# Artificial neuroprostheses as a solution for Parkinson's disease

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# 1. Introduction

Parkinson's disease is the second most common neurodegenerative disease worldwide after Alzheimer and, due to its growth-rate, will be the most common degenerative disease in 2040 (Dorsey & Bloem, 2018). Therefore, Parkinson's disease is a cause for degradation of quality of life. The aspect concerning reduced quality of life, relies on the difficulties in managing movement. Three well known symptoms associated with Parkinson's disease are 1) *tremor* (shakiness), 2) *bradykinesia* (slowness of movement) and 3) *rigidity* (stiffness) (Chou et al., 2011). Tremor, bradykinesia, and rigidity are major causes of loss in quality of life and approximately 8 to 10 million people will suffer from Parkinson's disease in Western Europe by 2030 (Dorsey et al., 2007). Parkinson's disease could be stated as a worldwide problem, as long as the disease is known.

The main cause of Parkinson's disease is neurodegeneration of dopaminergic neurons in the basal ganglia. The dopaminergic neurons die or are damaged, resulting in less dopamine transmission in the brain. A low concentration of dopamine is the cause of the symptoms tremor, bradykinesia and rigidity (Chou et al., 2011). A side effect of dopaminergic medication (next to motor system defects) which need to be dealt with are hallucinations. So, the disease makes the patient's life problematic but the pharmaceutical solutions as well.

The field of neuroprosthetics could offer a possible solution for the impairments faced by Parkinson's disease patients. Moreover, neuroprostheses have the goal to improve human quality of life. To establish improvements in quality of life, restoring the lost functionality caused by the disease is required. By stimulating electrical currents to targeted neural tissue, deviant messages are intercepted resulting in diminishing symptoms (Benabid, 2003).

Nowadays, neuroprostheses are already available in the domain of Parkinson's treatment. One of the best known neuroprosthesis in Parkinson's disease is Deep Brain Stimulation (DBS). In 1948, DBS was first applied to a living Parkinson's patient by neurosurgeon J.

Lawrence Pool, where the caudate (a basal ganglia structure) was stimulated for eight weeks (Chou et al., 2011). Components of DBS could be compared with a pacemaker used in cardiological diseases, although DBS concerns multiple areas in the body. As for the electrodes which are localized in the targeted neurological area to tackle symptomes like tremor, stiffness and other bradykinetic behaviour. By implanting invasive wires connected to a stimulator closely located to the heart, electrical stimulations and energy are delivered to the targeted brain area to induce certain mechanisms (Chou et al., 2011). DBS is not the only successful neuroprosthesis that we know and will know. With technology emerging, known inventions are improving their developments. Nowadays, Artificial Intelligence (AI) emerges in the medical sector and could enrich the life of a Parkinson's disease patient in the form of better and more specialized neuroprostheses (Factor & Weiner, 2008). Therefore, this thesis will address the question:

*"Which AI applications are available within neuroprostheses used in treatment of Parkinson's disease and which kind of applications might become available?"*

The general form of DBS is contemporary DBS (cDBS). cDBS is continuously stimulating the patient's brain and personal adjustment must be set by a clinical specialist. The dependency on a specialist, does not give a Parkinson's disease patient the optimal normal life. A solution could be an adaptive DBS (aDBS) with automated adjustments based on the neural activity (Swann et al., 2018). The still developing aDBS is a form of neuroprosthesis where AI is involved.

This research is considered to be a literature thesis. The goal is to examine the current state of affairs concerning neuroprostheses for Parkinson's disease patients and state possible future research areas with examined potential.

First of all, Parkinson's disease is examined. This chapter will contain the more general overview concerning the history, diagnose, symptomes, etiology and treatment of the disease. Understanding what Parkinson's disease is and how it affects the brain is the foundation for further AI solutions. The book "Rang & Dale's pharmacology" (2020) will be the foundation in the research to understand and clarify Parkinson's disease. During last year's neurology course, Parkinson's disease was one of the subjects with Rang & Dale's pharmacology as literature. Rang & Dale's pharmacology will be the basis for understanding the neurodegenerative disease and the University Utrecht search engines like PubMed, WorldCat and Google Scholar will be the way to explore and find supplementary literature available around the world on Parkinson's disease research.

Second of all, the general idea of neuroprostheses, the history and which are now known, will be discussed. Interesting here is to know what is already possible, how does it work and does it help? Again, literature found with the use of Google scholar and WorldCat, clarified the general concept of neuroprosthetics. Almost all literature concerning the topic "History of DBS" was supplied by professor Dhr. drs. van der Linden, currently working on a PhD regarding "History of deep brain stimulation in psychiatric disorders" at University Utrecht. The first steps of DBS being an approved method were found within this literature, as well as the merge of DBS and treating Parkinson's disease. University Utrecht search engines will be my main source for finding literature.

The third step regards future neuroprosthetic developments. Among other things, the upcoming neuroprostheses from Neuralink took my interest. The tech news pages filled with information about the new inventions made me do research in the company and applied to their update newsletter. Unfortunately, little scientific literature was available according to the new devices in the online Utrecht University library yet. So, to gather accurate information, available data was retrieved on the company's site and from the few accessible papers

concerning the topic. Online research showed a neuroprosthetic project executed by the Utrecht Medical Centre (UMC), with the aim to develop an easy way of communication for people with for instance ALS. The goal of this project seems similar to the ideas of Neuralink. One of the involved UMC scientists was emailed with the aim to gather future prospects for neuroprosthetics as well for treating Parkinson's disease. Unfortunately, no response was received. Combining the above research approaches led to a potential prospect for future innovations and recommendations.

This thesis will show that AI has innovative capabilities and supports life in a meaningful way. The field of neuroprosthetics is going to help people with a common disease to benefit from different innovations like Neuralink or other upcoming devices. After this thesis I hope to say the same as Elon Musk: "I think it will blow your mind", while he introduced a brain implant.

# 2. Parkinson's disease

## 2.1 Definition of Parkinson's disease

Parkinson's disease is a worldwide known movement disorder. The first descriptions that suggested a pathology similar to Parkinson's disease were found in traditional Indian texts and ancient Chinese sources approximately 1000 BC (Goetz, 2011). However, the surgeon James Parkinson became known as pioneer for describing Parkinson's disease in 1817. In his essay *An Essay on the Shaking Palsy*, Parkinson's disease was for the first time described as a disorder concerning neurological deficits (Przedborski, 2017).

Parkinson's disease is a progressive neurodegenerative disease (Ritter et al., 2020) and the second most common neurodegenerative disease after Alzheimer's disease (Schapira, 2009). Parkinson's disease is most common among elderly and according to demographic trends, the life expectancy will increase resulting in increased prevalence of Parkinson's disease (Jankovic & Tolosa, 2015). Furthermore, demographic predictions suggest a doubled number of Parkinson's disease patients in 2050 (Schapira, 2009).

As identification between variants of Parkinson's disease doesn't seem to be established in all studies, the following consequence is a misleading interpretation of the different scientific results (Rajput et al., 2008). The identification problem is due to the lack of a specific test to determine Parkinson's disease. A Parkinson's disease diagnosis is based on clinical criteria (Jankovic, 2008). In the clinical criteria is used the overall term *parkinsonism*. There is a difference between the two terms, so it's important to make a distinction between Parkinson's disease and parkinsonism. The term parkinsonism is an overall label, covering a variety of more than 30 conditions with similar symptoms (Przeborski, 2017; This Parkinson's UK, 2019). The term Parkinson's disease is used if patients qualify for 2 of the 3 symptoms (tremor, rigidity, or bradykinesia) and the causation determines the form of parkinsonism (Rajput et al.,

2008). For example, idiopathic Parkinson's is the most common form of Parkinson's disease, which has no clarified indication for the causation. Other well-known forms of parkinsonism are drug-induced parkinsonism, where neuroleptic drugs use causes parkinsonism and vascular parkinsonism which is the result of restricted blood supply to the brain (Rajput et al., 2008; This Parkinson's UK, 2019).

