addition to Deep Brain Stimulation, physical activity and exercise are interventions practicable for diminishing Parkinson's patient's motor symptoms. It is of importance to mention that the definitions of physical activity and exercise differ (Caspersen et al., 1985). The definition of physical activity is defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (Caspersen et al., 1985, p. 126). Thus, the movements by skeletal muscles executed voluntarily, or impulsively, belong to the definition of physical activity. Exercise belongs to the category of physical activity and has the characteristics that the activity is planned and done on purpose. In general, exercise is also repeated and systematic, this can for example be done to maintain or improve certain performances. Both physical activity and exercise have multiple possible health benefits, for health in general as well as for the symptom diminishing of Parkinson's patients (Speelman et al., 2011).

Patients experiencing Parkinson's disease continuously struggle with physical performance since there is a constant decline of motor functions, for example, a decline in keeping balance, body posture, and walking. These declined motor functions, together with the overall physical functioning, condition, and strength of the legs, could improve with physical activity and exercise. Exercise has multiple possible benefits for Parkinson's disease patients as well, with regards to motor function and non-motor functions. Namely, exercise may prevent depression and cardiovascular complications (Speelman et al., 2011). Moreover, it may improve drug efficacy, functional motor performance, cognitive function, and sleep. Keeping in mind that ageing will not be stopped by any form of physical activity, research demonstrated that exercise diminishes the physical effects of a sedentary lifestyle (Chodzko-Zajko et al., 2009). Additionally, physical activity curbs the progression of chronic diseases and thereby extends the expectancy of life. It is of importance to keep in mind to which extent physical activity and exercise differ, the comparison of various protocols should happen in an equal manner to prevent the comparison of different methods.

1.4. Thesis set-up

The interference of the motor symptoms of Parkinson's disease patients is of importance to prevent adaptation to a sedentary lifestyle. Therefore, the main question of this thesis is "*In what way are Deep Brain Stimulation, exercise, and physical activity viable interventions for Parkinson's disease?*". The interventions are meant to diminish the progressive nature of the motor symptoms.

The thesis is divided into different categories. First, the mechanism of Parkinson's disease will be discussed. Secondly, the different interventions will be discussed in detail, by comparing different conducted researches. Finally, a conclusion and a discussion will consider which treatments are applicable to Parkinson's disease patients for the treatment of motor symptoms and which interventions should be examined more.

2. Materials & methods

By searching through different databases literature research was conducted. SmartCat and Google Scholar were used to find scientific articles about the concepts ‘Parkinson's disease’ and ‘interventions’. As a result, knowledge was gained about different possible interventions to decrease the consequences of the symptoms of Parkinson's disease. This knowledge was converged to interventions that have the intention to prevent and diminish the progressive nature of the motor symptoms. Consequently, the subject of this thesis was generated. Accordingly, the terms ‘Deep Brain Stimulation’, ‘physical activity’, and ‘exercise’ were added separately to ‘Parkinson's disease’ in the literature search. The term ‘Parkinson's disease’ was consistently mentioned in searches, combined with the other concepts.

Different results from this article search were used for the in-depth concept of Parkinson’s disease. Additionally, a few findings were used as handholds for the comprehensive concepts of the mentioned interventions. Various results could be used, however, often the results of the search were not sufficiently comprehensive or the focus was on different clinical aspects. For these reasons, articles focusing on the proper aspects were utilized. The articles used mainly were:

- Balestrino and Schapira (2019);
- Fox et al. (2018);
- Krack et al. (2019);
- Ramirez-Zamora and Ostrem (2018);
- Schapira et al. (2017); and
- Speelman et al. (2011).

Supplementary articles were used to elaborate on different concepts. For example, the study of Caspersen et al. (1985) was used to clarify the difference between the definitions of 'exercise’ and ‘physical activity’. The articles used for Deep Brain Stimulation performed on the subthalamic nucleus and globus pallidus internus were:

- Balestrino & Schapira (2019);
- Deuschl et al. (2013);
- Odekerken et al. (2013);
- Ramirez-Zamora & Ostrem (2018);
- Weaver et al. (2012); and
- Limousin and Foltynie (2019).

