

Modulation of brain activity by electrical stimulation and external cues to treat Parkinson's disease symptoms



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List of abbreviations

BDI	Beck Depression Inventory
CM	Centromedian
cZI	Caudal Zona Incerta
DBS	Deep Brain Stimulation
fMRI	Functional Magnetic Resonance Imaging
FOG	Freezing Of Gait
GPe	Globus Pallidus External
GPI	Globus Pallidus Internal
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PD	Parkinson's Disease
Pf	Parafascicular
PMC	Lateral Premotor Cortex
PPN	Pedunculopontine Nucleus
RAS	Rhythmic Auditory Stimulation
rCBF	Regional Cerebral Blood Flow
rZI	Rostral Zona Incerta
SMA	Supplementary Motor Area
SNC	Substantia Nigra Pars Compacta
SNr	Substantia Nigra Pars Reticulata
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VIM	Thalamic Nucleus Ventralis Intermedius
VL	Nucleus Ventralis Lateralis

Abstract

Despite being one of the most common and best studied neurological disorders, Parkinson's disease symptoms remain difficult to treat. Pharmacological therapy has proven to be very effective to ameliorate parkinsonian symptoms, and remains the most common treatment method to this day. But because its positive effects decline over time and it can cause some serious side effect, some patients need to resort to other treatment methods. High frequency electrical stimulation of components of the basal ganglia or thalamus, called deep brain stimulation, has become increasingly popular over the last years to help patients with severe Parkinson's disease. But also noninvasive treatments can be effective, as certain external cues can improve gait patterns of patients. In this review, the effectiveness of these treatment methods are investigated and compared to each other. We found that both deep brain stimulation and external cues can be helpful to patients, but they affect different parts of the neuronal network involved in Parkinson's disease and therefore have a different effect on the parkinsonian symptoms. Deep brain stimulation generally affects a wide variety of symptoms, but has less effect on gait patterns, which are strongly affected by external cues. External cues may therefore be a beneficial addition to deep brain stimulation. However, it may be more effective to simulate the effect of an external cue with electrical stimulation. We will give suggestions for areas in the brain that may be effective targets for electrical stimulation, and give an overview of targets that have already been tested. We believe that modulation of several of these targets by electrical stimulation will be more effective than standard methods. The most effective treatment method is likely to be highly patient-specific, but with more brain areas available as potential targets for electrical stimulation, the treatment of parkinsonian symptoms may ultimately become more effective.

Chapter 1: Introduction

Parkinson's disease was first described by the English doctor James Parkinson in 1817. He described it as a progressive disease without a clear starting point, with symptoms such as a feeling of weakness and a tendency towards trembling with one or both hands. Nowadays Parkinson's disease (PD) is one of the most extensively studied neurological disorders due to its widespread occurrence. It is believed to affect approximately 0.3% of the whole population, and 1% of the people over 60 years of age, making it the second most common neurodegenerative disorder, after Alzheimer's disease (de Lau & Breteler, 2006; Nussbaum & Ellis, 2003).

PD is characterized pathologically by the loss of neurons in substantia nigra pars compacta, a component of the basal ganglia. In the mid 1950s it was described by Arvid Carlsson that 80% of the brain's dopamine is found within the basal ganglia, and Oleh Hornykiewicz found that the brains of patients with Parkinson's disease are deprived of dopamine. A few years later, Hornykiewicz and Walter Birkmayer found that the intravenous administration of L-dihydroxyphenylalanine (levodopa), the precursor of the neurotransmitter dopamine, provided a dramatic, although brief, relief of the symptoms of PD. The finding that regular oral administration of levodopa could significantly improve the quality of life for PD patients, was the onset for the modern era of pharmacological therapy. There were, however some drawbacks to this therapy such as side effects in the form of involuntary movements (dyskinesias) and motor response fluctuations. And despite the development of newer and more effective antiparkinsonian drugs, the positive effects of the therapy begin to wane after about five years.

For patients that show very little response to drug therapy, new therapies were needed. Surgical lesions of certain components of the thalamus or the basal ganglia, such as the thalamic nucleus ventralis intermedius (VIM), the internal segment of the globus pallidus (GPi), or the subthalamic nucleus (STN) have proven to be effective methods to alleviate PD symptoms. Within a complex interaction system such as the basal ganglia, it is believed to be better to have no input from certain components, than to have a distorted one.

Instead of lesioning part of the thalamus or basal ganglia, a new approach was applied by Benabid and colleagues at Grenoble, France in the mid-1980s. They applied high-frequency stimulation to the VIM, and just like after lesioning this area, tremors of the patient were severely reduced. In this way they showed, for the first time, that chronic, high frequency deep brain stimulation (DBS) is a definitive long-term alternative to destructive surgery for PD patients (A. Benabid, Pollak, Louveau, Henry, & De Rougemont, 1987). The use of DBS for PD patients, that do not adequately respond to drug therapies, has matured rapidly between its inception and the first US FDA approval in 1997, and has developed steadily since then (Coffey, 2009). DBS is now a widely used and broadly accepted therapeutic modality with stimulators implanted in patients each year.

However, there is still very much unknown about the exact mechanisms behind the way DBS works. Despite the widespread use of DBS on the subthalamic nucleus, there are now ideas suggesting other areas as being more effective targets for DBS to treat Parkinson's disease. Also the stimulation of multiple areas simultaneously has been proposed. And the finding of external cues being effective modulators to relieve PD symptoms, has led to the idea of applying brain stimulation to areas outside of the basal ganglia to simulate such an external

cue. All these stimulation methods differently affect the neuronal network involved in Parkinson's disease, which determines their influence on the symptoms. A better understanding of their effect is therefore essential in the search towards better treatments. This review will give a description of the latest developments in the research fields of deep brain stimulation and Parkinson's disease, and will give suggestions for possible future directions.

Chapter 2: Parkinson's Disease

2.1 Symptoms

The description of Parkinson's disease has changed little since James Parkinson first described it in 1871. It is still known as an idiopathic, progressive disease with a clear effect on the motor system of the patient. The most important motor symptoms of PD are (Fernandez, 2012):

- **Tremor at rest**, which can be subtle, such as only involving a thumb or a few fingers, and is absent in 20% of patients at presentation.
- **Rigidity**, which is felt by the examiner rather than seen by an observer.
- **Bradykinesia** (slow movements) **or akinesia** (impaired movements), which is characteristic of all Parkinson patients.
- **Gait and balance problems**, which usually arise after a few years, although occasionally these symptoms are present from the moment PD has been diagnosed. Patients typically walk with small steps with occasional freezing, as if their foot were stuck. Balance problems are the most difficult to treat among the motor problems.

Not all of these symptoms need to be present in PD patients. In some patients the disease is dominated by tremors, while in others bradykinesia and rigidity are the most profound symptoms (Zaidel, Arkadir, Israel, & Bergman, 2009). The same is true for gait problems, which can be very severe in some patients, while they are almost non-existent in others (Snijders et al., 2011). Even within a single patient, the magnitude of these symptoms can change independently from each other as the disease progresses. The underlying neural mechanisms are believed to be different for these symptoms, as different treatments often do not affect symptoms in the same magnitude. Rigidity and bradykinesia for example, are better treated by dopaminergic medication, while tremors are more affected by anticholinergic agents (Zaidel et al., 2009). It is suggested that tremors may even be a compensatory mechanism for the patient's bradykinesia and rigidity (Zaidel et al., 2009).

Beside the effect of PD on the motor system, it has also profound nonmotor symptoms, that can be even more disabling for the patient (Fernandez, 2012). Pain, for example, has only recently been recognized as a symptom of PD, but has a big influence on the patient's life and is very common among patients. The same is true for fatigue. Since motor symptoms become better controlled, and since patients tend to live longer nowadays, these nonmotor symptoms are becoming an increasing problem. Among the most difficult, are the neuropsychiatric disturbances, such as dementia, psychosis and depression. Other symptoms are: masked facies, urinary disturbance, sexual dysfunction, and sleep disturbance. The disease is also regularly progressive, so that medical treatment always needs to be adjusted over the course of several years. In short, Parkinson's disease is a complex disorder that has a great influence on many aspects of a patients life.

Disease rating scale

To quantify the severity of each of these symptoms, the 'Unified Parkinson's Disease Rating Scale' (UPDRS) was developed. This is especially important to test the effectiveness of novel treatments. The rating scale is based on clinical observation and patient interview. It consists of the following sections: evaluation of mental activity, behavior, and mood (part I); self evaluation of daily life activities (part II); clinician-scored motor evaluation (part III);

evaluation of complications of the therapy (part IV). Other rating scales such as the 'Hoehn and Yahr scale' and the 'Schwab and England Activities of Daily Living Scale' are sometimes incorporated in the UPDRS as part V and VI, respectively. Another rating scale that is often used, is the 'Beck Depression Inventory' (BDI) scale, as a measure for depression.

2.2 Neural basis

The basal ganglia, thalamus and motor cortex all play a major role in normal voluntary movement. Even though they have different functions, a disturbance in one of these areas can disrupt the complex interaction network, which can lead to several movement disorders. First indications of the importance of basal ganglia in movement disorders, came from postmortem examinations of patients with PD or Huntington disease. These examinations revealed pathological changes in the basal ganglia, which are believed to be the most important factor for the development of these diseases.

The basal ganglia consist of four nuclei that lie deep within the brain, below the neocortex. (Fig. 1). These are: 1. the striatum, 2. the globus pallidus (or pallidum), 3. the substantia nigra, and 4. the subthalamic nucleus (STN). Because of functional differences, the four components of the basal ganglia are often further subdivided. The striatum consists of the putamen and the caudate nucleus, the globus pallidus is divided into an internal (GPi) and an external (GPe) component, and the substantia nigra consists of the pars compacta (SNc) and the pars reticulata (SNr). It is the degeneration of the dopaminergic SNc that is very specific for patients with PD. The basal ganglia are known to be highly connected to virtually every part of the cerebral cortex, to the amygdala, the hippocampus, certain brain stem nuclei, other basal ganglia nuclei, and to the thalamus. The thalamus is located in close proximity to the basal ganglia (Fig. 1). It is known as a gatekeeper for sensory information that enters the brain. Input from every sensory system (except the olfactory system), passes through the thalamus before it reaches the cerebral cortex. But it also has a major role in the motor system, as it connects the basal ganglia output to the neocortex. However, neither the thalamus or the basal ganglia have direct input or output connections with the spinal cord, which is unlike other components of the motor system.

Because of its strong relation with common neurodegenerative disorders, the basal ganglia have been extensively studied. The discovery by William Langton that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) created a profound Parkinsonian state in drug addicts, allowed the development of an animal model of PD. Non-human primates exposed to MPTP developed symptoms typical to PD, and just like PD patients, had a selective loss of neurons in the SNc. Neurons in the SNc contain high concentrations of neuromelanin, a dark pigment derived from oxidized and polymerized dopamine, which gives the substantia nigra its name. Loss of these SNc neurons causes a deprivation of dopamine in the brain, which is responsible for PD symptoms. Studies with MPTP-treated monkeys allowed the creation of a model for basal ganglia function (Fig. 2).

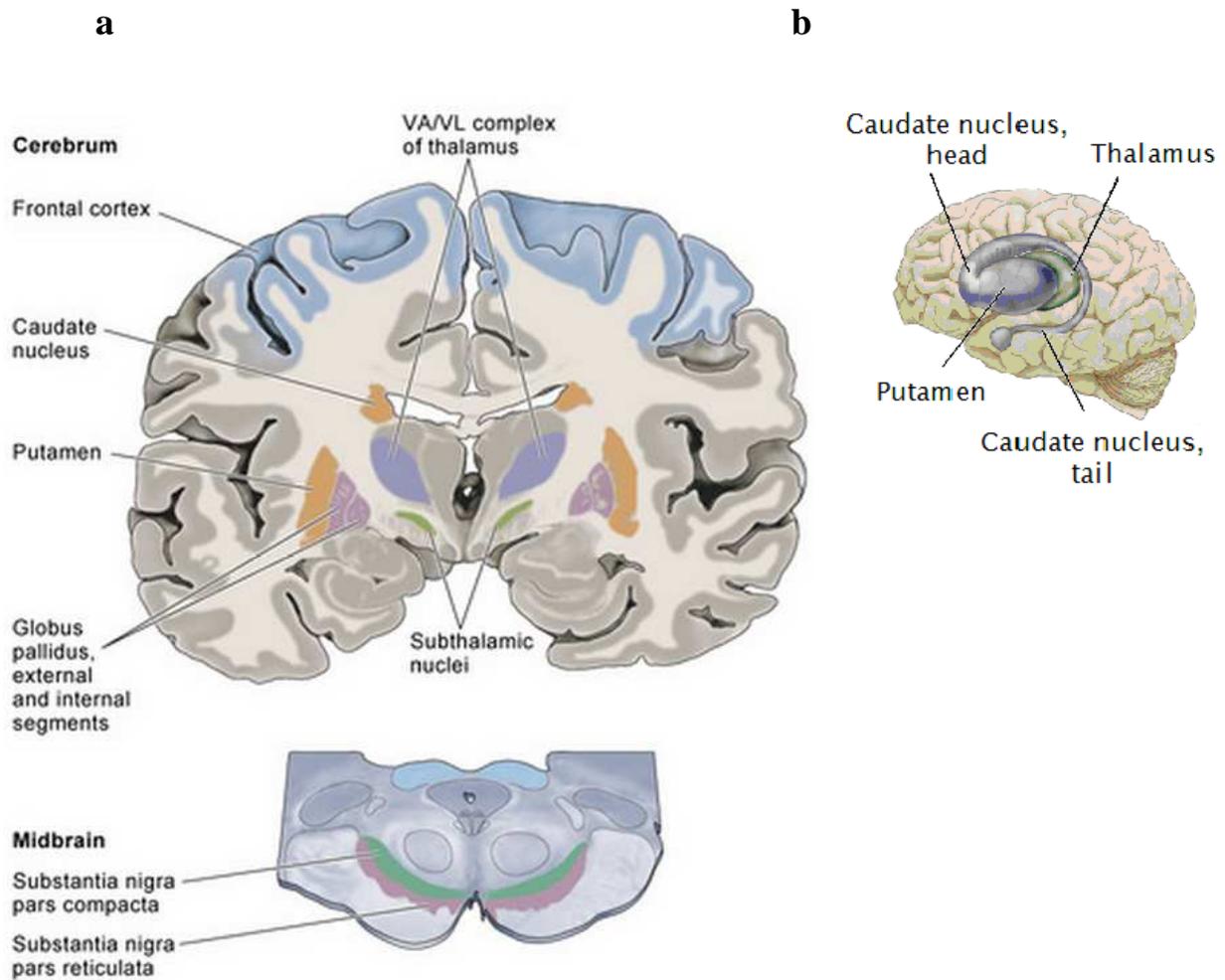


Figure 1. Locations of the basal ganglia components and the thalamus. **a.** An idealized coronal section through the brain. Most components of the basal ganglia are in the telencephalon, but the substantia nigra is located in the midbrain, and the subthalamic nucleus is located in the diencephalon together with the thalamus. **b.** A whole brain image with the striatum and thalamus visible in the brain (Purves et al., 2004).