The movement deficiencies are the consequence of dopaminergic neuron degeneration, so cell death of dopamine neurons in substantia nigra compacta. Not only dopaminergic neurons degenerate but other neurons involved in non-dopaminergic pathways as well. Cell death of the non-dopaminergic neurons (e.g., adrenergic, serotonergic and cholinergic neurons) cause mainly nonmotor symptoms (Przeborski, 2017; Schapira, 2009). Nowadays, there is still no cure for preventing the process of neuron degeneration, but the disease itself is no cause for mortality.

## 2.2 Symptoms of Parkinson's disease

Parkinson's disease is a visual recognisable disorder because of the patient characteristic shuffling gait (Ritter et al., 2020). The four core symptoms of Parkinson's disease are:

1) *Bradykinesia*, which means slow movement (Berardelli et al., 2001). Bradykinesia is the suppression of voluntary movements, caused by damage within the responsible mechanism for stopping and initiating motor activity (Ritter et al., 2020).

2) *Tremor,* appears mainly during rest (Ritter et al., 2020). For example, the "pill-rolling tremor" of the hands. The specific movement tremor is seen in 80% of the Parkinson's disease patients. The pill-rolling tremor is recognized by its pill-roll movement of the fingers that make a flexion and extension movement, in combination with thumb adduction and abduction. (Mengi-Ozsarac, 2008). The tremor diminishes when voluntary muscle movement is initiated.

3) *Muscle rigidity*, could be compared with a subjective feeling of stiffness (Klockgether, 2004). Muscle rigidity is characterized by resistance in muscle movement initiated by someone else, termed as passive muscle and or limb movement (Ritter et al., 2020). Dopaminergic medication effectively reduces the feeling of stiffness, implying that muscle rigidity originates from the deficiencies within the dopaminergic system (Mengi-Ozsarac, 2008).

4) *Cognitive impairments,* like depression, dementia and hallucinations. The cognitive impairments are mainly present in the later stage of Parkinson's disease (Ritter et al., 2020).

The early-stage symptoms for Parkinson's disease are not specifically clarified. The early symptoms could vary from specific stiffness, for example in the shoulders, to dry eyes due reduced blinking. The loss of muscle atonia of the eyes is also a cause for sleep disturbances, one of the most common symptoms of early Parkinson's disease (Samii, 2008).

## 2.3 Pathology of Parkinson's disease

### 2.3.1 Neurological impairment

The main structure affected in Parkinson's disease is the basal ganglia circuitry and corresponding transmission of the neurotransmitter dopamine. The basal ganglia is a group of different subcortical nuclei which, among other things, function as a component in initiating movement (Blandini et al., 2000; Borton et al., 2013). The following structures are part of the basal ganglia: the striatum (formed by the caudate nucleus and the putamen), the globus pallidus external (GPe), the globus pallidus internal (GPi), the subthalamic nucleus (STN) and the substantia nigra (divided into the substantia nigra pars compacta and substantia nigra pars reticulata) (Jankovic & Tolosa, 2015). The projections within the basal ganglia targeting the thalamus are central in initiating movement.

For a start, the thalamus has an excitatory output towards the motor cortex. Consequently, more activity arises in the motor cortex resulting in initiating voluntary movement. However,

before the thalamus is capable of exciting the motor cortex, all kinds of connections are inhibited or excited in the basal ganglia circuitry. A defect between the complex interactions could lead to deficiencies like Parkinson's disease. In 1960, a study performed by Hornykiewicz showed a remarkable low dopamine content (approximately 10% less in contrast to the control group) in the substantia nigra and striatum, using post-mortem brains of Parkinson's disease patients (Ritter et al*.,* 2020). Nowadays, it is known that Parkinson's disease is caused by the impairment of the dopamine tract (nigrostriatal pathway) between the substantia nigra pars compacta (SNpc) and the striatum. If the striatal dopamine concentration has fallen to 20%-40% compared to normal, symptoms that induce Parkinson's disease will appear (Ritter et al*.,* 2020).

As the main input structure of the basal ganglia, the striatum projects with the inhibitory neurotransmitter GABA towards the GPe, GPi and substantia nigra pars reticulata (SNpr). The GPi and the SNpr are known as the output nuclei, they target the motor thalamus. The striatal projections are the basis for the basal ganglia circuitry which consists of two pathways, known as competing motor patterns. The so-called *direct pathway*, initiating voluntary movement and *indirect pathway,* suppressing movement (Blandini et al., 2000; Graybiel, 2000).

*The direct pathway*

To begin with the pathway responsible for initiating voluntary movement. In normal circumstances is the thalamus inhibited by the output nuclei. To initiate voluntary movement is thalamus activity required, so the suppression needs to diminish. For abolishing the restraint on the thalamus, input is required to start the basal ganglia circuitry. The cerebral cortex is the main input source for the direct pathway. The input targeting the striatum involves the release of the excitatory neurotransmitter glutamate (Jankovic & Tolosa, 2015). So, exciting the striatum results in a severe inhibition of the GPi. Under normal circumstances the output nuclei

are responsible for inhibiting involuntary movement. To initiate movement, abolition of the so-called output nuclei is required. The reason for the abolition is the leash-like function of the output nuclei concerning the thalamus. If the leash from the GPi on the thalamus is less tight, excitatory activity in the thalamus arises and induces motor movement. Initiating movement following the direct pathway is supported by the *hyperdirect pathway* constructed by the STN and the substantia nigra. The frontal lobe excites the STN, which sends excitatory signals towards the GPi. However, this seems contradictory to the idea of suppressing GPi activity.

For movement, several motor pattern generators (MPGs) are activated. The desired MPG for voluntary movement needs to be enabled where the competing MPGs need to be discharged. The competing MPGs are inhibited by the hyperdirect pathway through excitation of the GPi. The inhibition projected from the striatum towards the GPi, aiming at initiating voluntary movement, is more powerful than the hyperdirect pathway. The dominant inhibition results in correct movement execution (Jankovic & Tolosa, 2015).

The substantia nigra pars compacta (SNpc) consists of dopaminergic neurons which project towards the striatum. The interaction between the SNpc and striatum is called the nigrostriatal pathway and is based on dopamine transmission (Ritter et al., 2020). Important is to distinguish two different types of dopamine receptors involved in the nigrostriatal pathway, localized in the striatum. The five types of dopamine receptors (D1-D5) are grouped into two families that induce different activity. On one hand the D1 family constituted of D1 & D5 receptors and on the other hand the D2 family consisted of the D2, D3 and D4 receptors. The D1 family causes activity of the postsynaptic neurons, resulting in excitation while the D2 family has an inhibitory effect (Jankovic & Tolosa, 2015). So, in the direct pathway the D1 receptors in the striatum are excited by dopamine transmission released by the SNpc. The binding of dopamine and the D1 receptors results in more inhibitory projections from the striatum, targeting the Gpi

and decreasing its activity. So, the direct pathway provokes more motor thalamus activity (Blandini et al., 2000).

The STN is the only nucleus of the basal ganglia that consists merely of glutamatergic neurotransmitters. One target of the STN is the SNpc, resulting in dopamine transmission between the SNpc and the striatum.

To conclude, the striatum is hyperactive in the direct pathway. Causing a severe inhibitory projection towards the output nuclei, which leads to disinhibition of the thalamus (Blandini et al., 200).