These articles comprehensively gave information about the stimulation of those specific brain areas. For exercise and physical activity the used studies:

- Bello et al. (2013);
- Fernández-del-Olmo et al. (2014);
- Lau et al. (2011);
- Nadeau et al. (2014); and
- Zoladz et al. (2014).

The three articles used for the comparison of treadmill training as an intervention for gait disturbances were Bello et al. (2013), Fernández-del-Olmo et al. (2014), and Nadeau et al. (2014). More studies regarding treadmill training are available but these did not comprise similar applied protocols. With attention to comparing articles with an equivalent applied method, these three studies were chosen.

3. Results

3.1. Parkinson's disease

In industrialized countries, the prevalence of Parkinson's disease is 0.3% in the general population, with ageing as the most common cause of the disorder (Lee & Gilbert, 2016). The prevalence of Parkinson's disease in the population aged above 60 years and 80 years was 1.0% and 3.0% respectively. Sex differences are another factor playing a role in developing Parkinson's disease, where males have an increased risk of developing the disease compared to females (Gillies et al., 2014). Parkinson's disease can be inherited and has been reported to be responsible for 5-15% of all Parkinson's cases (Gasser, 1998). Additionally, it is known that several environmental factors increase the risk of developing Parkinson's disease (Breckenridge et al., 2016). For instance, something related to or the smoking of cigarettes alone could be a cause of the disease development. Deviations like gene mutations or replications could be the cause for the development of Parkinson's disease (Schapira et al., 2017, ch. 5). For instance, this could occur in the genes that code for α-synuclein (SNCA), in the leucine-rich repeat kinase 2 (LRRK2), and in PTEN-induced kinase 1 (PINK1). The function of the α-synuclein protein is not known precisely, but it is recognized that the protein shapes the foundation for pathological aggregates.

Pathological characteristics of Parkinson's disease are the progressive abatement of dopaminergic neurons and the rising of intracellular inclusions, called Lewy Bodies (Balestrino & Schapira, 2019). Lewy Bodies are constituted by more than 90 proteins and are round, eosinophilic, intraneuronal inclusions (Wakabayashi et al., 2012). The main component of Lewy Bodies is α-synuclein. This protein has the potential to create β-sheet-rich amyloid aggregates after it has become misfolded and indissoluble. The β-sheet-rich amyloid aggregates accumulate and thereby constructs intracellular inclusions. Prion-like spreading of α-synuclein throughout the body seems to be the cause of pathological transformations. Lewy Bodies are found post-mortem in parts of the brain that are associated with the symptoms of Parkinson's disease (Schapira et al., 2017, ch. 5).

It is known that neuroinflammation contributes to the progression of Parkinson's disease and leads to neurodegeneration (Hirsch et al., 2012). Importantly, α-synuclein seems to be a key player in neuroinflammation (Schapira et al., 2017, ch. 5). This is due to the fact that the misfolding of the α-synuclein protein triggers the excitation of substances, like cytokines, involved in inflammatory reactions. Besides the Lewy Bodies that contain α-synuclein and the loss of dopaminergic neurons, the atrophy of grey matter is also a neuropathological characteristic of Parkinson's disease (Mak et al., 2013). The impairment of particular cognitive functions is commonly recognized in cases of mild Parkinson's disease, correlated with grey matter atrophy in the concerning brain areas.

As previously mentioned, Parkinson's disease influences the daily life of the patients. Not only the quality of life and the physiological functions decrease, but the healthcare costs increase and the dependence on a carer grows (Schapira et al., 2017, ch. 5). The major motor symptoms associated with Parkinson's disease is the rigidity of muscles, tremors, and alterations in both speech and gait (Hou et al., 2019). In addition, the patients can experience postural instability and abnormalities, but also hypomimia, micrographia, and alterations in blinking and the movement of the eyes (Balestrino & Schapira, 2019). The patients do not have a homogenous set of symptoms (Jankovic et al., 1990). Motor symptoms that the patients' show differs between individuals, varying from the onset and later stages of Parkinson's disease. Therefore, the treatment methodology and the used protocols for treating motor symptoms differ. Several different interventions, namely Deep Brain Stimulation, exercise, and physical activity are discussed below.