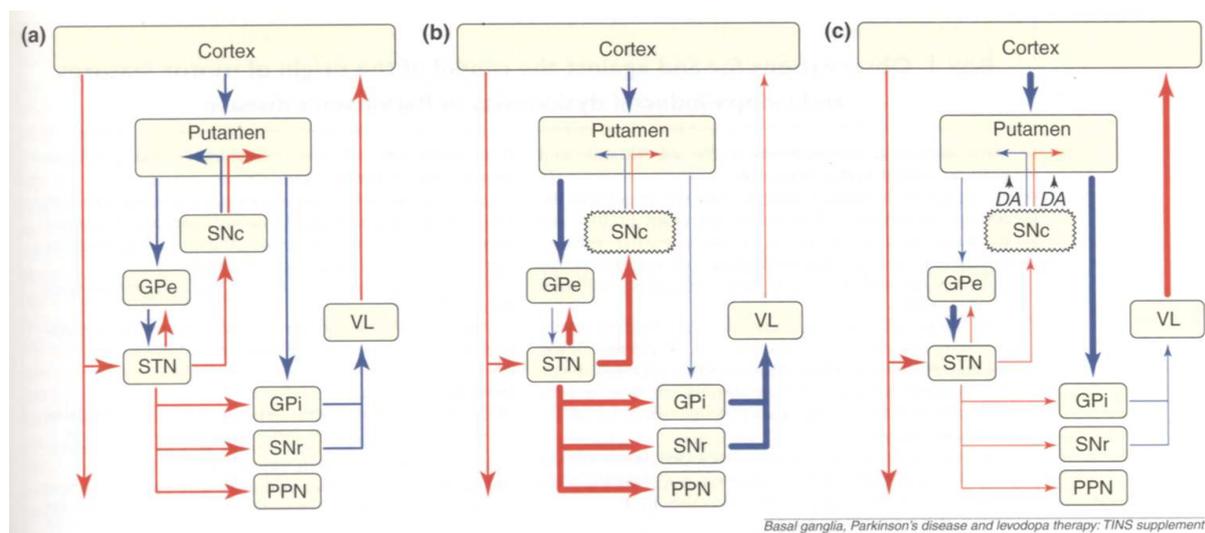
Classical model of basal ganglia function

In the healthy individual dopaminergic projections from the SNc affect the putamen in two different ways (Fig 2a). Dopamine binds to two different types of neurons in the striatum, exciting D1-receptor-expressing neurons and inhibiting D2-receptor-expressing neurons, that are part of the direct and indirect pathway, respectively. Just like 90-95% of the striatal neurons, those in the direct and indirect pathway, are inhibitory GABA-ergic medium-spiny projection neurons. The D1-receptor-expressing neurons of the direct pathway inhibit the activity in the GPi. Just like striatal neurons, cells in the globus pallidus use GABA as neurotransmitter. From the GPi, inhibitory projections reach the nucleus ventralis lateralis (VL; the region of the thalamus that plays a role in motor function), from where excitatory projections reach the motor cortex. In the indirect pathway, that starts with D2-receptor-expressing neurons of the putamen, GABA-ergic inhibiting projections reach the GPe. The GPe then inhibits the activity of the STN. The STN has excitatory, glutamergic projections to several other nuclei, such as the GPi, SNr, pedunculopontine (PPN), and the SNc. The projections of the STN are the only intrinsic connections of the basal ganglia that are excitatory. The output activity of the basal ganglia is therefore modulated by the opposing

effects of the direct and indirect pathway, which facilitates and suppresses motor activity, respectively.

In the parkinsonian state, there is a degeneration of SNc neurons, which causes a decline of dopaminergic projections to the putamen. This affects both the direct and the indirect pathway (Fig. 2b). Decreased dopaminergic input causes a decreased activity of D1-receptor-expressing neurons (direct pathway) and an increased activity of D2-receptor-expressing neurons (indirect pathway). This results in an increased GPi and SNr activity via both pathways, and therefore a decreased activation of the motor cortex by the thalamus. This culminates in a hypoactive state of the patient, which is characteristic for Parkinson's disease.

As mentioned before, symptoms of PD are treated with the administration of levodopa to the patient. This is believed to restore the dopaminergic input to the striatum, and therefore the functioning of the direct and indirect pathway. It often occurs, however, that the administration of levodopa results in dyskinesias such as chorea-ballism. The effect of excess dopamine on the model, is shown in Fig. 2c. There is a reduced inhibition of the thalamus by the GPi and the SNr, and therefore an increase in excitation of the motor cortex, i.e. the exact opposite effect of PD. Treatments by lesioning or high frequency stimulation can also result in dyskinesias because of a reduced inhibition of the thalamus.



Basal ganglia, Parkinson's disease and levodopa therapy: TINS supplement

Figure 2. Schematic of the classic model of the basal ganglia. Projections between the basal ganglia nuclei and other brain areas for the (a) normal, (b) parkinsonian, and (c) dyskinetic state are depicted by arrows. Blue arrows indicate inhibitory projections and red arrows excitatory projections. The thickness of the arrows indicates the relative strength of the projection compared to the normal state. Abbreviations: DA, dopamine; PPN, pedunculopontine nuclei; SNc, substantia nigra pars compacta; VL, ventralis lateralis (Obeso et al., 2000).

Problems with the classical model

This model serves as a good way to understand the basic workings of the basal ganglia and the thalamus. However, it also gives a too simplistic view of this complex, multidirectional system. There are numerous observations that do not cope with the classical model, such as paradoxical effects of PD treatments (see Obeso et al., 2000 for an overview). The model merely describes increases and decreases in activity of several brain areas, while it does not incorporate rhythmic firing of these areas. It therefore does not explain one of the most typical symptoms of PD, tremor at rest. Tremors are believed to result from rhythmical activity in the basal ganglia and thalamus. One study found that 19.7% of recorded cells in the pallidum of PD patients presented a rhythmic modulation of their firing rate during rest tremor episode at a frequency that was not statistically different from the rest tremor frequency. Also in the

thalamus, they found an interburst frequency of rhythmic low-threshold calcium spike bursts that was similar to, but not synchronized with, rest tremor frequency (Magnin, Morel, & Jeanmonod, 2000). Synchronization is believed to be an important aspect of basal ganglia functioning. Several studies have described functional synchronization in the subthalamo-pallidal-thalamo-cortical circuit in two frequency bands (<30 Hz and >60Hz) which could better explain the pathophysiology of certain PD symptoms (see Brown, 2003 for an overview). However, the classical model does not incorporate this synchronization as an aspect of basal ganglia functioning. Furthermore, the basal ganglia are known to have extensive and highly organized connections with areas such as the cerebral cortex, the hippocampus, and the amygdala which are not mentioned in this model. It can therefore not explain how neuropsychiatric disorders result from basal ganglia malfunction, or how external stimuli can have a profound influence on PD symptoms. Also, the influences of areas such as the pedunculopontine nuclei (PPN) and the centromedian parafascicular (CM-Pf) complex, which are intimately connected to the basal ganglia, are left out of this model. Despite these limitations, this model has served well in providing surgeons targets for lesioning and DBS which has been very successful in treating most of the PD symptoms, as will be described later on.

Chapter 3: Deep Brain Stimulation

3.1 DBS in general

Ever since the Italian physician and physicist Luigi Galvani discovered in the late 1700s that living excitable muscle and nerve cells produce electricity, people have been viewing the brain more and more as an electrical organ. It is only recent, however, that we try to modulate the brain to cure neurological diseases by injecting electrical current into it. At first, electrical stimulation was used to try to activate certain parts of the brain. This can be a possible solution for diseases that have their origin in a hypoactive brain structure. Later it was found that electrical stimulation can also inhibit the activity of a brain area. The frequency of stimulation is believed to be of crucial importance for the effect. In general it is believed that stimulation at physiological frequencies (30-60 Hz) has a stimulating effect on the brain, while high frequency (>100 Hz) stimulation inhibits the activity of a brain structure (A. L. Benabid et al., 2001; A. L. Benabid, 2003). However, the exact effect of high frequency stimulation is much more complicated. Neural recordings have shown that high frequency stimulation decreases activity of stimulated nuclei, but the output of these nuclei, on the contrary, show increased activity. This is based on the concept of de-coupled somatic and axonal firing of projection neurons during high frequency stimulation (see McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004 for an overview). Nevertheless, the effect of high frequency stimulation provides similar therapeutic outcomes as the ablation of the same area, even though this is likely achieved via different mechanisms (McIntyre et al., 2004).

In the mid 1980s high frequency stimulation was performed for the first time on the thalamic nucleus ventralis intermedius of Parkinson patients who were resistant to drug therapy (A. Benabid et al., 1987). They found that this deep brain stimulation was able to stop the pathological tremors of the patients, almost as effectively as stereotactic thalamotomy of this area. One of the major advantages of DBS compared to ablative procedures, is that it is reversible. For this reason many neurosurgeons started choosing DBS treatment over destructive surgery when this was possible. Nowadays it is a popular treatment for severe PD patients who no longer adequately respond to pharmacological therapy.

Mechanisms

To treat patients with deep brain stimulation, an internalized neuromodulator or stimulator is chronically implanted. It consists of 1 or 2 thin wires (the electrodes) that are carefully placed into a selected brain structure. These wires are connected to a small battery (pulse generator) located just beneath the skin, usually near the shoulder (fig. 3). It then provides continuous electrical stimulation to the deep lying brain structure. Electrical stimulation can also be used during surgery to search for the optimal location of the electrodes, before implanting them. The amplitude, pulse width and frequency can often be tuned to the patient's specific needs, and can be modified as the disease progresses.

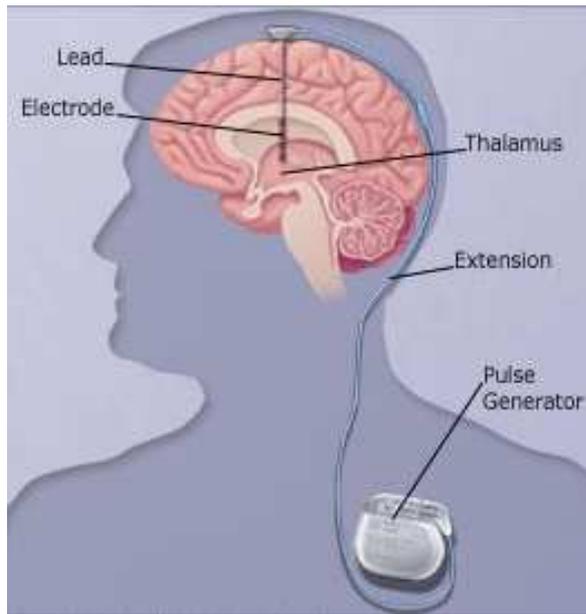


Figure 3. Deep brain stimulation. Stimulation is delivered at the tip of the tip of thin wire, the electrode, into a brain structure (i.e. the thalamus) located deep inside the brain. Electrical current is delivered by a pulse generator placed under the skin, usually near the shoulders (2002 WebMD, Inc.).

Targets for DBS

One of the most interesting questions in PD research nowadays, is which neural structure provides the best target for DBS. The first DBS performed on a PD patient, targeted the thalamic nucleus ventralis intermedius (VIM) since thalamotomy was a popular treatment for advanced PD at the time (A. Benabid et al., 1987). When DBS was validated in VIM, other brain areas previously used as lesioning targets, were quickly tested for DBS. Popular targets then became GPi and STN, with the latter being the most commonly used target nowadays. Other targets that are currently explored for the treatment of PD are the pedunculopontine nucleus (PPN), the caudal zona incerta nucleus (cZI), and the centromedian-parafascicular (CM-Pf) complex of the thalamus (Mazzone et al., 2006; Plaha, Ben-Shlomo, Patel, & Gill, 2006; Stefani et al., 2007). We will give an overview of several studies comparing these different brain areas to each other as targets for DBS.