*The indirect pathway*

Inhibiting movement is also coordinated by the basal ganglia. Whereas the thalamus is stimulated in the direct pathway, it is inhibited in the indirect pathway. The motor cortex targets the striatum through glutamate transmission. Subsequently, the globus pallidus external (GPe) is inhibited and sends less GABAergic projections to the STN (Blandini et al., 2000). Due to the decreased activity, the GPe is less able to inhibit the STN resulting in increased STN activity. Previously mentioned interaction between the STN and the GPi is in this situation increased in activity, resulting in an increase of inhibition output from the GPi towards the thalamus.

Lastly, the thalamus receives a severe inhibition which results in movement suppression. Not only in the direct pathway is the substantia nigra an important feature but in the indirect pathway as well. The increased STN activity stimulates the SNpc and subsequently dopamine transmission takes place towards the striatum. However, the neurotransmitter dopamine binds to the D2 receptors on postsynaptic glutamate neurons which connect to the GABAergic neurons in the striatum. Binding with D2 receptors does not have an excitatory effect. So, the striatum targets the GPe with less inhibitory GABAergic neurotransmitters which leads to more

GPe activity that subsequently decreases the activity in the STN. The Gpi is inhibited as well and therefore less inhibition of the thalamus takes place. So, dopamine induces attenuation of the leash between the output nuclei and the thalamus in the indirect pathway.

**Figure 1**

*Schematic Basal Ganglia circuitry in normal person and Parkinson's disease patient*

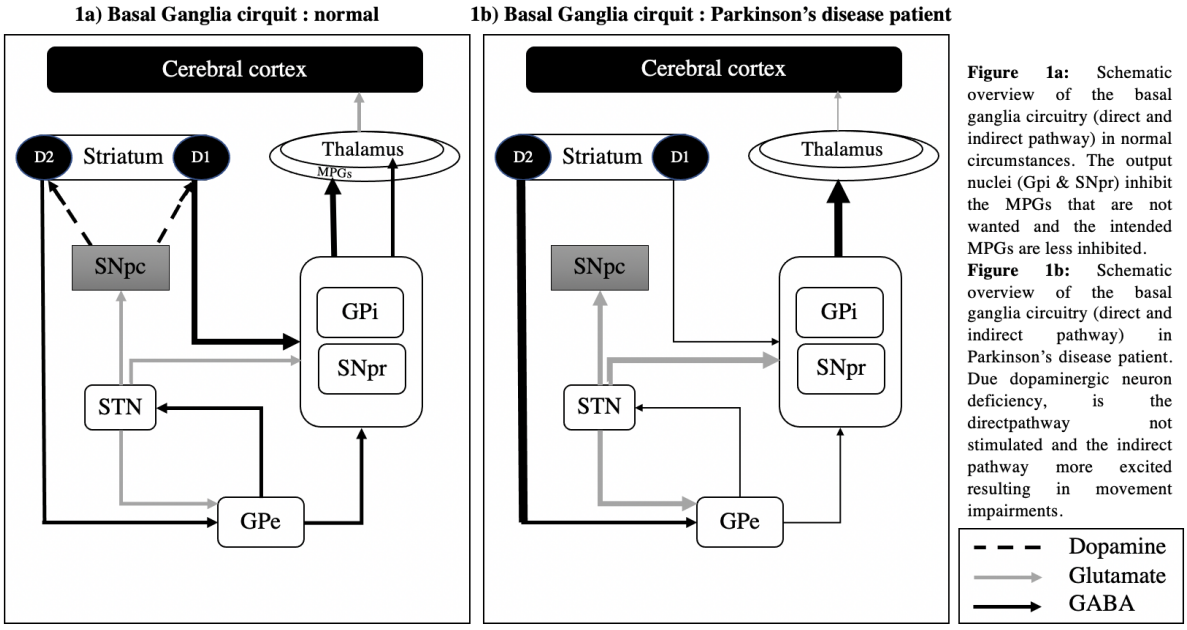



**Figure 1a:** Schematic overview of the basal ganglia circuitry (direct and indirect pathway) in normal circumstances. The output nuclei (Gpi & SNpr) inhibit the MPGs that are not wanted and the intended MPGs are less inhibited.
**Figure 1b:** Schematic overview of the basal ganglia circuitry (direct and indirect pathway) in Parkinson's disease patient. Due dopaminergic neuron deficiency, is the directpathway not stimulated and the indirect pathway more excited resulting in movement impairments.

Taken from Blandini et al., (2000) and according to Jankovic & Tolosa, (2015) adapted.

The motor-symptoms in Parkinson's disease are the consequences of neurodegeneration, specifically of dopaminergic neurons. Owing to SNpc impairment is dopamine transmission between the SNpc and striatum reduced or even vanished compared to a normal functioning neuronal network (figure 1). The lack of dopamine projection towards the striatum is the causation of deficiencies, resulting in an increased activity of the GPi and SNpr, known as the output nuclei of the basal ganglia circuitry. Since the STN isn't affected, the excitatory projections to the output nuclei will remain. The outcome of this deficit is increased motor

thalamus inhibition with the consequence of symptoms regarding movement inhibition (Blandini et al., 2000).

### 2.3.2 Etiology of Parkinson's disease

The neurodegeneration causing Parkinson's disease is due to protein misfolding and aggregation, known as Lewy bodies. Several processes abet neurodegeneration, namely oxidative stress, excitotoxicity, mitochondrial dysfunction, inflammation and programmed cell death termed as apoptosis (Ritter et al., 2020). The protein α-synuclein is prone to be misfolded and in turn propagates protein misfolding because of its ability to transport between cells (Przedborski, 2017). Hence, the disease process is stimulated and more Lewy bodies will breed. The function of α-synuclein suggests being related to synaptic vesicle recycling. Through misfolding, storage of dopamine neurotransmitters in vesicles is impaired (Ritter et al., 2020). A consequence is neurotoxicity and in the light of Parkinson's disease, apoptosis.

Increasing age, lower blood cholesterol and gene mutations benefit the Parkinson's disease process (Jankovic & Tolosa, 2015). Gene mutations are as well a possible causation for Parkinson's disease and induce mainly early-stage Parkinson's disease. These rare instances of hereditary Parkinson's disease, show mutation in the α-synuclein and parkin protein. Nowadays, different gene mutations code for mitochondrial dysfunction which implies oxidative stress and lead again to protein misfolding (Ritter et al., 2020).

Not only homeostatic impairments provoke Parkinson's disease but environmental features play a role as well. For example, drug abuse which is a typical cause for neurotoxicity. Specifically, a particular form of Parkinson's disease, popularly called "Frozen addict syndrome", was diagnosed within a group of young addicts. The reason why drug use led to Parkinson's disease was traceable to the pyridine MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which is found in relation to a heroin substitute (Ritter et al., 2020). MPTP

only destroys the dopaminergic neurons, localized in the nigrostriatal pathway. The damage of neurons in the nigrostriatal pathway is caused by the MPTP conversion to MPP+, a toxic metabolite (Ritter et al., 2020).

Several environmental associations decrease the risk of Parkinson's disease. For instance, smoking an average of 10 pack-years (1 pack of cigarettes a day for 10 years) reduces Parkinson's disease risk up to 15%-20% (Jankovic & Tolosa, 2015). Also, the regular intake of caffeine reduces the risk of Parkinson's disease up to 40%. A 30-year follow-up study showed a reduced diagnosis among men (group 1: 104 compared to group 2: 19, in a research group of 100.000) where group 1 drank no coffee and group 2 approximately 28 coffee a day (Jankovic & Tolosa, 2015).