3.2. Deep Brain Stimulation

Deep Brain Stimulation is applicable as an intervention for the motor symptoms of Parkinson's disease and is used to improve the patients’ quality of life (Ramirez-Zamora & Ostrem, 2018). Different components contributing to the procedure are of importance for the outcome and the success of the intervention (Balestrino & Schapira, 2019). Specifically of importance are the patient selection, the placement of the electrodes, the setting of the operation, the postoperative surrounding, and the modification of the pharmacological treatment. Deep Brain Stimulation especially affects the tremors of the patients (Fox et al., 2018). Tremor is one of the few motor symptoms that plausibly reacts better to surgery than to pharmacological treatment with levodopa. The surgery is efficacious and clinically useful to suppress the comprehensive framework of motor symptoms. The surgery of Deep Brain Stimulation can be implemented on specific brain areas. Namely, bilateral on the thalamus, the subthalamic nucleus, and the globus pallidus internus. In *Figure 1* the localization of the concerned brain areas is depicted.

The targeted brain area for Deep Brain Stimulation is mainly in accordance with the symptoms the patient displays (Ramirez-Zamora & Ostrem, 2018). Studies use different approaches but it is noticeable some studies utilize control groups and some do not (Deuschl et al., 2013). Taking this into consideration, it is not surprising that studies using a control obtained better results. Nevertheless, the severity of the motor symptoms of Parkinson's patients decreased in all studies. Taking everything into consideration, all studies show an improvement in motor symptoms. For this reason, it is possible to take studies with control groups as well as studies without control groups into consideration. Deep Brain Stimulation performed on the subthalamic nucleus used to be preferred over the globus pallidus internus since less information existed about the latter (Krack et al., 2019). However, both brain areas have been proven to be accessible and clinically available for Parkinson's disease patients (Fox et al., 2018). For this reason, this research paper focuses on the stimulation of these brain areas.

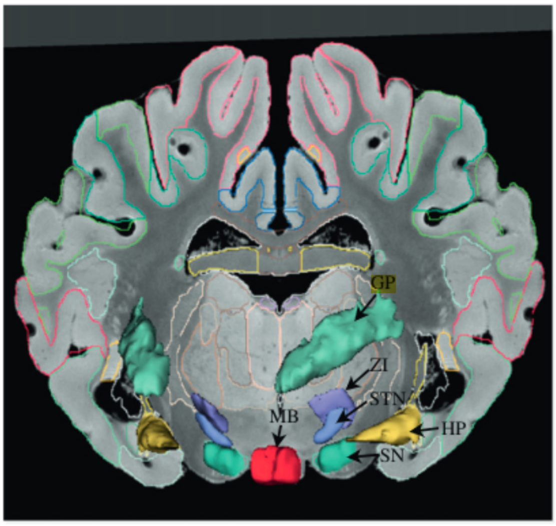

Figure 1 - Atlas-based location of the subthalamic nucleus and globus pallidus in a pig brain (Min et al., 2012). Abbreviations: GP: globus pallidus, HP: hippocampus, MB: mammillary bodies, SN: substantia nigra, STN: Subthalamic nucleus, ZI: zona incerta.

3.2.1. Subthalamic nucleus and globus pallidus internus

Results from Deep Brain Stimulation performed on the subthalamic nucleus show efficient control of the motor symptoms in general (Balestrino & Schapira, 2019). This intervention is for the most part beneficial if a major objective is to reduce the dopaminergic medication (Ramirez-Zamora & Ostrem, 2018). Additionally, with regards to reducing motor symptoms of Parkinson's patients, this intervention may be more beneficial compared to pharmacological treatment since it diminishes motor symptoms and the quality of life related to health improves (Deuschl et al., 2006). The research of Weaver et al. (2012) also showed that stimulation of the subthalamic nucleus improves the overall motor function of Parkinson's patients. The study demonstrated that stimulation of the subthalamic nucleus is capable of contributing to a decrease in the use of medication.