3.2 Thalamus

During the time when ablative surgery was the method of choice to treat PD, lesions were set in many different nuclei in and around the thalamus. All these areas were found to be effective targets for the treatment of cardinal symptoms of the disease, such as tremor, rigidity, and bradykinesia. The fact that the destruction of one of these nuclei can have similar effects, suggests a strong interaction within this system, that can not function without one of its components. It became the challenge to target that area, of which a lesion will achieve the desired relieve of symptoms, while the side effects of the treatment will be kept to a minimum. Ablation of the VIM was proven to be an effective target, since even small lesions in this area resulted in high therapeutic success. Smaller lesions are often preferred by the neurosurgeon because they decrease the danger of potential side effects. Another advantage of VIM, is that it is among the best studied nuclei in human neurophysiology. These reasons made VIM-lesioning a popular choice for neurosurgeons in the treatment of PD, and made it become widely used. It is therefore understandable that VIM became the first region to be targeted for DBS (A. Benabid et al., 1987).

To investigate the effectiveness of this new technique, tremor suppression and UPDRS scores were measured in 27 drug resistant PD patients before and after VIM-DBS implantation. Six of these patients were implanted bilaterally, coming to a total of 33 implanted stimulation devices that could be analyzed independently. They found that in 21 cases (64%), VIM stimulation resulted in total suppression of the patient's tremors. Six of them (18%) showed major improvement, which meant that tremors only appeared during stressful conditions, but still to a much lesser extent than without stimulation. In 4 cases (12%) improvement was described as minor, since tremors remained, but were less pronounced than without stimulation. Only in 2 cases (6%), no effect of the stimulation treatment was found. Based on the UPDRS, they found a mean improvement of 45% for the activities of daily living (UPDRS II), and an improvement of 43% based on the clinician-scored motor evaluation (UPDRS III), as is shown in fig. 4. They did, however, not observe any effect on other symptoms of PD, such as rigidity and akinesia. Side effects of the stimulation were relatively mild. Even though paraesthesias were observed in 27 cases, in all but 2 cases, this effect was only present for the first 5 seconds the device was turned on and then disappeared. In the 2 cases this effect was permanent, it did not impair the patient. Additional side effects were: mild dysarthrias (4 cases, 2 patients), marked dysarthrias (2 cases, 1 patient) and dysequilibria (1 case). The authors eventually concluded that VIM-DBS is an effective method to treat tremor in PD as well as in essential tremor patients. Compared to thalamotomy, its reversible and low-risk features make DBS an attractive alternative. It was found to be superior to thalamotomy when the patient was impaired by bilateral tremor or had already undergone a contralateral thalamotomy (Alesch et al., 1995).

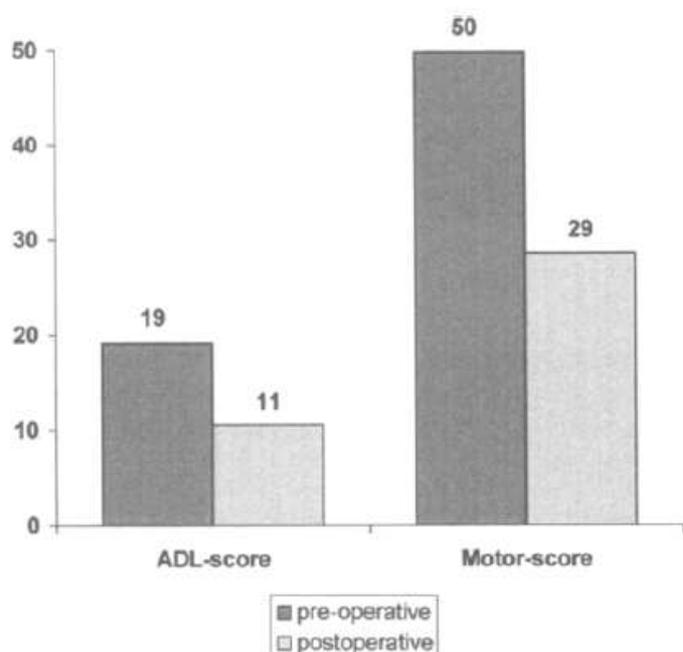


Figure 4. Pre- and postoperative scores of the activities of daily living (ADL), measured with UPDRS II, and the motor performance, measured with UPDRS III (Alesch et al., 1995).

3.3 Subthalamic Nucleus

As mentioned before, the VIM was a popular target for ablative surgery, especially to treat tremors. Lesioning of other nuclei in the thalamus or basal ganglia were believed to be less

effective. Nevertheless there was a reintroduction of pallidotomy in the 1980s, after its first introduction in the 1950s. The reason for this was because of its strong efficiency on the levodopa induced dyskinesias, a problem that was not yet present in the 1950s. Furthermore, it also had a greater effect on symptoms like akinesia and rigidity, making pallidotomy preferable to thalamotomy for some patients. When surgeons started to move from ablative surgery to high frequency stimulation, the limited effect of VIM-DBS on dyskinesias, akinesias, and rigidity became a serious issue. DBS in other areas, such as the GPi and the STN, was quickly explored. We will make a comparison between the effectiveness of DBS on these different areas, starting with what is nowadays the most used target, the subthalamic nucleus.

Health benefits of STN-DBS

The clinical benefits of bilateral STN-DBS were reported for 18 PD patients, 6 months after operation. Additionally, for 14 of these patients, effects after 12 months were reported. They measured the effect of stimulation while the patients were under their antiparkinsonian medication (drug "on" condition), and while they had stopped their medication overnight for at least 12 hours (drug "off" condition). Great improvements were observed several months after the operation. In the drug "off" condition there was a great improvement in the activity of daily living after 6 (UPDRS II -52%, $p < 0.01$) and 12 months (UPDRS II -60%, $p < 0.01$) after operation, and while the patients were under STN stimulation. Also pathological motor symptoms were greatly improved after 6 (UPDRS III -55%, $p < 0.001$) and 12 months (UPDRS III -62%, $p < 0.001$), while under STN stimulation in the drug "off" condition. No difference was noted with the presurgical assessment when the stimulator was turned off.

No significant differences were found for the UPDRS III motor scores before and after operation, in the drug "on" condition. However, there was a very significant reduction in motor fluctuations and dyskinesias in this condition when the DBS was on, 6 (UPDRS IV -76%, $p < 0.001$) and 12 months (UPDRS IV -91%, $p < 0.001$) after surgery. All observed results are shown in table 1 (Thobois et al., 2002).

Table 1. Results measured with UPDRS in the drug "on" and "off" condition (Thobois et al., 2002).

mean \pm SD, On period score						
Outcome measure	Score range	Before surgery	6 months DBS Off	6 months DBS On	12 months DBS Off	12 months DBS On
UPDRS I	0–16	1.5 \pm 1.6		2.1 \pm 1.8 ¹		2.1 \pm 1.5 ¹
UPDRS II (ADL)	0–52	5.3 \pm 2.6		8.1 \pm 4.7 ¹		7.5 \pm 5.2 ¹
UPDRS III	0–108	17.9 \pm 9.2	23.1 \pm 12.6 ¹	15.2 \pm 10.4 ¹	21 \pm 9 ¹	13 \pm 7.6 ¹
UPDRS IV	0–44	10.3 \pm 3		2.5 \pm 3*		0.9 \pm 1*

mean \pm SD, Off period score						
Outcome measure	Score range	Before surgery	6 months DBS Off	6 months DBS On	12 months DBS Off	12 months DBS On
ADL (UPDRS II)	0–52	26.9 \pm 6.5		12.7 \pm 7*		10.7 \pm 7*
UPDRS III	0–108	44.9 \pm 13.4	43.2 \pm 10.4 ¹	20.2 \pm 10 ^{*,2}	41.4 \pm 7.9 ¹	17 \pm 10 ^{*,2}

* statistically significant at $p < 0.05$ compared to the presurgical assessment

¹ not statistically significant compared to the presurgical evaluation

² statistically significant at $p < 0.05$ compared to the on medication DBS score

Similar results were found in a bigger study that comprised 60 PD patients with bilateral STN-DBS. Twelve months after surgery they found great improvements in motor symptoms (UPDRS III -55%), activities of daily living (UPDRS II -45%, Schwab and England Scale +142%) in the drug “off” condition, and dyskinesias in the drug “on” condition (-40%). Pharmacologic treatment with levodopa was decreased by 50%. On average, these patients were mildly depressed before surgery (BDI 10.4 ± 6.6), but 12 months after surgery, there was a small but significant improvement of mood after surgery (BDI 8.5 ± 4.1 , $p < 0.002$). The results from this study are presented in table 2 (Lagrange et al., 2002).

Table 2. Results based on several rating scales in the drug "on" and "off" condition before and 12 months after surgery (Lagrange et al., 2002).

Item (maximal score)	Medication	Before surgery	After surgery, on stimulation	Wilcoxon test
UPDRS I (16)		1.4 ± 1.1	2.5 ± 2.7	NS
UPDRS II (52)	“On”	11.3 ± 7.8	11.4 ± 6.4	NS
	“Off”	29.6 ± 8.8	13.4 ± 9.0	$p < 0.002$
UPDRS III (108)	“On”	20.3 ± 18.8	18.8 ± 12.7	NS
	“Off”	53.7 ± 19.1	24.3 ± 16.6	$p < 0.002$
S&E (100%)	“On”	77 ± 18	83 ± 14	NS
	“Off”	29 ± 19	70 ± 26	$p < 0.002$
Dyskinesias (28)	“On”	9.6 ± 4.0	5.8 ± 3.0	$p < 0.001$
LED		$1,010 \pm 425$	522 ± 400	$p < 0.001$
BDI (63)		10.5 ± 6.6	8.5 ± 4.1	$p < 0.002$

Values are means \pm SD. Except for the S&E, a reduction in the scores indicates an improvement in the function.

BDI = Beck Depression Inventory scale; LED = Levodopa equivalent dose in mg/d; NS = not significant; S&E = Schwab and England activities of daily living scale; UPDRS = Unified Parkinson’s Disease Rating Scale.

Parkinsonian symptoms would quickly reappear in patients that were not under their medication, after the stimulation device was turned off. Tremor worsened within several minutes, bradykinesia and rigidity within 30 to 60 minutes, and axial signs over 3 to 4 hours. There was a 90% worsening of the UPDRS motor score, only 2 hours after DBS was turned off. When their stimulator was turned on again, PD symptoms started to disappear in a similar order as they had appeared, but at a faster rate. These results further demonstrate the effectiveness of STN-DBS on PD symptoms. The particular order in which the symptoms appear and disappear, suggests that STN-DBS act by different mechanisms on the major parkinsonian signs (Temperli et al., 2003).

High frequency stimulation of the STN also improves standing posture and gait initiation, as was observed for ten PD patients with bilateral STN-DBS. Unilateral and bilateral stimulation showed qualitatively similar effects, but they were more robust in the latter condition. For the standing posture of the patient, they found a reduction of the forward trunk bending (n.s., unilateral and $p=0.0065$, bilateral), trend toward a lower inclination of the thigh and a significant decrease of the inclination of the shank ($p=0.0009$ unilateral; $p=0.0001$ bilateral) as an effect of STN stimulation. From EMG recordings it was measured that global motor output from the leg muscles was significantly reduced ($p=0.0099$ and unilateral, $p=0.0030$ bilateral). Moreover, in patients exhibiting lower limb tremor, the root mean square values of the affected muscles were significantly decreased ($p=0.0122$, unilateral and $p=0.0065$, bilateral). For the initiation of gait, a significant reduction in the duration of the imbalance phase ($p=0.0324$, unilateral and $p=0.0469$, bilateral stimulation) was observed in this study. The first step became longer ($p=0.0403$, unilateral and $p=0.0009$, bilateral) and faster ($p=$

0.0195, unilateral and $p=0.0006$, bilateral). Furthermore, there were significant increments of the gait speed, measured at the heel-strike of the trailing limb, with a progressive displacement toward the reference range on moving from unilateral ($p=0.0253$) to bilateral STN stimulation ($p=0.0009$). The authors concluded that STN-DBS resulted in a substantial improvement of the gait initiation process in patients with PD (Crenna et al., 2006).

Reduction of medical treatment

Surgery is most often performed on PD patients with severe symptoms that can no longer be adequately controlled with levodopa medication. The great relieve of parkinsonian symptoms as a result of STN-DBS, allows the patient to drastically reduce its medical dosage to approximately 30-50% (depending on the patient) of the dosage before surgery (A. L. Benabid et al., 2001; Thobois et al., 2002; Umemura et al., 2011). Depending on the DBS-induced improvements of the symptoms, levodopa administration was further reduced in the period following the surgery. Thobois and colleagues described an average 50% decline in drug dosage, two weeks after starting STN electrical stimulation, and an average 65.5% decline after 6 months. From the 18 patients studied, 6 had stopped completely with taking all antiparkinsonian drugs, including levodopa, and 3 others were no longer taking levodopa (Thobois et al., 2002).

Side effects of STN-DBS

As with all effective medical treatments, some profound side effects can be observed. One study focused specifically on these side effects (Umemura et al., 2011). These side effects are subdivided into three categories: 1. related to surgery 2. related to the device 3. related to the electrical stimulation. They reported the complications resulting from bilateral STN-DBS in a group of 180 PD patients over a period of seven years (from November 2003 to October 2010). A number of complications they observed are summarized in table 3. The overall surgical outcome of the treatment was described by the authors as acceptable. Mortality rate was 0% and most complications were transient and treatable. Surgery-related and device-related complications could be reduced with better surgical experience, and with new surgical equipment and technology. Of the complications that were classified as stimulation-related, the exact cause of the effect is not always clear. Excessive reduction of dopaminergic medication, change in social life, and further progression of PD are believed to be important factors.