## 2.4 Treatment

So far, Parkinson's disease is not cured. Therefore, different ways of treatment can only suppress the symptom expression but aren't able to prevent neurodegeneration. In the nineteenth century, Jean-Martin Charcot and William Gowers were the first neurologists who lay the basis for the now known treatments (Goetz, 2011). A plant-based drug, Belladonna alkaloids, was the first conventional drug which reduced tremor symptoms but turned out to be improving Parkinson's disease on a long-term basis. So, stated Charcot in 1872:

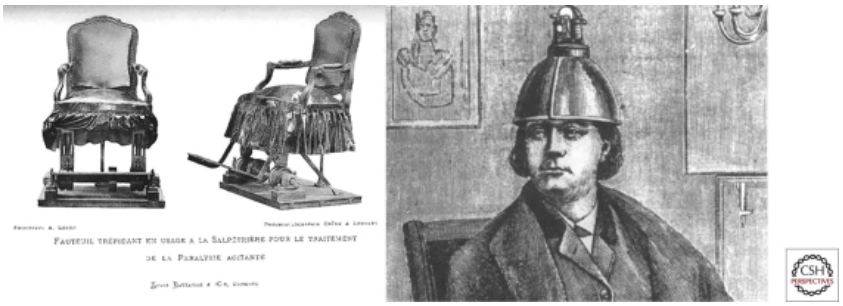
> Everything, or almost everything, has been tried against this disease. Among the medicinal sub- stances that have been extolled and which I have myself administered to no avail, I need only enumerate a few (section 2).

facing the fact pharmacologic treatments couldn't provide the sought solution, Charcot argued for a vibratory treatment. Parkinson's symptoms seemed to ameliorate by long exposure to body vibrations, for example horse and carriage riding. Hence, he introduced a "shaking

chair", electrical driven and replicated the shaking experience. Not much later, the shaking chair was converted into a shaking helmet (figure 2), which only vibrated the brain (Goetz, 2011).

**Figure 2**

*The vibratory chair and helmet*




Retrieved from Goetz, (2011).

In 1883, a suspension apparatus was introduced. This tricky manner of stretching the spinal cord used to reduce rigidity (Goetz, 2011). Unfortunately, it could not provide a solution for tremor. Surgery treatments were introduced in the beginning of the 1900 century. The use of electrical coagulation evolved approximately in the 1950s (Goetz, 2011). Some experiments consisted of fetal cells injections in the midbrain, retrieved from approximately five fetuses. However, due ethical convictions and severe dyskinesia developments the injection approach disappeared (Ritter et al., 2020). The medical treatment using levodopa developed around 1960, which overshadowed the growth of surgery opportunities (Goetz, 2011) as well.

The working mechanism of the medicine levodopa is to block dopamine receptors. Levodopa improves bradykinesia and rigidity for 80% of the treated Parkinson's disease patients (Ritter et al., 2020). Almost complete normal movement functioning is established in 20% of the patients, however drug treatment still doesn't cure Parkinson's disease. Declined

symptom expression is due the levodopa conversion to dopamine in the brain (Ritter et al., 2020).

According to the therapeutic effectiveness, levodopa therapy is a well-established Parkinson's disease treatment. Though, several negative effects raise the question if levodopa is indeed the best solution. First of all, long-term levodopa treatment declines in effectiveness over time. Secondly, during the peak therapeutic effect, dyskinesia occurs. Severe involuntary movements especially of the face and limbs appear. Levodopa treatment provokes an "on-off effect", consisting of severe rigidity and or bradykinesia for an undefined timespan. Patients suddenly interrupt their walk or are unable to raise from a chair. This is because levodopa is the instigator of more acute effects, for example, anorexia, nausea, and psychological effects (hallucinations, confusion, disorientation and schizophrenia) (Ritter et al., 2020).

Nowadays, with the emerging technologies, a new treatment evaluated namely Deep Brain Stimulation (DBS). This newly developed therapy decreases the disadvantages of an "on-off effect". Consequently, less peak-moments are diagnosed in patients resulting in diminished bradykinesia and or tremor (Levin, 2016). Around 1980, the STN was stimulated for the first time through electrical currents, with the aim to improve motor functioning in Parkinson's disease patients. Professor Benabid introduced the use of long electrodes which were stimulated by a modified pacemaker (Clément, 2019). The origin of this popular treatment will be discussed later in a more comprehensive chapter. Unfortunately, contemporary DBS is not a cure for Parkinson's disease but nevertheless a highlight in the first invasive clinical treatment (Ritter et al., 2020). So, the beginning of neuroprosthetics as treatment was established.

# 3. Neuroprosthetics

As discussed, nowadays DBS is the most popular treatment for Parkinson's disease due to symptoms that are reduced and less evoked compared to levodopa treatment. The invasive therapy has potential for future developments, even merged with AI. In view of the invasiveness of the therapy and the non-pharmaceutical treatment, DBS should be characterized as a neuroprosthetic, however later more on that. Contemporary, technical innovations combine with the field of healthcare, with the aim to enhance quality of human life. Seeing the amount of diagnosed Parkinson's patients, the absence of a neuroprosthetic solution is unthinkable. Therefore, it's necessary to clarify the basic concept of neuroprosthetics and subsequently combine the particular solution with the treatment of Parkinson's disease.

## 3.1 Definition of Neuroprosthesis

The emerging field of neuroprosthetics converts science fiction movies into reality. Take for example dr. Octopus from the spiderman marvels. He possesses multiple robotic arms and manages their movement only with his mind. Nowadays, people suffering from limb loss have acquired skills similar to dr. Octopus's, because of neuroprosthetics. In other words, neuroprosthetics play a part in developing the human body to a higher level and creating new possibilities, which were unreachable before. Neuroprosthetics attempt to improve different kinds of handicap and or disabilities, such as vision and hearing, thus not only covering motor impairments (Bavishi et al., 2018; Kilgore, 2015). So, neuroprostheses anticipate the neuronal network and try to tackle deficiencies by interfacing with non-biological devices and neural networks (Kilgore, 2015). Nowadays, development of neuroprosthetics for neurological diseases is in its infancy stage. Nevertheless, the first intelligent neuroprostheses developed

and are capable of modulating neuronal input and supply enhanced output but this development will be explained in section 3.2.4.

The so-called motor neuroprosthesis offers a solution for diminishing motor symptoms for Parkinson's disease patients and restoring quality of life. Before depicting neuroprosthetic solutions, it is important to clarify the general meaning of neuroprosthetics, especially according to Parkinson's disease treatment.

Motor neuroprostheses are invasive devices with the ability to (in)directly stimulate brain regions, readout brain signals and exchange the information with an external device (Guggenmos & Nudo, 2015; Leuthardt et al., 2006). Treatments using neuroprosthetics could be distinguished into two different categories, namely replacement and restoration treatments (Borton et al., 2013). Moving a robotic arm is an example for replacement neuroprosthetics. People with paralyzation or limb loss will benefit from a replacement neuroprosthetic. The brain activity corresponding to initiating movement is sensed by the neuroprosthesis and functions as input. Subsequently, the input is converted into control commands and induce artificial movement as output. Restoration treatments interfere in dysfunctional neural circuits, trying to fill in the disabled function (Borton et al., 2013). Restoration treatment has a different approach. Where replacement is more a substitute therapy, restoration therapy enhances the disturbed neuronal process (Borton et al., 2013). A well-known form of restoration treatment is Deep Brain Stimulation (DBS), the most common neuroprosthetic treatment for patients with Parkinson's disease. Hence, the focus in this paper will be on DBS and its development.

Both replacement and restoration treatments belong to open-loop neuromodulation systems (Guggenmos & Nudo, 2015). An open-loop system delivers a constant electrical pulse and does not adjust to the changing patient's profile, unless attuned by a specialist (Priori et al., 2013; Swann et al., 2018). Fixed settings in an open-loop system are often not optimal. Due to the variety and severity of symptoms, patients should be distinguished and therefore different

settings in DBS therapy are required. In addition, ongoing stimulation of neuronal tissue is unnecessary. Open-loop disadvantages, particularly for DBS, trigger envision for more sophisticated neuromodulation systems, which develop into closed-loop systems (this concept will be explained in subchapter 3.2). So, DBS treatment is the most common neuroprosthetic treatment for Parkinson's disease (Deuschl et al., 2013) and is still evolving.