In comparison to Deep Brain Stimulation performed on the subthalamic nucleus, the study of Odekerken et al. (2013) showed that the intervention performed on the globus pallidus internus is more beneficial for patients experiencing severe dyskinesia. These results indicated that a larger part of the individuals that underwent subthalamic nucleus stimulation still display dyskinesia. Deuschl et al. (2013) also demonstrated that the stimulation of the globus pallidus internus results in distinct dyskinesia improvements. Besides, this specific intervention gives the possibility to alter the usage pattern of medication.

Looking in particular at the motor symptom tremor, the outcome of the stimulation of the two brain areas does not differ (Ramirez-Zamora & Ostrem, 2018). Stimulation of both brain areas properly controls tremor. Furthermore, the stimulation of both brain areas improved the patients' overall motor functions (Weaver et al., 2012). Therewith, stimulation of a specific brain area is not important since the benefits of both areas last over 36 months. Deep Brain Stimulation both on the subthalamic nucleus and on the globus pallidus internus has the potential to be a complementary treatment for Parkinson's disease patients (Ramirez-Zamora & Ostrem, 2018). Consequently, different motor symptoms could be addressed. There is not one particular brain area that could be triggered to simultaneously diminish the individual motor symptoms. For this reason, personalized interventions are appealing treatments.

3.2.2. Postoperative

Following Deep Brain Stimulation, neuropsychiatric symptoms may occur (Krack et al., 2019). As a result, it is of importance to monitor the effects of Deep Brain Stimulation. Additionally, it is worth taking long-term effects into account. Limousin and Foltynie (2019) discussed the long term outcomes, concluding Deep Brain Stimulation of the subthalamic nucleus is capable of improving Parkinson's patients' motor function beyond 10 years. Additionally, stimulation of the globus pallidus internus improves dyskinesia of the patients in the long term. However, the results of the intervention differ per individual. The variations in outcome probably depend on the patients' symptoms just before the surgery, the age of the patients, and how the electrodes are positioned during the surgery.

3.3. Physical activity and exercise

As pointed out previously, progressive abatement of dopaminergic neurons and the accumulation of misfolded α-synuclein are two hallmarks of Parkinson's disease (Balestrino & Schapira, 2019). Specifically, dopaminergic neuron loss occurs in the substantia nigra. This degeneration is suggested to cause an increase in oxidative stress which in turn is partly a result of dopamine metabolism and neuroinflammation (Hwang, 2013). Hence, neuroinflammation and dopamine metabolism contribute to the neurodegenerative pathogenesis of Parkinson's.

Exercise is capable of inducing dopamine synthesis by neurons (Monteiro-Junior et al., 2015). The synthesis of dopamine delays the progressive nature of Parkinson's disease symptoms by amongst others inhibiting inflammation. Provided that the synthesis of dopamine is stimulated by exercise this mechanism functionally promotes neuroplasticity. Thus, it is manifested that both physical activity and exercise mitigate neuroinflammation which presents itself in neurological diseases (Spielman et al., 2016). Exercise is beneficial in both healthy and in diseased individuals, this can be seen in *Figure 2*. For Parkinson's patients, an increase in exercise, and thereby an increase in physical activity contributes to a reduced sedentary lifestyle.