Similar side effects as reported in table 3 have been observed in other studies looking at STN-DBS (A. L. Benabid et al., 2001; Lagrange et al., 2002; Thobois et al., 2002). They all concluded that STN-DBS is a relatively safe method, with its benefits outweighing the adverse effects. When side effects occur, they are often the result of excessive voltages or electrode mislocation, and can be dealt with by decreasing the voltage of the stimulation or replacing the electrode, respectively (A. L. Benabid, 2003). The most common stimulation-related complication was depression. Even though this is something to take into consideration, especially because of possible suicide attempts, the overall effect of STN-DBS on mood of the patient, was considered to be positive. Despite some cases of increased depression, significant improvements were measured with UPDRS II and even with the BDI scale (Lagrange et al., 2002; Thobois et al., 2002).

Table 3. Number of specific side effects that occurred in a group of 180 PD patients after STN-DBS was implanted (Umemura et al., 2011).

	Transient	Permanent
Early complications (within 3 months after surgery)		
Related to surgery		
intracerebral hemorrhage	0	2
chronic subdural hematoma	1	0
deterioration of psychotic symptoms	2	0
Related to device		
device infection	3	0
skin erosion	1	0
Related to treatment or stimulation		
intractable dyskinesia/dystonia	8	0
apraxia of eyelid opening	0	3
hypomania with trouble	5	0
impulse control disorder	2	0
depression	3	0
suicide attempt	1	0
rapid deterioration of cognitive function	0	1
back pain	3	4
restless leg syndrome	4	0
Late complications (more than 3 months after surgery)		
Related to device		
device infection	2	0
skin erosion	4	0
implantable pulse generator malfunction	2	0
Related to treatment or stimulation		
intractable dyskinesia/dystonia	2	1
apraxia of eyelid opening	0	8
dysarthria	0	7
depression	2	0
suicide attempt	1	0
back pain	2	1
restless leg syndrome	2	0

3.4 Globus Pallidus Internal

Because the GPi had proven itself to be a successful target for ablative surgery, GPi-DBS was quickly explored, just like STN-DBS. With many PD patients implanted with either a GPi or STN stimulation device, many studies have compared the effectiveness of both types of stimulation (Anderson, Burchiel, Hogarth, Favre, & Hammerstad, 2005; Follett et al., 2010; Krack et al., 1998; Krause et al., 2001). In one of the earlier studies, 5 patients with GPi-DBS were compared to 8 patients with STN-DBS. All these patients had the onset of Parkinson's disease before the age of 40, had severe levodopa induced motor complications, and were bilaterally operated. The scores of UPDRS II and III were compared before and 6 months after surgery, in the drug "on" and "off" condition, for both patient populations.

The results of this study are given in table 4. In the drug "off" condition the authors observed an increase in activities of daily living (UPDRS II) and motor score after either GPi-DBS or STN-DBS, but the improvement was greater in the latter case ($p < 0.05$, UPDRS II and $p < 0.01$, UPDRS II). From the UPDRS subscales they found a significantly greater effect of STN stimulation on akinesia ($p < 0.05$), gait score ($p < 0.05$), and hand tapping score ($p < 0.01$)

compared to GPi stimulation, and no significant effect on tremor or rigidity. In the drug "on" condition there was no significant difference between the GPi and STN group based on UPDRS II and III. Levodopa induced dyskinesias were found to be much more decreased by GPi-DBS (-82%) than by STN-DBS (-41%), and this difference was significant ($p < 0.05$). However, these dyskinesias were effectively managed by a decrease in levodopa dosage and a progressive increase in voltage over a period of months. In the STN group it was also possible to decrease drug dosage to a further extent (-56%) than in the GPi group (-29%) and all stimulation parameters were significantly lower in the STN group. Furthermore, a mild aggravation of akinesia was observed in the GPi group compared to the STN group. Based on these results, the authors concluded that STN-DBS is superior to GPi-DBS with severe levodopa induced motor complications (Krack et al., 1998). A similar study came to the same conclusion, GPi-DBS may be more effective in reducing medication side effects, but the allowed decrease of drug dosage for patients with STN-DBS, makes the STN the target of choice for high frequency stimulation (Krause et al., 2001).

Table 4. Comparison between the differences in UPDRS II and III scores before and 6 months after surgery in the STN and GPi group. Given for both the drug "off" and "on" condition (Krack et al., 1998).

Drug "off"	Bilateral STN stimulation ($n = 8$)			Bilateral GPi stimulation ($n = 5$)			P-value*
	Preoperative	Postoperative	Difference	Preoperative	Postoperative	Difference	
UPDRS II	33.3 ± 5.4	9.1 ± 3.9	-24.1 ± 6.3	27.8 ± 8.2	15.0 ± 6.4	-12.8 ± 3.8	<0.05
UPDRS III	57.5 ± 14.5	17.1 ± 8.2	-40.5 ± 15.4	53.6 ± 10.4	32.5 ± 12.4	-21.1 ± 13.5	<0.05
Drug "on"	Bilateral STN stimulation ($n = 8$)			Bilateral GPi stimulation ($n = 5$)			P-value*
	Preoperative	Postoperative	Difference	Preoperative	Postoperative	Difference	
UPDRS II	7.9 ± 4.8	4.6 ± 4.1	-3.3 ± 6.2	13.6 ± 4.9	10.6 ± 6.8	-3.0 ± 7.0	n.s.
UPDRS III	18.2 ± 10.6	14.7 ± 9.1	-3.5 ± 8	23.2 ± 4.0	26.5 ± 6.5	+3.3 ± 10.1	n.s.

STN = subthalamic nucleus, GPi = globus pallidus internus; n.s. = not significant. *Pre- and postoperative score differences are compared across the two groups.

However, bigger, randomized, and more recent studies mention that it is premature to exclude the GPi as an appropriate target for DBS (Anderson et al., 2005; Follett et al., 2010). One of these studies compared 152 PD patients that were randomly assigned to bilateral GPi-DBS to 147 patients that were randomly assigned to bilateral STN-DBS. All patients had persistent motor disabilities, such as dyskinesias and motor fluctuations, despite antiparkinsonian medication (Follett et al., 2010).

The results based on the motor score (UPDRS III) are summarized in table 5. We will first run through results based on the intention-to-treat analysis. Unlike Krack et al., they did not observe a significant difference between pallidal or subthalamic stimulation in the drug "off" condition, after 6 months of stimulation ($p=0.48$), nor after 24 months of stimulation ($p=0.50$). In the drug "on" condition, patients with GPi or STN-DBS both had a slight decrease in motor scores after 6 months, while after 24 months motor scores were worse than after 6 months in the GPi group, and even slightly worse than before surgery in the STN group. These findings seem to contradict the results of Krack et al. (table 4), but are not significant. Biggest differences between the GPi and STN group were found in the condition without medication and without deep brain stimulation. In this case the patients with GPi-DBS had an improvement of the motor symptoms (i.e. a reduction in UPDRS III score) after 6 and 24 months, while STN-DBS patients suffered from a worsening of symptoms after 24 months.

The difference between stimulation targets was greatly significant after both 6 and 24 months ($p < 0.001$). The overall results based on the intention-to-treat analysis are consistent with those based on the mixed-model analysis.

Table 5. Primary outcome and other motor scores based on UPDRS III. Intention-to-treat-analysis treats missing data from 6 months follow up as having no change in score. In the mixed-effects model analysis were made on the assumption that data were missing at random, and the time evaluation was considered as categorical variable (Follett et al., 2010).

Variable	Mean Score [†]		Mean Change from Baseline at 24 Mo (95% CI)		P Value
	Pallidal Stimulation	Subthalamic Stimulation	Pallidal Stimulation	Subthalamic Stimulation	
With stimulation, without medication[‡]					
Intention-to-treat analysis					
Baseline	41.8±13.1	43.0±15.0			
6 Mo	30.0±13.7	32.2±16.2	-11.7 (-13.8 to -9.6)	-10.6 (-12.8 to -8.5)	0.48
24 Mo	30.0±14.2	32.1±15.6	-11.8 (-14.1 to -9.5)	-10.7 (-12.9 to -8.5)	0.50
Mixed-effects model					
Baseline	41.8 (39.6 to 44.1)	43.0 (40.7 to 45.2)			
6 Mo	28.4 (26.1 to 30.7)	29.9 (27.6 to 32.3)	-13.4 (-15.6 to -11.2)	-13.0 (-15.3 to -10.7)	0.81
24 Mo	28.7 (26.4 to 30.9)	30.1 (27.7 to 32.4)	-13.1 (-15.5 to -10.8)	-12.9 (-15.4 to -10.4)	0.90
With stimulation, with medication					
Intention-to-treat analysis					
Baseline	22.6±11.9	22.4±11.9			
6 Mo	20.3±10.4	21.4±12.5	-2.3 (-3.9 to -0.6)	-1.0 (-2.4 to 0.4)	0.25
24 Mo	21.4±11.8	23.2±12.0	-1.2 (-2.8 to 0.4)	0.8 (-0.9 to 2.4)	0.09
Mixed-effects model					
Baseline	22.6 (20.7 to 24.5)	22.4 (20.5 to 24.4)			
6 Mo	19.9 (18.1 to 21.7)	20.6 (18.7 to 22.4)	-2.7 (-4.4 to -1.0)	-1.9 (-3.6 to -0.1)	0.52
24 Mo	21.2 (19.3 to 23.1)	22.9 (20.9 to 24.9)	-1.4 (-3.1 to 0.4)	0.4 (-1.4 to 2.3)	0.17
Without stimulation, without medication					
Intention-to-treat analysis					
Baseline	41.8±13.1	43.0±15.0			
6 Mo	36.9±13.8	42.9±16.0	-4.8 (-6.9 to -2.7)	0 (-1.9 to 2.0)	<0.001
24 Mo	38.1±14.6	45.1±14.6	-3.7 (-5.9 to -1.4)	2.2 (-0 to 4.5)	<0.001
Mixed-effect model					
Baseline	41.8 (39.5 to 44.0)	43.0 (40.7 to 45.2)			
6 Mo	36.2 (33.7 to 38.7)	42.6 (40.1 to 45.2)	-5.6 (-7.8 to -3.3)	-0.3 (-2.6 to 2.0)	0.001
24 Mo	37.7 (35.4 to 40.1)	44.8 (42.3 to 47.3)	-4.0 (-6.4 to -1.6)	1.9 (-0.7 to 4.4)	0.001

* Scores on the Unified Parkinson's Disease Rating Scale range from 0 to 108 points, with higher scores indicating more severe motor symptoms. All evaluators were unaware of study-group assignments. P values for interactions between time and study group in the mixed-effects analyses of motor scores were as follows: $P = 0.97$ for the evaluation with stimulation and without medication, $P = 0.37$ for the evaluation with stimulation and with medication, and $P = 0.002$ for the evaluation without stimulation and without medication. CI denotes confidence interval.

[†] Plus-minus values are means ±SD. Values in parentheses are 95% CIs.

[‡] This mode of evaluation was the primary outcome.

After 24 months of stimulation, the quality of life was improved for both patient populations (based on UPDRS II and similar scales), with no significant differences between the two groups. For the measures of neurocognitive function, slight decrements were observed in both groups, without significant differences between each other. Only exception was the measure for processing speed index, which was found to have a greater decline in the STN group compared to the GPi group ($p=0.03$). Overall scores on the BDI revealed a slight improvement for the GPi group, and a slight worsening for the STN group ($p=0.02$). Serious adverse events did not occur more often or to a greater extent in of the two patient groups after 24 months. The different stimulation targets did result in significant differences in drug dosage and stimulation parameters. STN-DBS patients reduced their medication of levodopa equivalents by 408 mg and GPi-DBS patients by 243 mg ($p=0.02$). Stimulation of the STN happened on average at 3.16 V with 75.9 μ s pulse width, while stimulation of the GPi was done at 3.95 V with 95.7 μ s pulse width ($p=0.001$).

In this extensive, randomized study (Follett et al., 2010), differences between the STN and GPi group were often not significant. These results are very similar to a smaller, randomized study (Anderson et al., 2005). Unlike much smaller, non-randomized studies (Krack et al., 1998; Krause et al., 2001) no difference was observed for the UPDRS II and III in the drug "off" condition. Only without medication and stimulation, a difference was observed, which favored GPi-DBS. The pallidum also seems to be the target of choice for improving depression. Only when the patient would greatly benefit from reducing medication dosage, STN-DBS seems to be superior. Non of the here described studies observed a significant difference in side effects between the STN and GPi group (Anderson et al., 2005; Follett et al., 2010; Krack et al., 1998; Krause et al., 2001). Follett and coauthors came to the conclusion that both the GPi as the STN are feasible targets for DBS, and clinicians should take many different factors in consideration when choosing the optimal target for their patients, and not only improvement of the motor symptoms (Follett et al., 2010).

3.5 Other targets

Because parkinsonian symptoms emerge from the dysfunction of a very complex system, it makes sense that we still have not found the optimal target area for DBS. Several studies have therefore analyzed the effect of DBS on some unconventional targets, such as the centromedian-parafascicular complex (Mazzone et al., 2006), pedunculopontine nucleus (Stefani et al., 2007), and the zona incerta (Plaha et al., 2006).

Centromedian-parafascicular complex

The parafascicular (Pf) and centromedian (CM) nucleus are intralaminar nuclei of the thalamus. They are standard targets for a variety of functional disorders and have been tested as early as the late 1960s as potential targets for the amelioration of motor impairment. It has been suggested that the CM-Pf complex may play an important role in levodopa induced dyskinesias (Caparros-Lefebvre, Blond, Feltin, Pollak, & Benabid, 1999). To test whether DBS of the CM-Pf complex influences motor scores in PD patients, 6 patients were bilaterally implanted with a stimulation device targeting both the GPi and the CM-Pf complex. 2 patients were targeted for implantation in the CM, while the remaining 4 were implanted in the Pf, we therefore refer to CM/Pf-DBS for these 6 patients. UPDRS III scores were measured before and after surgery in the drug "on" and "off" condition without stimulation. The effect of stimulation was tested for CM/Pf and GPi stimulation separately and together in the drug

"off" condition, and finally with congruent CM/Pf and GPi stimulation in the drug "on" condition.