### 3.1.1 Brain-Computer Interfaces (BCI)

Most of the time, reading technical developments in interaction with the human brain, the term Brain-Computer interface (BCI) is used. But what does it really mean? Neuroscientific research denotes the term BCI, as an upcoming subject present-day. The term BCI was introduced in the 1970s and developed many synonyms: Brain-machine interface (BMI), Neural Interface (NI) and Mind-Machine Interface (MMI). Thirty years later, the first international meeting on BCI gathered (Leuthardt, 2006). The general idea of BCI is similar to some neuroprosthetics. BCI functions by reading neural tissue signals and uses this information to interact with electronic systems that could result in stimulation of specific structures and or nerves (Clément, 2019; Lee et al., 2019). So depicted Clément in his book: "Brain-Computer Interface Technologies" a general concept of BCI:

- **B**rain: covers all involved body parts for example the nervous system, spinal cord and or involved organs.
- **C**omputer: could be termed as machine as well. Representing the (non)invasive electronic devices.
- **I**nterface: signal uptake and stimulation from/to brain structures or electrodes (p. 3)

Introducing BCI reflects the AI innovation, where the brain communicates with machinery with the aim to enhance human deficiencies (Moxon & Foffani, 2015). Standard brain output is not required for BCI functioning, this communication system is a substitute channel to

intercept impairments (Leuthardt, 2006). To make an adequate distinction between the terminologies BCI and neuroprosthetics is rather difficult. Perhaps it's possible to clarify the difference by stating the fact that BCI could be a component of the overall term neuroprosthetics (Bavishi et al., 2018). So, the goal BCIs try to achieve is fulfilled by the use of some neuroprostheses, which are able to readout brain activity and supply feedback (Borton et al., 2013). Therefore, the use of the term BCI is appropriate for neuroprostheses, for example adaptive DBS, which are compatible with the BCI concept (adaptive DBS will be explained in section 3.2.4). Both concepts are appropriate for the aim of depicting a solution in treatment for Parkinson's disease.

## 3.2 Deep Brain Stimulation (DBS) as a neuroprosthetic

It's time to depict the most commonly used neuroprosthesis for treating Parkinson's disease, namely Conventional Deep Brain Stimulation (cDBS or DBS). DBS is a bilaterally surgical treatment, which was first practiced around 1980. The additional disadvantages (for example dyskinesia) induced by medication treatment for Parkinson's disease led to the consideration of using DBS treatment instead (Velarde et al., 2017). Lesion surgery is assumed to be the forerunner of DBS treatment, however more concerning the DBS origin will be illustrated in the history of DBS for Parkinson's disease section. The general concept of DBS entails two leads with electrodes placed in the brain to target specific brain tissue, which are linked to an implantable pulse stimulator (IPG). The IPG is comparable to a pacemaker and generates electrical pulses, it's therefore possible to stimulate brain areas. The leads are connected with the IPG by the extended wires that follow the path from the scalp to the inferior and anterior chest area, where the IPG is located (Clément, 2019; Santaniello et al., 2018). The electrodes

in the targeted area are meant to inhibit unwanted neuron firing, the underlying cause of tremor and dyskinesia, managed by high-frequency pulses (Ahlskog, 2015).

Not all Parkinson's disease patients are qualified for DBS surgery. Because DBS cannot be applied to all Parkinson's disease patients, it illustrates the fact DBS doesn't improve quality of life for all Parkinson's disease patients yet. The shortcomings can be taken into account for future developments, to offer all Parkinson's disease patients a proper treatment.

First of all, the majority of DBS patients are diagnosed with advanced Parkinson's disease, meaning the diagnosis is 12-15 years before the surgery is established (Santaniello et al., 2018). Secondly, refractory motor symptoms like dyskinesia and or tremor need to be ascertained in the potential DBS patient, corresponding to the clinical picture of advanced Parkinson's disease. The qualified patients receive most of the time chronic levodopa treatment and start to find issues in the medical treatment (Lozano et al., 2019; Levin, 2016). Extreme fluctuations in movement control, the so-called "on-off effect" is a particular disadvantage of long-term levodopa use (Marsden & Parkes, 1976). The on-off effect induced by dopaminergic medications, leads to severe dyskinesia. Whereas medication should improve the motor symptoms, on the long term its effect is controversial (Santaniello et al., 2018). Nevertheless, is responsiveness to dopaminergic medications a necessity for receiving DBS. Hence, patients are observed during on-off medication use to determine the effectiveness before applying DBS therapy. Showing no response to dopaminergic medications, is the success of DBS treatment not guaranteed (Levin, 2016). So, patients will not benefit from DBS treatment if they are not competent to the above stated requirements.

DBS is partially a substitute for medicine treatments to reduce the additional side effects and reduce the motor symptoms up to 50% (Santaniello et al., 2018). Still offers DBS not a cure for Parkinson's disease however, quality of life is restored compared to life with medicine disadvantages. Further are the appearances of dementia and depression crucial for disapproval

of DBS treatment. Both syndromes are worsened by DBS treatment and this is contradicting the idea of ameliorating the patient's clinical picture (Levin, 2016). As well, brain surgery is always a high-risk treatment and not all candidates are willing or capable to undergo this risk (Ahlskog, 2015).

DBS surgery trajectory is divided into two stages and requires a multidisciplinary team. The constitution of the team must include a DBS neurosurgeon for implanting the electrodes, a DBS neurologist who is responsible for programming the DBS and a neuropsychologist for determination for absence of dementia or depression (Chou et al., 2011; Levin, 2016). The first phase of implanting a DBS, involves placement of the electrodes. Traditionally is this surgery executed when the patient is fully conscious and only numbing medication is injected at the scalp for the incisions. Later another placement technique emerged called intraoperative MRI, where patients are under full anesthesia and the placement takes place in a radiology room. Using MRI makes placing of the electrodes more precise and quicker. Phase two is placing the IPG below the collarbone and making connection through a specific tunnel system with the extended wires, at ear height (Chou et al., 2011).

### 3.2.1 History of DBS for Parkinson's disease

For enhancing DBS possibilities, it's important to know more about the historic perspective. Not only the underlying process of Parkinson's disease needs to be taken into account but the origin of DBS as well. What kind of solutions for treating Parkinson's disease were already tried? Or how and when did we start using DBS-like techniques? It's possible to learn from the developments and the pace in which these developments took place. So, combining Parkinson's disease with acquired historical knowledge concerning DBS, will benefit upcoming inventions.

Before DBS systems were implemented in humans, much research took place. Implementing a device invasively and stimulating the brain with an electrical current was

unthinkable in the early days. The history of DBS goes back to the first time stimulating the human brain with electrical pulses took place. In 46 BC, the paper "Compositiones medicamentorum" described a treatment for headache. The Roman physician Scribonius Largo placed the electrical transmitting fish Torpedo torpedo on the head of the patient with pain reducing effect (Sironi, 2011). Concerning ethical standards, experimenting on the human brains does not conform to the valued norms of now known society. For this reason, experiments like the above are not simply carried out anymore. Nevertheless, priori in time thoughts were different and people made use of experimental possibilities and changes available. For example, through the work of Giovanni Aldini in the beginning of the nineteenth century, cortical stimulation was concluded to be possible. Aldini used decapitated prisoners and stimulated the brain with facial expression as a result (Sironi, 2011). Consequently, more experimenting took place in the nineteenth century with many animals as clinical trial subjects. For instance, muscle contractions in dogs as a result of cortical stimulation were concluded in 1870 and two years later specific brain targets related to movement were identified in monkeys.