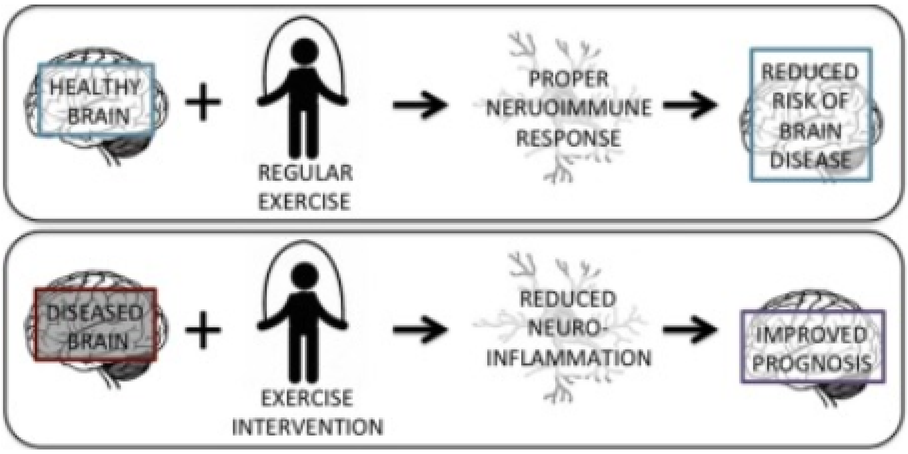

Figure 2 - Graphical abstract from Spielman et al. (2016). Regular exercise in combination with a healthy brain makes a proper neuroimmune response, which leads to a reduced risk of brain disease. Exercise used as an intervention for a diseased brain results in reduced neuroinflammation, which leads to an improved prognosis.

3.3.1 Neuroinflammation

When comparing different studies, the studies should include equally implemented methods. Because of this, it is of importance to compare equivalent applied protocols when looking at physical activity and exercise as interventions for motor symptoms (Fox et al., 2018). On the other hand, corroborating studies with other studies is also a possibility. Animal studies are good alternatives since these models diminish the number of fluctuations in the results (Andersen & Winter, 2019). Since there are similarities in the used environments and due to the fact that animals with an equivalent genetic background can be used, there are lesser result variations.

For instance, Lau et al. (2011) showed the neuroprotective effects of exercise. During this study, different effects of exercise on a chronic mouse model of Parkinson's disease were monitored. In particular, an increase in brain-derived neurotrophic factor (BDNF) was observed. BDNF is a protein that is necessary for neuron survival in the brain (Karamohamed et al., 2005). Additionally, the study of Lau et al. (2011) demonstrated that exercise used as an intervention in the chronic Parkinson's mouse model increased the levels of dopamine in particular parts of the brain in comparison to a mouse model with low activity. Therefore, the alteration of Parkinson's patients' lifestyles with an increased amount of exercise is a plausible non-pharmacological intervention for the neurodegenerative processes.

This animal study can be corroborated by a study performed with humans. Zoladz et al. (2014) showed that moderate-intensity interval training decreased the amount of inflammation in Parkinson's patients. During this research, an 80% increase in the level of serum BDNF was observed. Notwithstanding, a decrease of tumour necrosis factor-α (TNF-α) by 9% and a decrease of the level of serum vascular cell adhesion molecule (VCAM) by 25% were perceived. Tumour necrosis factor-α is a factor stimulating the inflammatory reaction in the body (Aronson, 2016). Levels of the vascular cell adhesion molecules can be associated with the severity of Parkinson's disease (Perner et al., 2019). The data demonstrated the attenuation of inflammation in Parkinson's disease patients after an increase in exercise (Zoladz et al., 2014). Thus, the animal study of Lau et al. (2011) and the human study of Zoladz et al. (2014) showed that exercise can be used as an intervention for the motor symptoms of Parkinson's patients.

3.3.2. Treadmill training as an intervention

Prospectively, an increase in physical activity and exercise are interventions to prevent and improve the motor symptoms of Parkinson's disease in general. Gait disturbance is one of the motor symptoms Parkinson's disease patients display, which is mainly affected by a reduced amplitude of stride length (Morris et al., 1996). The improvement of this symptom is thought to be one of the main objectives in interventions for Parkinson's patients. The studies of Bello et al. (2013), Nadeau et al. (2014), and Fernández-del-Olmo et al. (2014) looked into the effect of treadmill training on the gait of Parkinson's patients. It is believed that treadmill training improves the patients' gait and accordingly this contributes to the prosperity of exercise as an intervention. The studies are comparable since the used protocols are approximately similar.

Previous research showed that TNF-α levels reduced when one exercise activity was added in a week (Stewart et al., 2005). Therefore, the number of exercise activities per week should be about the same. In *Table 1*, an overview of the applied protocols of the compared studies can be found. For the following comparison, the mentioned examinations perform an equal amount of training per week, but the length of the studies differ. Patients participating in the studies did not change the used medications and other daily activities.