The UPDRS III mean values \pm SEM are presented in table 6. Interestingly, motor scores had significantly decreased after surgery in the drug "off" condition, even when the stimulation device was off (-12.7%, $p < 0.05$). But this reduction was more pronounced with stimulation in the CM/Pf (-35.4%, $p = 0.01$), the GPi (-41.5%, $p = 0.01$), or in both areas (-49.9%, $p < 0.005$). The effect of surgery is much less present in the drug "on" condition, however there is a strong reduction of 46.9% in motor scores when CM/Pf and GPi stimulation are congruent. Next to motor scores, the authors analyzed the influence of CM/Pf-DBS on symptoms as freezing of gait (FOG) and abnormal involuntary movements. They found that CM/Pf-DBS was particularly effective in treating FOG, which was significantly different from GPi-DBS, that had no statistical effect on this symptom. Congruent CM/Pf and GPi stimulation had a slightly stronger effect than CM/Pf stimulation alone. The effect of CM/Pf-DBS on treating levodopa induced voluntary movements was, contrary to GPi-DBS, not significant. However, congruent CM/Pf and GPi stimulation, was slightly better in reducing these involuntary movements. CM/Pf-DBS is found to be an effective target for DBS to treat parkinsonian symptoms. Even though its effect on general motor scores and dyskinesias is less than that of GPi or STN stimulation, it does have a particularly strong effect on treating freezing symptoms. This can be very valuable for some patients, especially since these symptoms are usually less sensitive to conventional targets and pharmacological therapy. Furthermore, the addition of CM/Pf-DBS to a conventional target, such as the GPi, was found to be particularly effective for all symptoms. This is especially relevant considering the absence of additive side effects by CM/Pf-DBS (Mazzone et al., 2006).

Table 6. UPDRS III mean value \pm SEM and relative decrease (%) related to stimulation (STIM) or medication (drug) for the different modalities studied (Mazzone et al., 2006).

	Presurgery				Postsurgery			
	L-dopa OFF	L-dopa ON	L-dopa OFF	L-dopa ON	CM/Pf ON	GPi ON	CM/Pf ON + GPi ON (no drug)	CM/Pf ON + GPi ON + L-dopa
UPDRS III \pm SEM	71.4 \pm 4.05	34.5 \pm 3.5	62.3 \pm 4.9	33.8 \pm 3.7	40.2 \pm 4.8	36.4 \pm 4.5	31.2 \pm 4.1	18.3 \pm 2.8
% decrease STIM-dependent			12.7		35.4	41.5	49.9	
% decrease drug-dependent		51.6		45.7				-41.3

Pendunculopontine nucleus

As is known from studies using MPTP treated non-human primates, the pedunculopontine nucleus (PPN) is intimately connected to the basal ganglia. It is known that lesions of the PPN may produce akinesia, while driving the PPN activity with low frequency electrical stimulation can increase motor activity. Like the CM/Pf complex, the PPN is also believed to have an important role in gait disorders and other axial symptoms. It has therefore been investigated whether this region is an effective target for DBS in PD patients (Stefani et al., 2007). 6 patients suffering from severe PD with unsatisfactory control of axial signs such as gait and postural stability were bilaterally implanted with electrodes in the STN and PPN. While the STN was stimulated at high frequency (130-185 Hz), PPN stimulation was performed in the low-frequency band (25 Hz), which is generally believed to drive activation of the target structure (A. L. Benabid et al., 2001; A. L. Benabid, 2003).

The effect of DBS on the motor scores (UPDRS III), 3 months after surgery (which was classified as steady state) is shown in fig. 5. In the drug "off" condition (fig. 5a), stimulation in the PPN, STN or both areas resulted in a significant decrease of motor symptoms ($p < 0.001$). The impact of STN-DBS alone (-54%) or together with PPN-DBS (-56%) was significantly greater than the effect of PPN-DBS alone (-33%, $p < 0.01$). And the addition of PPN-DBS to STN-DBS did not result in a significant effect. To measure the specific effect on the axial signs, the UPDRS III subscores for item 27 (rising from chair), 28 (posture), 29 (gait), and 30 (postural stability) were pooled together. PPN-DBS was relatively more effective for these subscores than for total UPDRS III score. PPN-DBS, STN-DBS, and STN&PPN-DBS all significantly lowered the patient motor score for these items ($p < 0.01$), while there was no significant difference amongst the three DBS conditions.

In the drug "on" and stimulation "off" condition the UPDRS III scores decreased on average by 50.2% compared to drug "off" condition without stimulation ($p < 0.001$). This value was further decreased by stimulation of either the PPN (-44.3%, $p < 0.01$) or STN (-51%, $p < 0.01$), compared to drug "on", stimulation "off" condition (fig. 5b). STN&PPN-DBS resulted in the most dramatic decrease (-66.4%, $p < 0.01$), which was even significantly greater than that of PPN-DBS or STN-DBS alone ($p < 0.05$). A similar effect was found on the axial subscores, with a slightly stronger effect of PPN-DBS compared to STN-DBS. The mean walking capability (item 29) was particularly affected by STN&PPN-DBS, with 4 out of 6 patients manifesting a normal gait.

Also according to activities of daily scales (Schwab & England scale and UPDRS II) STN&PPN-DBS was found to be superior to STN-DBS alone. Additive side effects from PPN-DBS were limited. The only relevant finding was a transient paraesthesia involving the inferior limbs after the PPN-DBS was switched on. Overall, the addition of low frequency PPN-DBS to standard high frequency STN-DBS seems to be a promising treatment for patients with advanced PD, especially for those patients whose response to STN-DBS have deteriorated over time. PPN-DBS alone has significant effects on PD symptoms, but these are generally inferior to effects from STN-DBS. Only for axial symptoms a trend towards a relatively better effect of PPN-DBS was observed. Nevertheless, best effects were always observed during congruent STN and PPN stimulation. The additive effect of PPN-DBS is especially effective in the drug "on" condition, which makes the STN&PPN-DBS a particular interesting treatment (Stefani et al., 2007).

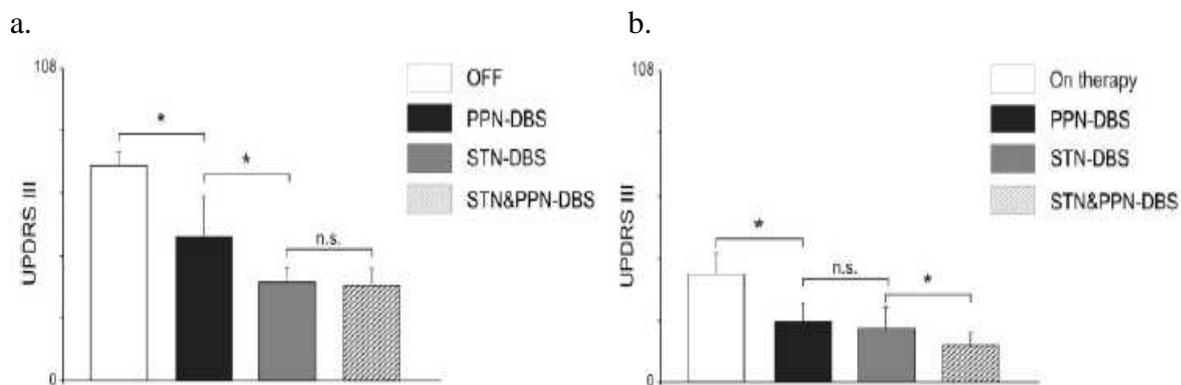


Figure 5. Motor scores (UPDRS III) of patients without stimulation, with PPN-DBS, with STN-DBS, and with STN&PPN-DBS. **a.** The drug "off" condition. **b.** The drug "on" condition. *=significant difference at $P < 0.05$, n.s.= not significant (Stefani et al., 2007).

Comparing the effect of PPN-DBS with CM/Pf-DBS is difficult since they were performed in different studies in combination with DBS in different areas (STN and GPi, respectively). However, their effects on the UPDRS III scores seem to have a very similar impact in the drug "off" condition when stimulated alone (-35.4% CM/Pf-DBS and -33%, PPN-DBS) or in combination with a conventional target (-49.9% GPi&CM/Pf-DBS and -56%, STN&PPN-DBS). Also in the drug "off" condition this difference was relatively small when performed in combination with a conventional target (-46.9% GPi&CM/Pf-DBS and -66.4%, STN&PPN-DBS) (Mazzone et al., 2006; Stefani et al., 2007). Thus, at this point it is not possible to view one area as a superior additive target, and both should be viewed as feasible.

Caudal zona incerta

Even though the CM, Pf, and PPN are interesting targets for DBS, they mainly have an additive value. When stimulated exclusively, targets like the STN and GPi tend to have a stronger effect on most PD symptoms. There have, however, been indications that a more effective contact area for DBS electrodes lies dorsal/dorsomedial of STN in the region of pallidofugal fibres and the rostral zona incerta (rZI). Plaha and colleagues therefore targeted this area for high frequency DBS (Plaha et al., 2006). Unfortunately, a few patients suffered from speech deterioration after stimulation in this area. When moving the electrodes from the rZI to deeper and more posterior contacts, towards the caudal zona incerta (cZI) was found to avoid speech deterioration, but still affect PD symptoms. The authors made a comparison between these two contact areas and the STN, thus having three groups of patients with different DBS targets: 1. postero-dorsal STN; 2. dorsomedial/medial to the STN; 3. within the cZI. 35 patients were implanted with in total 64 DBS leads. Of these, 17 were implanted in therapeutic best contact region in the STN (group 1), 20 with active contacts dorsomedial/medial to the STN (group 2), and 27 had contacts in the cZI (group 3). Patients were not always implanted bilaterally in the same area because optimal contact with the DBS electrodes may lie within the STN on one side, while it may lie outside it on the other side. They therefore measured the contralateral motor scores, to test the effect of a unilateral stimulation on motor outcomes.

The scores of several motor tests, medication dosages, and stimulation parameters are given in table 7 for the three groups in the off/off condition (no medication, no stimulation) and off/on condition (no medication, stimulation turned on) 6 months after surgery. Scores of the off/on condition were adjusted for the off/off score, based on disease severity, sex, and age group. Both crude and adjusted scores are presented. They found a significant trend ($p < 0.001$) for UPDRS III score improvement. STN stimulation resulted in 55% improvement, dorsomedial/medial to STN stimulation in 61% improvement, and cZI stimulation in 76% improvement. Also for contralateral tremor scores, the improvement from cZI-DBS (93%) is significantly higher than that of STN-DBS (61%, $p < 0.01$). Dorsomedial/medial to STN stimulation improvement score (86%) was very close to that of cZI-DBS, and the trend for these improvements were not found to be significant. Contralateral rigidity, timed hand movements and bradykinesia also had the best scores in the cZI group, with significant trends, except for the latter ($p = 0.002$, $p < 0.001$, $p = 0.17$ respectively). For dyskinesia scores and drug dosages, the maximal reduction was found in the dorsomedial/medial to STN group, but these effects could have been due to chance ($p = 0.56$, $p = 0.11$, respectively). Also for the stimulation parameters, no statistical differences were found between the three groups. The authors therefore concluded that stimulation of the cZI is superior to stimulation in the STN. The region dorsomedial/medial to the STN was also effective for treating PD symptoms, but was related to speech and balance problems in some patients in group 2. No serious side effects from cZI-DBS were observed in this study (Plaha et al., 2006).

Table 7. Mean motor scores, relative improvement (%) as an effect of stimulation, and p-values 6 months after surgery. Off/off= drug "off", stimulator "on"; off/on= drug "off", stimulator "on" (Plaha et al., 2006).

Location of DBS	STN	Medial to STN	Caudal ZI	P-value for trend
No of DBS leads	17	20	27	
Contralateral UPDRS III				
Crude off/off score (Mean)	12.7	13.8	15.7	
Crude off/on score (Mean)	5.7	5.4	4.4	
Adjusted off/on score (Mean)	5.7	4.9	3.1	
Adjusted per cent improvement (95% CI) [†]	55%	61% (46–76)	76% (65–87)	
P-value		0.42	<0.001	<0.001
Contralateral tremor ^{††}				
Crude off/off score (Mean)	2.31	3.27	4.29	
Crude off/on score (Mean)	1.08	0.33	0.29	
Adjusted off/on score (Mean)	1.66	0.63	0.29	
Adjusted per cent improvement (95% CI) [†]	61% (37–85)	86% (73–98)	93%	
P-value	0.01	0.19		0.21
Contralateral rigidity				
Crude off/off score (Mean)	4.2	4.1	4.3	
Crude off/on score (Mean)	2.1	2.0	1.1	
Adjusted off/on score (Mean)	2.1	2.0	1.0	
Adjusted per cent improvement (95% CI) [†]	50%	52% (32–72)	76% (60–93)	
P-value		0.86	0.003	0.002
Contralateral Bradykinesia				
Crude off/off score (Mean)	6.8	7.3	8.1	
Crude off/on score (Mean)	2.8	3.2	3.1	
Adjusted off/on score (Mean)	2.8	3.0	2.4	
Adjusted per cent improvement (95% CI) [†]	59%	56% (40–72)	65% (54–75)	
P-value		0.74	0.28	0.17
Timed hand movements (s)				
Crude off/off time in sec (Mean) [‡]	13.7	13.5	16.0	
Crude off/on time in sec (Mean) [‡]	10.3	9.0	7.9	
Adjusted off/on score (Mean)	10.3	9.2	7.5	
Adjusted per cent improvement (95% CI) [†]	25%	33% (24–40)	45% (39–52)	
P-value		0.08	<0.001	<0.001
Dyskinesia scores on medication*				
Crude percentage improvement	41	65	56	
Adjusted percentage improvement (95% CI) [†]	41%	63% (32–93)	56% (21–91)	
P-value		0.16	0.40	0.56
L-Dopa equivalent medication (mg)				
Pre-op (mean)	1152	918	1130	
Post-op (mean)	631	542	764	
Adjusted per cent improvement (95% CI) [§]	45%	47% (32–61)	32% (14–50)	
P-value		0.98	0.18	0.11
Stimulation parameters				
Voltage (mean)	2.65	2.49	2.71	
P-value		0.54	0.83	
Pulse width (mean)	81.2	84.0	82.2	
P-value		0.63	0.83	
Frequency (mean)	160.6	150.5	149.6	
P-value		0.21	0.17	

Also shown are the improvement in dyskinesia scores, L-dopa medication reduction and the stimulation parameters.