The first electrical stimulation in consciousness human beings followed up in 1874. The electroshock performed on patients who suffer from psychosis, made the beginning of clinical treatment of humans with electrical pulses (Sironi, 2011). Approximately around the 1950s the stereotactic neurosurgery technique which entails localizing brain targets for surgery with the use of an external frame (Galloway & Maciunas, 1990), amplified its potentials by the usage of an electrical device. Patients diagnosed with psychiatric disorders were treated by lesioning specific brain areas with the use of stereotactic technique. Before surgery, the location of the targeted brain area needed to be determined. Electrical stimulation played a part in providing this mapping. Combining the surgery technique and the exploring electrical stimulation led to DBS and ultimately damaging the brain was no longer necessary (Hariz et al., 2010). Gradually studies noticed the effect of electrical stimulation was about similar as the ablation of brain

tissue and more interest grew for treating neurological (movement) disorders with DBS (Lozano et al., 2019).

Above illustrated is a short timeline of the development of DBS. The clinical observations related to Parkinson's disease also influenced the gathering of the disease and DBS as a potential treatment. The assembly between DBS and Parkinson's disease started with the already mentioned "Frozen addict syndrome", caused by MPTP. In 1983 the compound found in the designer-drugs led to monkey research with the aim to resolve the correlation between MPTP and the appearance of movement disabilities (Burns et al., 1983; Langston et al., 1983). Between 1983 and 1990, years of MPTP injected monkey research followed and significant STN activity was for the first time connected with the observed Parkinson's symptoms (Alexander et al., 1990; Mitchell et al., 1989). Because of the pronounced role of the STN in Parkinson's disease, the monkey research as well examined the effects of lesioning the STN. Parkinson's symptoms were thought to originate from a lack of neuronal activity in the STN, but the opposite seemed to be the case. By lesioning the STN, so consequently reducing its neuronal activity, motor disturbances reduced (Aziz et al., 1991; Bergman et al., 1990). As previously stated, DBS therapy shows equivalent results as early days lesioning therapy. Given these points, the step to combine DBS and Parkinson's disease treatment became a question of time. In 1993 the first patients received STN stimulation (Benabid et al., 2009). DBS became a suitable therapy for treating Parkinson's disease due the insights extracted from the animal models. Contemporary, over 160,000 Parkinson's disease patients received DBS and makes Parkinson's disease the most common treated movement disorder. (Lozano et al., 2019)

### 3.2.2 Technical DBS design

The totally invasive DBS system consists of three important parts: the leads, the extension wires and the implantable pulse generator. The condition of the patient decides if a unilateral

stimulation or a bilateral stimulation is implemented. Meaning a single lead is placed in one hemisphere or in both sides of the brain. The size of an inserted lead has a diameter of 1.2 mm and a length of 40 cm (Chou et al., 2011). Localized at the end of the lead are four rings, named contacts. The contacts have direct connection with the targeted brain tissue and deliver the electrical stimulation. For adjustment is a changeable pattern needed. Therefore, the contacts are provided with the ability to switch and deliver electrical pulse signalling independently (Clément, 2019). Within the leads are four wires, the extension wires, extending under the scalp through the neck towards the IPG and forming the connection. The IPG is the battery of the system and enables the electrical pulse to transfer towards the leads. The size of an IPG varies, depending on the patient's needs. Moreover, IPGs need protection, for making implementation in the human body possible. Therefore, metal cases surrounding the IPG are used. The protection box diverses in size from a credit card to a pack of playing cards (Chou et al., 2011). Because of the continuous pulse, IPGs are not capable of generating electrical stimulation during a full lifespan. Hence, emerged a new IPG with a pulse supply for 10 years (Clément, 2019).

### 3.2.3 DBS in the brain of a Parkinson’s disease patient

DBS treatment for Parkinson’s disease concerns the basal ganglia circuitry. The two brain structures commonly targeted are the STN or the GPi. By usage of high frequency stimulation (HFS) arises chemical reactions which influence the whole brain mechanism. The precise working mechanism of DBS is not perfectly clarified. But one of the known achievements caused by DBS is an inhibitory effect in the targeted areas. The closest neurons are affected, resulting in inhibition. Other neurons, more distant from the electrode show different reactions (Fang & Tolleson, 2017). As for astrocytes, when stimulated they transmit Ca+ causing other neurons to transmit the neurotransmitter glutamate and adenosine. As last is cerebral blood

flow stimulated and positively influences the process of neurogenesis (Okun, 2012). Concluding, DBS evokes inhibitory and excitatory effects in and surrounding targeted brain areas. The HFS used in DBS which targets the STN has a positive effect on the pathways normally regulated by dopamine and therefore fulfilling the same effect as levodopa (Lozano et al., 2002). DBS treatment targeting the STN is the most common target for DBS (Schüpbach, 2009). Nevertheless, when the GPi is chosen as target, the inhibitory effect is caused by a low-frequency stimulation (approximately 10 Hz) which causes a depolarization stop for almost 20ms after a generated pulse (Lozano et al., 2002). On the other hand, inhibition of the STN is obtained at a high-frequency pulse.

Motor symptoms like bradykinesia, rigidity and tremor reduce remarkably. Hence, levodopa intake is reduced up to 60%, resulting in decreased Parkinson's disease symptoms induced by levodopa medication regarding dyskinesia and motor fluctuations (Benabid et al., 2009). A hypothesis concerning STN treatment suggests the process of jamming glutaminergic neurons located in the STN, attenuating the neurodegeneration process of dopaminergic neurons in the SNpc (Benabid et al., 2009). Even though there is no significant cognitive impairment difference between STN and GPi after DBS, targeting GPi reduces medication to a lesser extent (Odekerken et al., 2016).

One of the most important parts of the DBS therapy is programming the software. Before surgery, programming visits take place which will continue after the electrode placement. Once the DBS is placed, short stimuli pulses will be stimulating the targeted area. The additional parameters such as pulse rate, amplitude and width in respect to the electrical pulses differ and need alterations according to the patient's needs (Velarde et al., 2017). As previously stated, DBS targeting the STN makes use of high frequency stimulation. The general frequency parameter setting starts at 130 Hz with a maximum of 185 Hz (Gupta & Agrawal, 2019).

However, a generalized setting for a DBS is not available, each patient has its own specific adjustments.

An open-loop DBS does not adjust to the fluctuating symptoms and this lack of adaptation is the cause for reprogramming. Besides, the continuous stimulation requires a lot of energy, resulting in frequent IPG replacement every few years (Beudel & Brown 2016). The limitation of DBS such as non-responsiveness and continuously stimulating the brain is a serious shortcoming with induced side-effects. Emerging technologies provide opportunities to develop more efficient mechanisms which are capable of improving the disadvantages, namely an adaptive DBS which is capable of adjusting to the patient's needs.

### 3.2.4 Adaptive DBS (aDBS)

For the development of aDBS, some critical modifications were needed to the current DBS system. By fine tuning the DBS are motor fluctuations and additional side effects managed in a short period of time, in contrast to long term scheduled reprogramming appointments (Priori et al., 2013). Additionally, less IPG replacement surgeries are necessary. Because of the adapted stimulation, IPGs consume a minor amount of energy and fulfil more extended time. Hence, patients experience lower risk of surgical infection and or material damage (Lee et al., 2019).