Firstly, the research of Bello et al. (2013) studied 22 patients that trained three times a week for five weeks. The research group was randomly divided into two groups, with one group training on a treadmill and the other group walking overground. The results of both groups demonstrated that the preferred speed walking was improved. Accurately, the results of the treadmill training group show that both balance and stride length were improved. Moreover, improvements in gait performance were preserved in the treadmill training group one month after the end of the training program. The authors concluded that treadmill walking was a feasible intervention for improving the balance and stride length of Parkinson's patients. Thus, treadmill training is plausibly useful as an effective intervention for gait disturbances.

Secondly, the research of Fernández-del-Olmo et al. (2014) consisted of 22 patients with a three times per week training for five weeks. The patients were also randomly divided into two groups, with one group training on a treadmill and the other group walking overground, which is similar to the study of Bello et al. (2013). The results of this research showed that low-intensity treadmill training continuing for five weeks improved the walking gait pattern of Parkinson's patients. The gait improvements of the patients can be explained by the progress in the patients' stride length. Correspondingly, the findings of Fernández-del-Olmo et al. (2014) validated the findings of Bello et al. (2013).

Lastly, the study of Nadeau et al. (2014) endured 24 weeks with 34 patients. These patients were randomly divided into three groups and had one-hour sessions three times per week. The groups were divided as follows: speed treadmill training, mixed treadmill training, and control. Measurements were performed at the three and the six months' time points. The results show that treadmill training, both the speed and the mixed, substantially increased walking speed and enhanced walking endurance. These enhancements were observed along with a continuous decrease in the variability of gait until the end of the six months training period. Additionally, an improvement of quality of life related to health was noticed in the treadmill training groups. Interestingly, it seemed that patients displaying poor baseline performance profit the most from treadmill training. The control group did not show any progress.

The research of Nadeau et al. (2014) is notably longer compared to the other studies included in this overview. For this reason, it is important to mention that improvements in motor symptoms as a result of the treadmill training were already observed after 3 months. Supplementarily, these improvements continued at the 6 months' time point. In light of the above, the research of Nadeau et al. (2014) adds to the studies of Bello et al. (2013) and Fernández-del-Olmo et al. (2014). Altogether, the studies indicated treadmill training is an effective intervention for gait disturbances.

Table 1 - An overview of the applied protocols of the studies Bello et al. (2013), Fernández-del-Olmo et al. (2014), and Nadeau et al. (2014). The studies focused on the improvement of gait disturbances through treadmill training.

Study	**Study duration**	**Number of patients**	**Type of groups**	**Protocol**
Bello et al. (2013)	5 weeks	22 patients	Treadmill training	3 times a week 4 times 4 minutes training at a (preferred) constant speed with 3 minutes rest; every week a round of 4 minutes was added
			Walking overground	3 times a week walking 10 meters between two auditory cues at the patients' preferred walking speed; in an indoor facility 60 meters long and 10 meters wide
Fernández-del-Olmo et al. (2014)	5 weeks	22 patients	Treadmill training	3 times a week 4 times 4 minutes training at a (preferred) constant speed with 3 minutes rest; every week a round of 4 minutes was added
			Walking overground	3 times a week walking 20 meters between two auditory cues at the patients' preferred walking speed; in an indoor facility 60 meters long and 10 meters wide
Nadeau et al. (2014)	24 weeks	34 patients	Speed treadmill training	3 times a week 1 hour; speed next session increased by 0.2 km/h with the condition the participant experiences the physical effort as moderate or less
			Mixed treadmill training	3 times a week 1 hour; speed next session increased by 1%
			Control	3 times a week 1 hour; low-intensity exercises. For example, Latin dancing or coordination movement sessions

3.4. Overview of results

An unambiguous overview of the discussed results can be found in *Table 2*.

Table 2 - An overview of the discussed results, including the intervention, the target/objective of the intervention, the article from which it is derived, and the effectiveness of the intervention.