[†]Adjusted for sex, age group, off-off score and clustering; ^{††}ZI group taken as baseline and 15 patients omitted as their 'off/off' score was zero and they could not show improvement; [‡]geometric mean; *dyskinesia was scored as per CAPSIT protocol;

[§]adjusted for sex, age group, baseline medication dosage and clustering.

Chapter 4: External Cues

4.1 Noninvasive treatment

Before it was common to treat PD patients with pharmacological therapy, physical therapy was often used to help relieve PD symptoms. With the advance of levodopa, which many saw as a cure for PD, did the interest in physical therapy as a treatment for PD decline. Only after the realization that there are some serious problems associated with levodopa therapy, such as side effects and insensitivity over time, did the general interest started to turn to other treatments again. A revival of ablative surgery appeared, which was quickly followed by the rise of DBS treatment. But the invasiveness of these treatments can be a big threshold for many patients. Logically, interest in physical therapy by clinicians reappeared again. Several studies have described the effect of physical therapy, often with significant improvements on PD symptoms (see Rubinstein, Giladi, & Hausdorff, 2002 for an overview). However, due to the varied methodologies of these studies and lack of randomized controlled studies, evidence for the effectiveness of physical therapy on PD is not strong (Rubinstein et al., 2002). For example, gait and motor function is improved by physical therapy, but not just for PD patients. Relatively unfit age-matched controls improved their gait and motor function, after physical therapy, in a similar way (Scandalis, Bosak, Berliner, Helman, & Wells, 2001). Even though physical therapy may be useful for PD patients, it may not be dealing with PD pathology directly (Rubinstein et al., 2002).

There are, however, noninvasive therapies that did prove to be more effective for PD patients than their age-matched controls. These therapies incorporated specific cues to help the patients in improving their gait (Lim et al., 2005; Rubinstein et al., 2002). A cue is a stimulus coming from the environment (external) or generated by the subject (internal), and is used by the subject, consciously or not, to perform a (motor) task. Several external cues have been described as effective modulators of gait disorders of PD patients. The majority of these are rhythmical auditory stimuli (RAS) (Almeida, Wishart, & Lee, 2002; Heremans et al., 2011; Rochester et al., 2007; Rochester, Baker, Nieuwboer, & Burn, 2010; Thaut et al., 1996) and special visual stimuli (Azulay et al., 1999; Heremans et al., 2011; Rochester et al., 2007; Wegen et al., 2006). Somatosensory cueing is also believed to be effective, but very little evidence of its effect exists (Lim et al., 2005). Next to external cues, can internal cues also ameliorate disrupted gait patterns (Rochester et al., 2010). The influence of cues on gait disorder are of special interest, since these are generally mildly affected by dopaminergic medication (Thaut et al., 1996). Also conventional DBS (i.e. STN-DBS or GPi-DBS) usually mildly affects gait disruption (Mazzone et al., 2006). We will give an overview of the effectiveness of several external cues and some of the neural mechanisms behind it. Finally, we will suggest a simulation of the effect of an external cue by electrical stimulation.

4.2 Auditory cues

Several observations have indicated that RAS, such as a metronome beat, can increase walking speed, cadence (steps/min), and stride length of PD patients (see Lim et al., 2005 for an overview). To investigate the effectiveness of RAS as a treatment for PD patients, a 3-week home based training program was developed with instrumental music (Thaut et al., 1996). RAS was added to this music in the on/off beat structure with metronome-pulse patterns. Three groups of PD patients were compared to each other: the experimental (EXP)

group consisting of 15 subjects, the self (internally) paced (SPT) group consisting of 11 subjects, and the no training (NT) group consisting of 11 subjects. Both the EXP and SPT group followed the 3 week training program, but only in the EXP group the RAS was added to the music. The stride and electromyogram (EMG) patterns were measured without the rhythmic timekeeper before (pretest) and after (posttest) the training program. Stride patterns were subdivided in velocity, cadence, and stride length and were analyzed for a flat walk. Velocity was also measured for an incline-step walk. All patients were on a stable medication regimen during the study.

The pretest and posttest results are listed in table 8. The EXP group significantly increased its velocity for the flat walk (24.1%, $p=0.007$), and the incline-step walk (26.1%, $p=0.009$), while the SPT group only slightly increased its velocity for the flat and incline-step walk (7.4% and 8.4%, respectively). This increase was not believed to be due to familiarization with the laboratory environment, since the NT group actually decreased slightly in velocity for the flat walk (-7.3%) and the incline-step walk (-10.5%). Also for the cadence and stride length, significant increases were observed in the EXP group (10.4%, $p=0.01$ and 12.0%, $p=0.009$, respectively). In the SPT group only the stride length was increased after the training program (7.9%), but this was to a lesser extent than in the EXP group. There were no differences between pre- and posttest cadence in the SPT group. All differences between the pre- and posttest values in both control groups (NT and SPT) were statistically nonsignificant. ANOVA post hoc comparisons revealed a significantly greater increase in velocity in the EXP group than in the NT group (FLAT: $p=0.0001$, INCLINE: $p=0.0052$) and the SPT group (FLAT: $p=0.0307$, INCLINE: $p=0.0347$). Improvements of the EXP group in the cadence were only significantly greater than the SPT group ($p=0.0340$), and improvements in stride length were only greater than the NT group ($p=0.0045$).

Table 8. Means and standard deviations (SD) of three gait parameters before (Pre) and after (Post) training program, and the relative change (%). EXP= experimental group; NT= no training group; SPT= self paced group (Thaut et al., 1996).

	Velocity (m/min)			Cadence (steps/min)			Stride length (m)		
	Pre	Post	Change (%)	Pre	Post	Change (%)	Pre	Post	Change (%)
Flat walk									
EXP									
\bar{x}	48.7	58.3	24.1	96.8	105.7	10.4	0.99	1.10	12.0
SD	13.6	12.6	12.3	13.5	11.5	13.5	0.19	0.17	12.8
NT									
\bar{x}	42.1	38.7	-7.3	88.5	96.6	5.7	0.93	10.84	-10.3
SD	15.5	16	15.8	13.4	9.6	11.9	0.24	0.32	17.9
SPT									
\bar{x}	47.9	51.9	7.4	92.6	92.2	-0.4	1.04	1.12	7.9
SD	7.3	12.5	10.7	7.6	8.4	1.7	0.16	0.21	9.2
Incline-step walk									
EXP									
\bar{x}	40.8	49.4	26.1						
SD	14	13	30.9						
NT									
\bar{x}	35.8	30.2	-10.5						
SD	15	13	20.9						
SPT									
\bar{x}	40.7	43.9	8.4						
SD	9.3	11.6	16.2						

EXP group, $n = 15$; NT and SPT groups, $n = 11$.

Furthermore, posttest EMG activation periods in the EXP group had increased significantly in the anterior tibialis and vastus lateralis muscles ($p=0.0471$ and $p=0.0303$, respectively). In conclusion, the addition of RAS to a training program greatly improved the patients gait and changed EMG activation patterns to a more normal profile. Already in 3 weeks a significant effect was obtained during a test that had no auditory cueing. This is especially remarkable

since time estimation, recall, and reproduction are often impaired in PD patients (Thaut et al., 1996).

The study of Thaut et al. has showed us that training with external cues (EXP group) is superior to training with internally generated cues (SPT group). Nevertheless after training, the EXP group was capable of internally generating the rhythm to improve their performance on the test day. The influence of internal and external cues on gait performance remains therefore not clear. Almeida and coauthors suggested, based on their own study results, that external cues by themselves do not necessarily improve gait performance, but that improvement is due to a shift in attention. However, they did emphasized the importance of further research in this field (Almeida et al., 2002).

Recently, a study was designed to investigate the effect of internal (attentional strategies) and external (auditory rhythmical) cues on selected gait characteristics of PD patients, and how this is influenced by dopaminergic medication (Rochester et al., 2010). 50 PD patients were studied in their drug "on" and "off" status. They performed two trials with each cue in randomized order. The subjects were required to focus their attention on increasing their step length (internal cue), or they had to associate a metronome beat (external cue) with taking a large step. The stride patterns analyzed were: walking speed, stride amplitude, step frequency (i.e. cadence), stride time, and double limb support (DLS) time. The latter two are measures of postural control during walking and were calculated from the mean and standard deviation and described as coefficient of variation (CV).

The results of this study are given in table 9. In the noncue conditions, dopaminergic medications significantly improved velocity (5.37 m/min, $p=0.001$), stride amplitude (0.11m, $p<0.001$), and stride time CV (1.69%, $p=0.001$), but did not significantly influence step frequency or DLS CV. To explore the main effects of medication and the interaction between internal and external cues, a repeated measures analysis of variance with post hoc tests was used. From this they found that both internal and external cues significantly improved stride amplitude ($p<0.001$), velocity ($p<0.001$), and step frequency (internal cues, $p<0.001$ and external cues, $p=0.002$). External cues were found to have a significantly greater effect than internal cues on the velocity of the stride ($p=0.001$), while internal cues had a greater effect on decreasing the step frequency ($p<0.001$), and there were no significant differences between the effect of the cue types on stride amplitude. Even though dopaminergic medication significantly improved gait patterns in the noncued condition, there was no significant effect of medication in the cued conditions. This was likely due to the very high response to cues. Stride time CV was found to be reduced under influence of medication ($p=0.007$) and external cues (drug "on", $p<0.001$ and drug "off", $p=0.008$), while internal cues only had an effect in the drug "on" condition ($p=0.007$) and not in the drug "off" condition. External cues were more effective than internal cues or medication ($p<0.001$). No significant interaction effects on DLS CV were observed, but there was a main effect of cues ($p<0.001$) and medication ($p=0.03$). External cues significantly reduced DLS CV in the drug "off" condition ($p<0.001$), while internal cues had no effects. These results show that both internal and external cues have significant effects on gait patterns, often even more effective than pharmacological treatment. External cues were more effective for improving velocity and modifying stride time and DLS variability. Internal cues were particularly effective on reducing step frequency. Both cues thus have positive effects for PD patients, but external cues may have special clinical value because reduced time CV is believed to increase gait stability and therefore reduce the risk of falling (Rochester et al., 2010). We will therefore focus on external cues.

Table 9. Mean (\pm SD) of several gait parameters with either an internal cue, an external cue, or no cue. The top rows are in the drug "off" condition and the bottom rows are in the drug "on" condition (Rochester et al., 2010).

Gait variable	Off noncue	Off + internal cue	Off + external cue
Velocity (m/min)	41.85 (13.86)	48.96 (15.85) ^a	51.61 (16.94) ^{a,b}
Stride amplitude (m)	0.82 (0.24)	1.07 (0.28) ^a	1.06 (0.29) ^a
Step frequency (steps/min)	101.84 (12)	91.48 (13.79) ^a	97.77 (15.09) ^{a,b}
Stride time CV	6.12 (2.49)	5.26 (1.31)	3.0 (1.40) ^{a,b}
DLS CV	7.73 (2.46)	7.76 (2.29)	5.33 (2.84) ^{a,b}
	On noncue	On + internal cue	On + external cue
Velocity (m/min)	47.23 (10.92)	54.98 (17.95) ^a	57.26 (16.71) ^{a,b}
Stride amplitude (m)	0.93 (0.25)	1.17 (0.31) ^a	1.14 (0.26) ^a
Step frequency (steps/min)	102.42 (11.72)	94.02 (15.66) ^a	99.8 (14.73) ^b
Stride time CV	4.43 (2.03)	5.45 (1.58) ^a	2.64 (0.87) ^{a,b}
DLS CV	6.94 (2.25)	6.96 (2.44)	4.6 (2.33) ^{a,b}

^aSignificant changes compared with the noncue trials ($P = 0.05$; post hoc comparison).

^bSignificant changes between cue types ($P = 0.05$; post hoc comparison).

4.3 Visual cues

Next to auditory cues, it is known for a long time that visual cues can have a positive effect on PD symptoms. In 1967 Purdon Martin described that only certain visual stimuli were effective: transverse lines, an inch or more wide, 18 inches or so apart, and of a colour contrasting with that of the floor (white lines on a dark ground). While zigzag lines, lines parallel to the line of movement, very narrow lines, lines wider than 6 feet or stripes without contrast of colour had no effect on gait. In a study of Azulay et al. they showed that PD patients significantly improved their gait velocity and stride length when transverse lines were added to the walking surface and with normal illumination, while this was not the case for healthy age-matched controls. These improvements were suppressed when the patients had to do the same task with stroboscopic illumination, demonstrating that it is the perceived motion of stripes, generated by the person walking, that is responsible for the improvement in gait patterns for PD patients (Azulay et al., 1999).