One of the most important features for an aDBS, is the ability to collect neuronal activity as input and respond with suitable feedback. So, the working mechanism of an aDBS is similar to the concept BCI, thus the aDBS could be categorized as an intelligent neuroprosthesis. The adaptivity in the aDBS is based on understanding the brain activity and supply fitting feedback (Little et al., 2013). Challenging hereby is the dual-task of the implanted electrodes, namely recording and stimulating of the brain (Swann et al., 2018). Applying the adaptive mechanism in DBS results in stimulation induced by neuronal signals that qualify as motor impairments,

in contrast to continuous stimulation (Swann et al., 2018). So, it is important to ascertain specific neuronal activity which indicates the requirement of stimulation. With the utilization of electrophysiologic activity recordings, are the incorrect motor patterns inducing motor impairments ascertained. The implanted electrodes have the ability of recording neuronal activity, comparable to an invasive EEG. Recordings are measured as local field potentials (LFP). Data collected from LFPs function as specific biomarkers which are necessary for establishing the feedback algorithm. The biomarkers used are in this case specific frequency bands, which are oscillations inferring impairment in neuronal activity inducing Parkinson's disease symptoms. Different frequency bands are categorized in terms of power. So, for example the beta frequency band is the category of various oscillations between approximately 12-25 Hz (Purves et al., 2008). Deviant LFPs of beta band frequencies retrieved from the STN are remarkable for movement disabilities, for example rigidity and bradykinesia (Arlotti et al., 2016). Furthermore, high narrowband gamma oscillations of approximately 60-90 Hz imply dyskinesia (Neumann et al., 2019). Nevertheless, beta band frequencies are influenced by voluntary movement. Activity of the hyperdirect pathway seems to correlate with high beta frequency bands as well (Neumann et al., 2019), therefore these kinds of biomarkers can complicate their use as characteristic for programming the algorithm (Swann et al., 2018). Moreover, beta frequency band oscillations seem not to be characteristic for tremor even likely to be suppressed by the presence of the specific symptom. The idea of beta oscillations as primary biomarker for tremor-patients is therefore less successful (Neumann et al., 2019), but still a foremost indicator for bradykinesia and rigidity. Making use of LFPs doesn't change the surgical treatment of implanting the DBS system. Because electrodes contain the ability to measure neuronal activity and stimulate, no extra measurement devices are required which is beneficial for the patient as for the surgeons. All in all, LFPs are an important control variable and crucial for creating a closed-loop system.

Before stimulation is generated in an aDBS system, the input needs to be conveyed. The collected data is transferred to the intelligent neurostimulator, in contrast to the blind IPG in an open-loop DBS. The Activa® PC+S DBS system introduced by Medtronic, is one of the first neurostimulator used for aDBS. In 2016, Activa-RC® became available with the capacity to recharge, whereby IPG replacement became even more postponed (Sette et al., 2019). Stimulation caused by the IPG depends on the implemented software and the chosen biomarkers.

According to the beta band frequencies as biomarkers, thresholds are determined. The aDBS activity depends on crossing a certain threshold. Compared to the open-loop DBS, aDBS reduced its activity to 50% (Velisar et al., 2019). As already mentioned, particular gamma frequency band oscillations are typical for dyskinesia. The adverse effect caused by medication treatment or even evoked by open-loop DBS, could be reduced using aDBS. The working mechanism of aDBS relies on established boundaries. However, the aDBS is turned off if the signal is below the threshold boundary. No deviant signals induce normal brain activity, so stimulation is unnecessary (Tinkhauser et al., 2017).

Admittedly, aDBS haven't been optimized to an optimal level yet. There are still some limitations that need to be reviewed. For example, the dual-task concerning the electrodes, may cause complications. Signals induced by stimulation cause disruptions in the measurement of neuronal activity. The quality of the data, functioning as input, is thereby diminished (Neumann et al., 2019). Another obstacle concerns the feedback algorithm and signal. Establishing correlations between the biomarkers and the fitting clinical parameter setting remains complex, again because patients show distinct disease states (Mohammed et al., 2018). Moreover, applying aDBS possibly provokes symptoms expressed within a certain delay, which could lead to unknown damaging effects (Neumann et al., 2019). So, the challenge for an aDBS mainly relies on the adjustment of stimulation settings and additional algorithms. Moreover,

reviewing the complexity of the different biomarkers inducing distinct symptoms, is an elaborate deep learning network needed. Based on the various retrieved data from the electrodes and the patient's clinical profile, are the parameters optimized. Establishing a well-trained deep learning neural network is a tremendous amount of data required. International cooperation for sharing data would be sufficient and optimize the computational network. Anonymized aDBS data in combination with personal profile improves the learning process, potentially resulting in a more generalized model (Neumann et al., 2019).

# 4. Future prospects

The future perspective of AI in healthcare is promising. Fast technical innovations in combination with improved knowledge of the functioning of the human body in relation to specific disease characteristics has shown the ability to improve people's life. Treatment of Parkinson's disease with DBS is an example on how technology can support, improve or even (in the future) cure without traditional medication. Research on DBS is creating new knowledge every day. Not only is the development of Parkinson's disease treatment focused on DBS, but also new AI applications are introduced in the healthcare market like Connectomics together with StimVision v2 and Neuralink. All of which will be covered in the following paragraphs.

## 4.1 Connectomic and StimVision v2 for DBS

Neuroscience is mainly associated with the idea of linking neurological processes with specific brain areas. So, an extraordinary behaviour or disease presumably originates from a specific dysfunctioning part of the brain. The emerging field of connectomics, however, shifts the idea of specific dysfunctioning to a perspective in which a problem is manifested in a dynamic and complex system. Connections and additional activity maintain the neuronal network. Connectomics presents a neuronal map, defined as the connectome, that shows high detailed connections with visualized axonal pathways. The MRI technique diffusion tensor imaging (DTI) results in a tractography visualization of the connectome (Fornito et al., 2015; Noecker et al., 2021). This way more insight into the personal topology of the patient's brain is obtained and creates an advanced clinical perspective based on eventual disease spread and or disease development (Fornito et al., 2015). By keeping track of the patient's clinical condition based on the connectome a potential display of the misfolded proteins, which are mainly responsible for Parkinson's disease causation and their ability to transport between cells, can contribute to personalized treatment. So, the combination of connectomics and DBS offers direct results of

the stimulation, because of the direct mapping and modulation of the personalized neuronal network (Noecker et al., 2021). Therefore, the connectomic DBS research benefits for instance the placement of the electrodes and optimizes the prevention of potential complications.

As an example, on how connectomics is translated into a functional application is shown by Case Western Reserve University. At this University they developed a connectomic based software application named StimVision, specialized for connectomic DBS in the STN regions. As stated in the article of Noecker et al. (2021) the emerging software StimVision supports the optimization of DBS by combining and integrating the following four components:

- Medical image visualization
- Axonal pathway visualization
- Electrode positioning
- Stimulation calculation (p. 1)

As a result, the visual connectome provides detailed information for each individual patient, allowing more personalized treatments. Specialization for DBS stimulation of the STN targeted regions was realized in StimVision v2. Localizing electrode implants will be enhanced and the influence of stimulation on brain activity is rapidly evaluated (Noecker et al., 2021). With StimVision it is possible to compare the predictions and the executed procedure, which shows correlations important for improving the system. StimVision v2 provides highly detailed information regarding neuronal pathways, especially axon interactions in the STN regions. Therefore, multiple positions for electrode placement within the STN regions are required to obtain potential positive effects on treatments. Perhaps resulting in a more preferable procedure for specific patients because of reduced disadvantages (Noecker et al., 2021).

## 4.2 Neuralink

DBS is not the only neuroprosthetics involved in treating Parkinson's disease. Currently new ideas and or variants in respect to DBS arise with the same goal, improving quality of human life. The entrepreneur Elon Musk, known for for example Tesla and SpaceX, introduced his new company Neuralink in 2017 (Kulshreshth, 2019). With the introduction of Neuralink, interaction between the human brain and technology is placed in a new perspective. Neuralink is developing an implantable device, called "The Link", with the objective to treat neurological diseases in the near future. Also, the Link will be the first BMI capable of direct interaction with external devices, like personal computers or smartphones. This development will increase quality of life for people diagnosed with paralysis, just by installing the Neuralink app. Just by thinking about several actions or movements people are able to control electrical devices, a "think and walk" idea. Nowadays the first goal is to help people diagnosed with paralysation and extend later on to helping people with neurological diseases like Parkinson's disease (Neuralink, n.d.).