Intervention	Target/objective	Article	Effectiveness
Deep Brain Stimulation	Subthalamic nucleus	Balestrino & Schapira (2019)	Improvement of overall motor function
		Weaver et al. (2012)	Improvement of overall motor function
	Globus pallidus internus	Deuschl et al. (2013)	Particularly improvement of dyskinesia
		Odekerken et al. (2013)	Particularly improvement of dyskinesia
	Subthalamic nucleus & globus pallidus internus	Ramirez-Zamora & Ostrem (2018)	Improvement of overall motor function and properly control of tremor
		Weaver et al. (2012)	Improvement of overall motor function
	Deep Brain Stimulation in the long term	Limousin and Foltynie (2019)	Improving motor function beyond 10 years
Exercise and physical activity	Neuroinflammation	Lau et al. (2011)	Exercise has neuroprotective effects, tested with a mouse model
		Zoladz et al. (2014)	Exercise attenuates inflammation, neuroprotective effects
	Treadmill training	Bello et al. (2013)	Treadmill training improves gait disturbances
		Fernández-del-Olmo et al. (2014)	Treadmill training improves gait disturbances
		Nadeau et al. (2014)	Treadmill training improves gait disturbances

4. Conclusion & discussion

Different conclusions can be drawn regarding the research question "*In what way are Deep Brain Stimulation, exercise, and physical activity viable interventions for Parkinson's disease?*". Deep Brain Stimulation is a viable intervention for diminishing the motor symptoms of Parkinson's patients since it has become clear that the consideration and assessment of the patients' individual symptoms are of importance. Therewith, possible personalized Deep Brain Stimulation may occur since specific brain areas are associated with specific motor symptoms. In addition, the results indicated that the stimulation of both the subthalamic nucleus as well as the globus pallidus internus is relevant since the general motor function of the patients improved. The stimulation of both brain areas is possibly supplementary and thereby might be capable of addressing different motor symptoms. Concerning exercise, and thereby physical activity, it has been shown that greater amounts of exercise resulted in improvement of symptoms in patients with Parkinson's disease. Exercise features neuroprotective effects for Parkinson's patients. Specifically for gait disturbances, it is demonstrated that treadmill training is a functional intervention.

4.1. Deep Brain Stimulation

Subthalamic nucleus stimulation showed an improvement in the displayed motor symptoms in general and is useful if the goal is to reduce medication usage. However, intervening in this brain area is possibly the cause of an increased risk of falls (Ramirez-Zamora & Ostrem, 2018). Consequently, the advantages and the disadvantages have to be taken into account before performing the surgery. For some symptoms, non-pharmacological interventions may be preferable over pharmacological treatments. Specifically, Deep Brain Stimulation might be more advantageous regarding the reduction of motor symptoms (Deuschl et al., 2006). For future research, it is therefore interesting to investigate the reduction of the usage of specific medicines. Additionally, since non-motor side effects have been observed after Deep Brain Stimulation, looking into side effects in the long term is essential.

Some studies suggested a particular preferred targeted brain area for Parkinson's patients. For example, the study of Odekerken et al. (2013) proposed the subthalamic nucleus as the preferable brain area to be stimulated. However, there are also studies that state there is no definite determination about which of the two discussed brain areas can be better stimulated (Ramirez-Zamora and Ostrem, 2018; Weaver et al., 2012). Deep Brain Stimulation will eventually help in understanding the functioning of the brain (Krack et al., 2019). Therewith, it possibly becomes clear what brain areas should be targeted for specific motor symptoms. Besides the mentioned brain areas, concerning motor symptoms, there could also be looked into the stimulation of the areas globus pallidus externus, the spinal cord, the pedunculopontine nucleus, and the ventral lateral thalamus (Lozano et al., 2019). An interesting development is closed-loop Deep Brain Stimulation, in which the stimulation is dependent on the feedback signals of the symptoms (Krack et al., 2019). This method possibly accomplishes fewer side effects. Elaborating on potential side effects, looking into performing Deep Brain Stimulation on asleep or awake patients is intriguing (Kochanski & Sani, 2018). Currently, the intervention is conducted on awake patients. Investigating if it is possible to have the same short-term and long-term outcomes with sleeping patients is pertinent for the patients' surgery experience.