To capture the effect of visual rhythms and optic flow on parkinsonian gait patterns, 21 PD patients and 7 age-matched healthy controls were asked to walk on a treadmill with and without visual stimuli. The PD patients consisted of drug-naïve ($n=8$) and medicated patients ($n=13$). Visual stimuli were given with the aid of a projection screen in front of the treadmill and LED lights attached to a pair of glasses. The subjects had to walk on the treadmill under 5 conditions, offered in random order: 1. blank screen; 2. projection of a virtual corridor; 3. projection of virtual corridor with rhythmic spatial cueing (transverse lines); 4 blank screen with rhythmic temporal cueing (flashing LED lights from the glasses); 5. projection of virtual corridor with rhythmic temporal cueing. Gait performance was given as a measure of stride frequency (Hz/m) for the three groups of test subjects and are presented in fig. 6. The stride frequencies were significantly lower (i.e. the stride lengths were longer) in the conditions 3,4, and 5 than in condition 1 for all three groups ($p<0.05$). No significant differences were found between condition 1 and 2, or between conditions 3, 4, and 5. This shows that both rhythmic spatial cueing (moving transverse lines) and temporal cueing (flashing lights) are effective methods for improving gait patterns, while a virtual corridor had no effect. However, since the same effect occurred in healthy controls, this effect may not be directly related to PD pathology (Wegen et al., 2006).

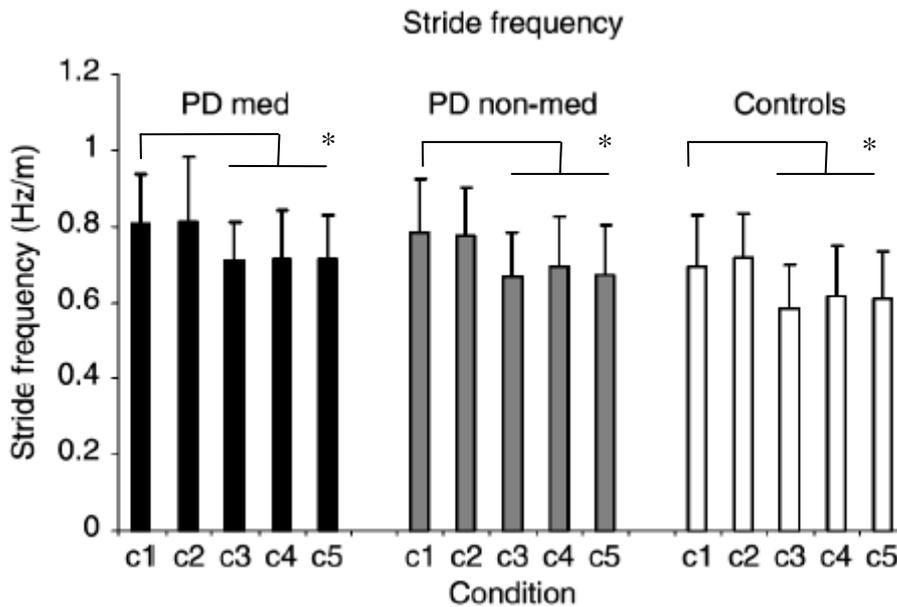


Figure 6. Means and standard deviations of the stride frequency (normalized for leg-length) of the patient group with medication, without medication, and the healthy controls in five different conditions: c1= blank screen; c2= projection of a virtual corridor; c3= projection of virtual corridor with rhythmic spatial cueing; c4= blank screen with rhythmic temporal cueing; c5= projection of virtual corridor with rhythmic temporal cueing. *= significant differences at $p < 0.05$ (Wegen et al., 2006).

Auditory and visual cues are both effective in improving a PD patient's gait (Almeida et al., 2002; Azulay et al., 1999; Rochester et al., 2010; Thaut et al., 1996; Wegen et al., 2006). Some studies indicate that auditory cues are more effective in improving gait patterns or imagining movement than visual cues (Heremans et al., 2011; Rochester et al., 2007), which is probably related to the finding that PD patients are influenced less by visual stimuli than healthy controls (Poliakoff, Galpin, Dick, Moore, & Tipper, 2007; Praamstra, Stegeman, Cools, & Horstink, 1998). Nevertheless, the influence of auditory and visual cues is likely to have a similar effect on the patient's brain.

4.4 Neural basis

As mentioned before, Parkinson's disease is a complex disorder with many symptoms. Dysfunctioning of the basal ganglia, caused by a depletion of the brain's dopamine concentration, is believed to be the most important factor for the development of many parkinsonian symptoms. Gait disorders on the other hand, are believed to have a different neural basis, due to its weak response to dopaminergic medication or high frequency stimulation of the basal ganglia (Mazzone et al., 2006; Thaut et al., 1996).

Neural basis of gait disorders

Studying the neural activation of patients with severe gait disorders is challenging, because most non-invasive neuroimaging methods are ineffective for studying gait (Snijders et al., 2011). To bypass this difficulty, Snijders and colleagues made use of motor imagery (Snijders et al., 2011). 24 patients with PD and 21 age-matched controls were required to imagine walking along a path (motor imagery task) or seeing a disc moving along the path (visual imagery control task). They performed these tasks while their cortical activity was measured with functional magnetic resonance imaging. The patient group consisted of 12 patients with FOG and 12 patients matched for disease severity and duration. When comparing brain

activity during the motor and visual imagery task, significantly higher activations were found in the left and right supplementary motor area (SMA), left and right superior parietal lobule, right anterior cingulate lobule, and left putamen of the healthy controls during the motor imagery task compared to the visual imagery task ($p < 0.05$, ROI analysis). For the PD patients without FOG a significant increase in brain activity during the motor imagery task was found in the right and left SMA ($p < 0.05$, ROI analysis). ROI analysis of the brain activation in the group of PD patients with FOG, revealed no significant differences between motor imagery and visual imagery, but whole brain analysis revealed a strong effect in the mesencephalic locomotor region (posterior mid-mesencephalon) ($p = 0.004$). The mesencephalic locomotor region is a neurophysiologically defined region that includes the pedunculopontine nucleus, cuneiform nucleus, periaqueductal grey and locus coeruleus.

The differences in increased activation during motor imagery compared to visual imagery were compared between PD patients and controls. With ROI analysis, a significant decrease in activity of the superior parietal lobule ($p = 0.019$) and anterior cingulate cortex ($p = 0.025$) was found in PD patients. When using ROI analysis to compare differences between the two patient groups, a trend was found towards a higher imagery-related activity in the left SMA ($p = 0.061$) and the right SMA ($p = 0.074$) of patients without FOG compared to patients with FOG (fig. 7). Only when using whole brain analysis, a significant increase in imagery-related activity was observed in the mesencephalic locomotor region (fig. 7, $p = 0.049$). The differential activity in this region was found to correlate with FOG severity within the group of patients with FOG ($r = 0.60$, $p = 0.041$). It did not correlate significantly to disease duration within the group of patients with FOG ($r = 0.53$, $p = 0.08$), but did so when taking both patient groups into account ($r = 0.58$, $p = 0.003$). The authors also found a significant decrease in grey matter volume in the mesencephalic locomotor region of patients with FOG compared to patients without FOG (fig. 7, $p = 0.028$). However, this decrease in gray matter did not correlate to FOG severity ($r = 0.28$, $p = 0.37$) or to the difference in imagery-related activity ($r = 0.17$, $p = 0.60$).

The authors suggest that the increased mesencephalic locomotor region activity acts as a compensatory mechanism during stable gait, but under more demanding circumstances, a pathological contribution may be involved. The lower activation in the SMA by PD patients with FOG, is also thought to be crucial for gait related problems. The SMA receives many projections from the basal ganglia, which can explain its underactivity in PD patients (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999). In this study a relation was found between SMA activation and increased step length (during walking outside the scanner). Failure to generate steps of adequate amplitude could ultimately produce FOG. Also the decrease in activity of anterior cingulate cortex and superior parietal lobule in the patient group is believed to create a precondition for the manifestation of FOG. To summarize, gait disorders are suggested to emerge from structural and functional changes in the mesencephalic locomotor region, combined with altered cortical control of gait by the SMA (Snijders et al., 2011).

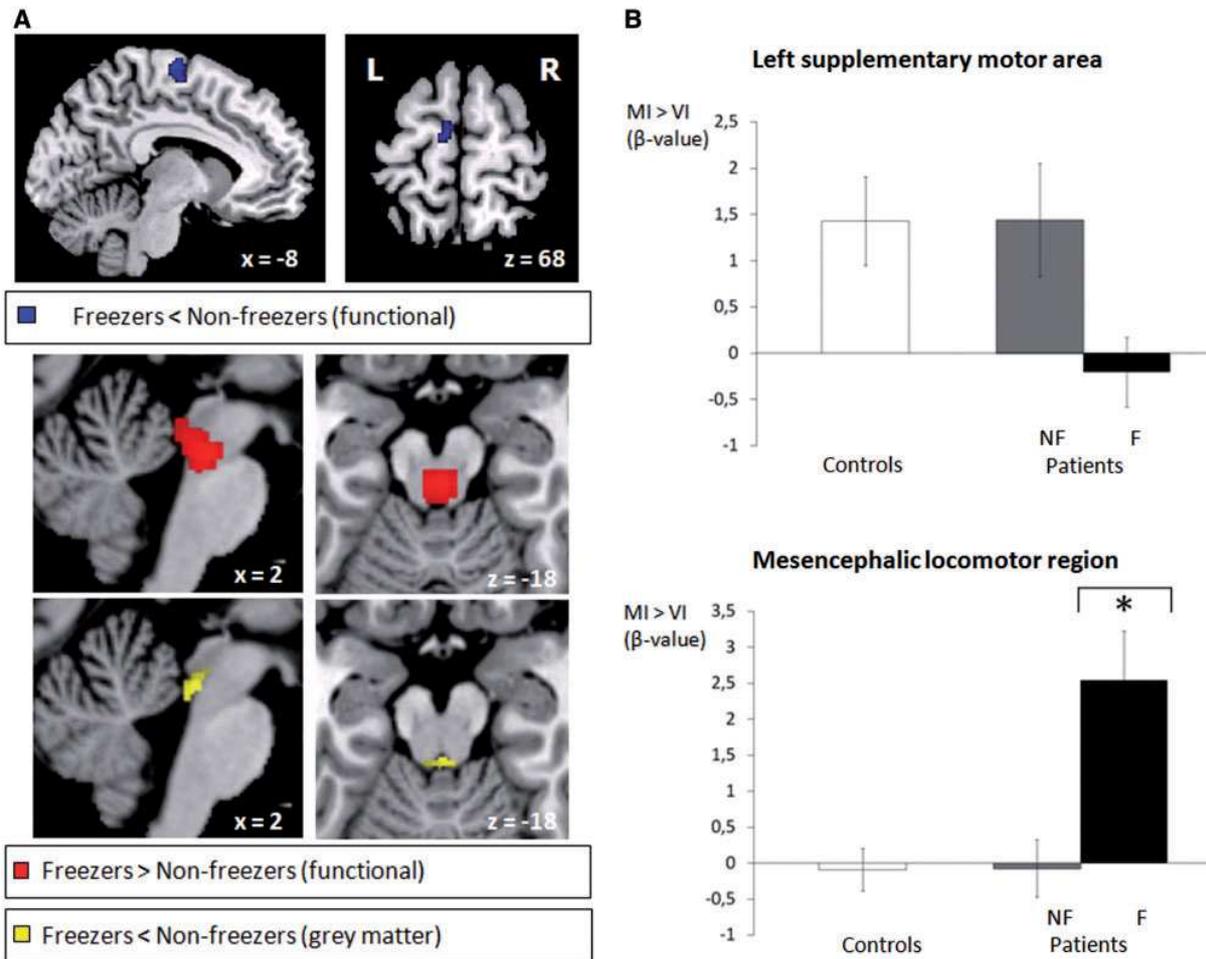


Figure 7. Imagery related brain activity in the areas where there was a difference in the relative increase in activation during the motor imagery (MI) compared to visual imagery (VI) between PD patients with FOG (freezers) to PD patients without FOG (non-freezers). In the top of the image is the left supplementary motor area that had a trend towards a significant decreased activity in patients with FOG (ROI analysis, $p=0.061$). And in the lower part of the image is the mesencephalic locomotor region that had a significant increased activity in patients with FOG (whole brain analysis, $p=0.049$) and a decreased grey matter volume ($p=0.028$). **a.** Statistical parametric map superimposed on a sagittal brain section (left side) and transversal brain section (right side). **b.** β -weights of the contrast between MI and VI (mean \pm SEM) in controls, PD patients without FOG (NF), and PD patients with FOG (F). *=significant difference between NF and F patients at $p < 0.05$ (Snijders et al., 2011).

Physiological effect of external cues

Since external cues are known to be effective moderators of gait patterns of PD patients, it is interesting to investigate the physiological effect of these cues on neural activity. The influence of lines oriented transversely to the direction of walk, on regional cerebral blood flow (rCBF) was therefore examined with single-photon emission computed tomography (Hanakawa et al., 1999). With this technique it was possible to obtain rCBF images which reflect neural activity over a period of several minutes after tracer administration. In this way it was possible to study human brain functions without constraining subjects performing a walking task. The subject group consisted of 10 PD patients and 10 age-matched controls. The subjects had to walk over a treadmill guided by two different visual cues: transversal or parallel white lines that were fixed on the black artificial rubber of the treadmill.

Consistent with other studies, the effect of transversal lines on cadence was significantly greater in PD patients than in controls ($p < 0.005$) (Azulay et al., 1999; Wegen et al., 2006). When comparing neural activation in the condition with transversal lines to the condition with parallel lines, there was a significant rCBF increase in the bilateral posterior parietal cortex,

left dorsolateral prefrontal cortex, left insula, and left cerebellar hemisphere within the control group (fig. 8a). The PD patients showed in this case an increase in the bilateral posterior parietal cortex, left cerebellar hemisphere, right lateral premotor cortex (right PMC), and right anterior cingulate gyrus (fig. 8b). No significant decrease in activation was measured in either group. When comparing the PD patients with the control group, a significantly greater rCBF activation evoked by transversal lines was found in the right PMC.