As well as with DBS, electrodes are used in the Link for recording brain activity. The implantable Link with a size comparable to a big coin, connects with the brain tissue through many tiny threads capable of recording neuronal activity. The brain recordings are retrieved from up to 1024 electrodes divided over the threats (Neuralink, n.d.). The process of implanting the Link is almost fully executed by a specific robot system. The need of a robot during the surgery is among other things important for the severe precision and accuracy. The Link is charged at night wirelessly, so the battery capacity limitations (like in DBS systems) is hereby tackled.

The Link distinguishes itself from the nowadays known neuroprosthetics for its two-way street interaction. In a DBS system it is only possible to manipulate the brain and read out the necessary information. The Link makes it possible to manipulate the electrical devices as well,

with the brain as a manipulator. The Link is operated by the Neuralink app, which is controlled by your thoughts. A Bluetooth connection takes care of the necessary communication needed for interaction.

This way a new symbiosis is established by sending and receiving data between both components, namely the brain and electrical devices. Maybe over 50 years is everybody provided with a Link and is the human race integrated with multiple electrical devices. Think about turning the coffee machine one, just by one thought or text your parents that you will be late for dinner. Perhaps a scary thought, but on the other hand imagine a world without neurological disease, independent paralyzed people or maybe even no more cancer. Maybe it becomes possible to program a certain lifestyle creating more consciousness in human behaviour concerning the environment. To get back to the point, Neuralink is willing to invest in Parkinson's disease treatment, but how is not specifically clarified yet. Seeing the capabilities of recording neuronal activity is promising and comparable to the aDBS. However, the Link is now more focused on interaction between devices and the human brain which primarily improves the quality of life for paralyzed patients. If the Link is able to fulfil the dual-task likewise the electrodes in DSB, less invasive equipment is necessary. Perhaps another treatment approach rather than stimulation of the STN, will be found.

Neuralink creates thoughts for the unthinkable and provides the future with many opportunities. But such drastic changes come with risks as well. Would it be possible to be hacked? If people possess the intelligence to create a marvellous cure for degeneration of the human brain and even create a new way of interaction, there must be a downside. Such as the idea of someone taking over your thoughts or even programming your actions are disturbing. The adverse possibility could be a reason for patients to refuse such treatment. Neuralink is aware that a good level of security of each compartment of the Link is mandatory to diminish

these anxieties. The ability to manage these anxieties will determine the pace of acceptance of these new solutions enabling human species to get to a higher level.

## 4.3 Conclusion

To conclude, treatments reducing Parkinson's disease symptoms are required to establish quality of life. Neuroprosthetics in the form of DBS foresee this criterion. As a matter of fact, technology offers a solution in healthcare, which provides us with a less pharmaceutical dependent perspective. Rapid technical innovations take place in small steps like improved DBS and much faster supported by neuroscientific companies like Neuralink. The combination of existing medication with small technical improvements, plus the new fast upcoming inventions will transform the way we're able to prevent and maybe cure diseases. Enhanced treatments reactivate lost human functions and even potentially improve quality of life posts disease. All in all, the innovations will come and will exceed human expectation.

It all started with the role of neuroprosthetics within the treatment of Parkinson's disease. Overall, it is convenient that Parkinson's disease influences daily life intensely and now it's possible to conclude DBS offers quality of life rather than the traditional levodopa treatment. Disadvantages caused by levodopa treatment, such as deteriorating long-term results, the on-off effect and induced dyskinesia, are determined by DBS treatment. The majority of DBS receivers are advanced Parkinson's disease patients and face already the above stated disadvantages. To intervene with new developments on a shorter notice could maybe prevent the emerging disadvantages and offer a more pleasant life sooner. Moreover, the development of aDBS covers already disadvantages such as unnecessary stimulation, poor lasting battery power and the inability to adjust to the patient's needs. As a result of the aDBS abilities, enhanced personalized treatment can be applied. The closed-loop system provides self-sufficiency and a less patient-like awareness. Also, unrelated to symptom diminishing is an

independent, healthy mood critical for quality of life. If the confrontational clinical appointments are reduced, which is obtained with aDBS, is the patient's daily life more similar to nonpatients. Thus, aDBS reduces the patient's symptoms and is more independent of hospital appointments.

As for aDBS multiple improvements are possible. Upcoming research institutions and corporations will contribute to the enrichment of neuroprosthetics. In the near future are advancements in aDBS most plausible. New software developments like StimVision v2 give rise to fitting treatment for each specific patient. Besides, it takes time to collect data which is used to improve deep learning algorithms. Subsequently, parameter settings adjust more precisely to the patient's clinical state and are able to intercept deviant neuronal activity. On the other hand, with companies as Neuralink rising are neuroprosthetic developments accelerating. Neuralink established in 2016 has already a working neuroprosthesis nowadays. With this in mind, it's unthinkable what capabilities are possible over 5 years. Maybe it is time to think about AI approaches which are not stuck to the idea of obligated invasiveness. Obviously is an invasive neuroprosthetic the optimal solution but to make improvements other angles need to be considered as well. Seeing the fact that combining connectomics with aDBS leads to treatment improvements, are also different approaches considerably. A recent remarkable development which should be taken into account is the company Kernel. The reason the development isn't mentioned before concerns the fact Kernel didn't develop a neuroprosthesis (yet). Nevertheless, Kernel shows different and promising perspectives with their different approach. In 2020 Kernel introduced the Flow 50 which is a non-invasive helmet, exposing insight about people's own brain activity (Kernel Neurotech, 2020). The new brain-interface is comparable to Neuralink because of their joined future prospect, namely establishing a symbiose between the human brain and technology. By making use of techniques comparable to fMRI, brain activity is recorded through the skull. Normally, fMRI is rarely used

in the field of neuroprosthetics because of the massive equipment only accessible in hospitals and or research institutions. Therefore, the Flow 50 introduces the first wearable fMRI which should be available for everyone in 2033 (Kernel Neurotech, 2020). The future prospect concerning Kernel is for now outside the neuroprosthetic and thereby the invasive field. Nevertheless, the developmental goals are promising. Treating Parkinson's disease is not part of Kernel's programme yet, however the first steps towards improving health care are made. A partnership between Kernel and the biotechnical company Cybin has been announced. Kernel will support research on mental illness by offering direct brain results caused by psychedelic therapy (Kernel Neurotech, 2021). Collaborations like Kernel and Cybin's create positive expectations. Perhaps, it will be possible in the future to implement an invasive Flow 50 and personalized brain activity display becomes a daily routine. This will benefit depicting the patient's clinical neurological state, like connectomics ambition in aDBS.

It's challenging to cover all the various symptoms and clinical states caused by Parkinson's disease, so each patient needs a neuroprosthetic adjustable to each individual. Inventions like the Link and upcoming devices like the Flow 50 are new AI approaches that will enrich the neuroprosthetic field within maybe 20-30 years. This will be in a way we never expected. As a final point we see a world where pharmaceutics primarily offered the solution in health care. This changes. AI is offering new possibilities which will benefit humans. I'm not sure what to think about the technical biological symbioses for everything. Thoughts like the above raise other ethical issues, really interesting but beyond the scope of this thesis. Nevertheless, I find no disadvantages in AI improving healthcare. Why not improve life? Maybe it's possible to cure Parkinson's disease and I'm willing to find out.

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