As previously mentioned, only some studies regarding Deep Brain Stimulation include controls. Despite this, all studies showed benefits regarding motor symptoms. The use of a control group is an ethical issue since the control group will most likely not experience Deep Brain Stimulation. A study with a control group will thus have a certain exclusion of a group of patients for improvements regarding symptoms. On that account, animal studies with control groups prior to the usage of humans in studies is the preferable option during the research for new aspects.

4.2. Exercise and physical activity

It is debatable if exercise is specifically beneficial for the symptoms of Parkinson's patients since exercise improves health in general (Speelman et al., 2011). Nevertheless, the patients experienced an improved quality of life related to health, thus it is definite to say exercise is favourable. Most of the discussed studies are performed with humans, with different lifestyles and different medications. Taking animal studies into consideration is of importance since there are fewer variations in results considering circumstances can be easily controlled and maintained equally (Andersen & Winter, 2019). Therefore, the individual animals can meet the same standards and can follow the same protocols, this makes the results better comparable.

Adjustment to a sedentary lifestyle is mostly done to prevent further obstacles (Speelman et al., 2011). The risk of injuries and falls is increased for Parkinson's patients while a more active lifestyle further increases this (Haskell et al., 2007). Accordingly, an increase in physical activity has possible risks for Parkinson's patients. Adding to this, looking into the motivation of patients is interesting for research. This is a valid matter since it might be hard to keep motivated while the symptoms progressively still worsen (Speelman et al., 2011). Given these points, keeping motivated and not adjusting to a sedentary lifestyle is crucial in the prevention of the progression of motor symptoms.

Ultimately, it would be interesting to study the utilization and the different combinations of interventions to diminish the motor symptoms and to improve the quality of life to a further extent. The study of Duncan et al. (2018) describes a pilot which aims to investigate the efficacy of physical therapy on Parkinson’s patients with Deep Brain Stimulation on the subthalamic nucleus. The participants are randomly assigned to physical therapy with exercise to improve balance and gait or to a control group. However, the results of this pilot have not been published. Other studies regarding a combination of the interventions have not been conducted. For that reason, in the future, these interventions can be performed together and optimistically this combination is capable of achieving improved results. In addition to this, for intervention combinations there can be thought of working memory training, creativity as a dopamine agonist, and dance and music therapy for gait rehabilitation. These approaches have separately been proven capable of intervening in Parkinson's diseases. First, the neural efficiency of Parkinson's patients is increased by working memory training (Giehl et al., 2020). Secondly, creativity is associated with dopamine agonist therapy in Parkinson's disease (Lhommée et al., 2014). Finally, gait and cognition are possibly encouraged by dance and music therapy (Pereira et al., 2018). These interventions are simple, non-invasive and easy to implement. Therefore, looking into different combinations of interventions is of interest in future research.

5. References

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Epilogue

Writing my thesis about Parkinson's disease was a remarkably instructive process and made me curious about future developments regarding the diminishing of symptoms. Not only did I learn a lot about neurodegenerative diseases in general, but it was also very interesting to learn more about the mechanisms of Parkinson's disease and how different interventions could diminish the symptoms. Therefore, I would like to thank my supervisor Eddy van der Zee. Especially for guiding the writing process of this thesis. Not only the guidance concerning the planning but also the advice on different topics was very educational and helpful.

Furthermore, I would graciously like to thank the help of my family and friends who gave me the motivation to keep going with the writing process. Their sympathetic and uplifting words helped me, and their acts of kindness gave me the motivation to continue the writing process. During these times of the corona pandemic, it is sometimes hard to stay motivated and to keep working. However, studying together and having some nice distraction every once in a while, makes it easier to stay motivated. Hopefully, the end of the tunnel is nearby, so activities in person can happen again. The opening of public buildings, like the university for students, helps in planning in-person meetings. Accordingly, motivation is confidently easier to gain and maintain.

The thesis writing was the last course of the Bachelor Biology. Unfortunately, therewith also my last course as a student of the University of Groningen, for the time being. This summer I am moving to the beautiful city of Utrecht. I can say with confidence that I take all the things I have learned in the past years to Utrecht, and will certainly come to visit Groningen every once in a while.

Thank you for reading my thesis!