These results show that the bilateral posterior parietal cortex and cerebellum (that receives visual information from the posterior parietal cortex) are influenced by transversal lines in both PD and control group, suggesting an anatomical basis for performing the task. This is interesting since activity in the posterior parietal cortex was found to be decreased in PD patients during motor imagery (Snijders et al., 2011). Similar results were found for the anterior cingulate cortex, which was also hypoactive in PD patients (Snijders et al., 2011) and positively affected by visual cues (Hanakawa et al., 1999). This may suggest a possible role of attention or emotion, influenced by an external cue, on the improvement of gait patterns. The overactivation of the PMC in PD patients evoked by external cues, is believed to compensate for the underactivation of other cortical areas, especially the SMA (Snijders et al., 2011). It therefore seems that lateral cortical areas, induced by particular external cues, play an important role in alleviating gait disorders by compensating for central cortical areas affected by PD (Hanakawa et al., 1999).

(A) TL minus PL in Control

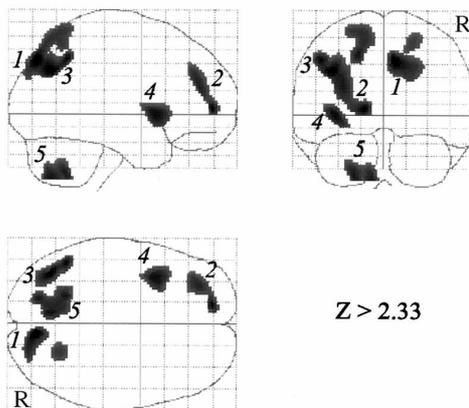
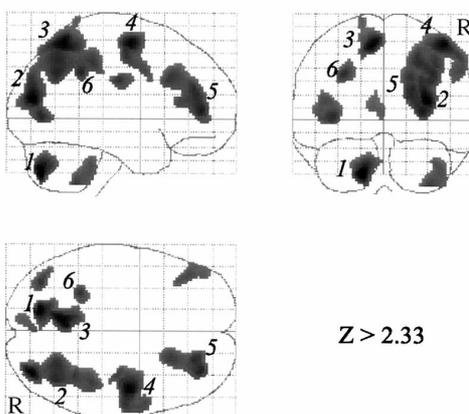


Figure 8. Brain activation maps during treadmill walk. Depicted are three orthogonal projections of the areas that showed a significant regional cerebral blood flow increase in the condition with transverse lines (TL) compared to the condition with parallel lines (PL) in the (A) control group and (B) PD patient group. A Z-score greater than 3.09 (uncorrected $p < 0.001$) was considered significant, but in this figure the threshold was set at a Z-score of > 2.33 for display purposes only. Numbers in (A) the control group correspond to: 1. right precuneus; 2. left medial frontal gyrus; 3. left inferior parietal lobule; 4. left insula; 5. left cerebellar hemisphere. In the (B) PD patient group they correspond to: 1. left cerebellar hemisphere; 2. right middle occipital gyrus/right inferior parietal lobule; 3. left precuneus; 4. right middle frontal gyrus (lateral premotor cortex); 5. right anterior cingulate gyrus; 6. left inferior parietal lobule (Hanakawa et al., 1999).

(B) TL minus PL in PD



4.5 Simulation of external cues with brain stimulation

When comparing treatment methods DBS and external cues with each other, it is clear that there are some profound differences. Even though they are both effective methods to treat PD symptoms, they generally affect different symptoms. Conventional DBS is known to treat a variety of PD motor symptoms, such as tremor, rigidity, bradykinesia, but also nonmotor symptoms such as depression. External cues, on the other hand, affect primarily gait disorders, which is exactly what is not strongly affected by conventional DBS. DBS is also known to have several side effects such as dysarthria or depression, and several device and surgery related complications (Umemura et al., 2011), while no side effects have been reported in studies looking at external cue effects. Furthermore, the mechanisms behind it are completely different. DBS is invasive and directly affects pathological brain areas by either inhibiting activity (high frequency stimulation) or increasing activity (low frequency stimulation). External cues are noninvasive and indirectly activates brain areas important for PD symptoms via a sensory pathway. The noninvasive character of external cues gives it great advantages compared to DBS, such as low costs and no risks associated to surgery or the device. There are, however, also some serious disadvantages. One of the most effective visual cues, for example, are transversal lines (Azulay et al., 1999; Hanakawa et al., 1999). Needless to say, it would be impossible to have these lines placed everywhere in front of the patient. Luckily, repetitive flashing light emitted from a pair of glasses can also be effective (Nieuwboer et al., 2007; Wegen et al., 2006). Also auditory stimuli can easily be delivered by a portable device (Fernandez del Olmo & Cudeiro, 2003). But a problem with these approaches is that important sensory systems have to be constantly burdened during walking. Also, many PD patients have reached an age when sight and hearing problems become more common. And finally, being exposed to the same repetitive sensory stimulus over a prolonged period of time can be experienced as unpleasant by some subjects (Thaut et al., 1996), and thus not be the most ideal solution for improving their quality of life. A chronically implanted device may therefore have the preference of some people. We are interested if the positive effect of external cues can be achieved by electrically stimulating certain areas of the brain.

Mesencephalon

A stimulating device that can evoke the same effect as external cues can be of great help to PD patients with severe gait disorders. Such a device could be a good addition to a DBS device in the basal ganglia, but not a replacement. As mentioned earlier, conventional DBS treats a wide variety of PD symptoms, while external cues mainly affect gait patterns. To treat gait disorders of PD patients with electrical stimulation, it is important to understand the pathology of gait disorders. Snijders and colleagues found an increased activity of the mesencephalic locomotor region activity in PD patients with severe FOG compared to patients without FOG during a motor imagery task (Snijders et al., 2011). They suggested that this increased activity is mainly a compensatory mechanism. If this is the case, stimulation of this area would improve gait patterns. Some evidence points in this direction.

Using DBS to activate the PPN, which is a component of the mesencephalic locomotor region, was found to be more effective on improving gait than the inhibition of the STN through DBS (Stefani et al., 2007). Especially the combination of PPN-DBS and STN-DBS was very effective on axial symptoms. However, the PPN may not be the perfect contact area to stimulate the mesencephalic locomotor region, as the maximum cluster of activity was located dorsomedial to the PPN. It should also be taken into account that if the mesencephalic locomotor region is compensating for the decreased activity of another brain region, it may be more effective to directly stimulate that region.

Cortical motor areas

The cortical brain areas involved in movement: the motor cortex, the supplementary motor area, and the lateral premotor cortex are thought to be essential for PD symptoms (Pagni et al., 2005). According to the classical model of basal ganglia function (fig 2.), disrupted basal ganglia activity is the basis of PD, but it is the altered cortical activity that is eventually responsible for the development of syndromes. It therefore makes sense to see the cortex as a possible target for stimulation. A reduced activity was found in the SMA of PD patients with FOG compared to PD patients without FOG or healthy controls during motor imagery (Snijders et al., 2011). The SMA receives many projections from the basal ganglia, which can explain its reduced activity in PD patients (Hanakawa et al., 1999). It is thought that the decreased SMA can be compensated by an increased activity of the PMC (Hanakawa et al., 1999). The PMC is mainly regulated by cerebellar inputs, and was affected by visual cues in PD patients. This effect was significantly different from healthy controls (Hanakawa et al., 1999). Direct stimulation of the PMC to increase its activity can thus hypothetically have the same effect as external cues on gait patterns. However, like the PPN, if the increased activity in this region is a compensatory mechanism, it may not be the most ideal target. Direct stimulation of the SMA would then be more suitable.

To our knowledge, direct electrical stimulation of the SMA as a treatment for PD symptoms has not been tried yet. But there have been studies that applied electrical stimulation to the motor cortex, which resulted in an increased activity in the SMA (Fasano et al., 2008; Tani et al., 2007). Motor cortex stimulation is applied below the threshold that triggers muscular jerks (1.8-8 Volt) with low to high frequencies (20-130 Hz) (Fasano et al., 2008; Pagni et al., 2005; Tani et al., 2007). Studies investigating motor cortex stimulation as a treatment method for PD patients are severely limited, but there are several case studies with promising results, especially for gait disturbances (Fasano et al., 2008; Pagni et al., 2005; Tani et al., 2007). One case described a 67 year old woman with severe gait disturbances (but without other characteristic PD symptoms), that improved her walking speed and step size respectively by 400% and 200%, one year after the implantation of a motor cortex stimulation device (Tani et al., 2007). The effects on PD patients were less dramatic, but still promising. First results presented by the study group of the Italian neurosurgical society revealed the effect of motor cortex stimulation on 16 PD patients. These patients had very advanced PD and 15 of them were not eligible for DBS. Motor cortex stimulation affected the whole spectrum of PD symptoms for most patients, and the effect on axial symptoms was most profound (Pagni et al., 2005). The restored activity of the SMA is suggested as the underlying physiological mechanism for the amelioration of PD symptoms (Pagni et al., 2005). Direct electrical stimulation of the SMA may then possibly be a more effective method for the treatment of gait disturbances. However, Tani and coauthors reported that high frequency repetitive transcranial magnetic stimulation on the SMA did not improve akinesia, while this was the case when applied to the primary motor cortex (Tani et al., 2007). Still, further research in this field is required to understand the impact of stimulation on the cortical motor areas, and its possible role in treating PD symptoms.

Other brain areas

Several other brain areas showed a significant increase in activity when a condition with cues was compared to a condition without cues in PD patients (fig. 8b) (Hanakawa et al., 1999). Among these areas are the posterior parietal cortex and anterior cingulate cortex. These cortices were found to have a lower activation in PD patients than in healthy controls when the subjects were asked to perform a motor imagery task (Snijders et al., 2011). These findings suggest that hypoactivity in these regions may underlie PD symptoms and an

increase in activation in these areas improves gait patterns of PD patients. Thus making these regions possible targets for therapeutic electrical stimulation. An increase in activity, under influence of external cues, was also observed in the cerebellum (fig. 8b) (Hanakawa et al., 1999). This is probably linked to the increased activity in the posterior parietal cortex, from where it receives visual information. The cerebellum is known as a very important brain area for several motor actions, such as the control of postural balance and in the fine tuning of movements, which is often impaired in PD patients. It may therefore be that improvements in gait patterns, evoked by external cues, are directly related to increased cerebellar activity and indirectly to increased posterior parietal cortex activity. Some studies have proposed a cerebellar circuit that by-passes the damaged basal ganglia to improve gait patterns (Azulay et al., 1999; Wegen et al., 2006). This could also make the cerebellum an effective target for brain stimulation. Hypoactivity in the cerebellum during motor imagery was not observed in PD patients (Snijders et al., 2011), but it could be that the cerebellum is not strongly affected by imagery tasks.

Chapter 5: Conclusions

Even though an actual cure for Parkinson's disease is still elusive, there have been major advances over the last decennia in treating the symptoms of PD. Deep brain stimulation has proven itself as an effective treatment method for PD patients that no longer adequately respond to pharmacological treatment. Benabid et al. even described: "Never in medicine has a reciprocal exchange between diseased patients, surgical and medical therapy and neuroscientists been so intense, common and surprisingly quickly profitable on the therapeutic grounds for the immediate benefit of the patients." (A. L. Benabid et al., 2001). External cues are effective in helping PD patients improving their gait patterns, which are often not strongly affected by dopaminergic medication or DBS. But, despite their effectiveness, external cues are not widely used as treatment methods for PD patients. And despite advancements in the field of DBS, it may not be exploited to its full potential. Furthermore, modulation of brain areas outside the basal ganglia and thalamus by electrical stimulation may be effective in treating PD symptoms.

Deep brain stimulation

DBS was originally applied to the thalamic nucleus ventralis intermedius (Alesch et al., 1995; A. Benabid et al., 1987), but then moved to regions in the basal ganglia, such as the subthalamic nucleus (Crenna et al., 2006; Lagrange et al., 2002; Temperli et al., 2003; Thobois et al., 2002; Umemura et al., 2011) and globus pallidus internal (Anderson et al., 2005; Follett et al., 2010; Krack et al., 1998; Krause et al., 2001). The STN is generally the preferred target for DBS (A. L. Benabid et al., 2001; A. L. Benabid, 2003; A. L. Benabid & Torres, 2012), but the GPi may be more effective for some patients (Anderson et al., 2005; Follett et al., 2010). Other areas have also been explored as targets for DBS. Of these, the centromedian parafascicular complex and the pedunculopontine nucleus are great additional targets to the conventional STN and GPi, especially to improve gait disturbances (Mazzone et al., 2006; Stefani et al., 2007). DBS of the caudal zona incerta, on the other hand, was actually found to yield better results than STN-DBS (Plaha et al., 2006). What would be the most ideal type of DBS will depend on the patient. A clinician will have to make a careful analysis of the patient symptoms, before deciding the type of DBS. Based on the results presented in this review we would give the strongest preference to DBS of the cZI. GPi-DBS would be preferred if the treatment of depression is an important factor, or if a reduction of pharmacological treatment is unwanted. The addition of CM/Pf-DBS or PPN-DBS seems to have big advantages without extra complications, and thus should always be considered. It is not yet possible to suggest one of these two areas as a superior target.

External cues

To use external cues as a treatment is not straightforward, but it has definitely potential. More emphasis should be put on physical therapy with external cues, since this is a low cost and noninvasive alternative to pharmacological and surgical treatment methods (Lim et al., 2005; Rubinstein et al., 2002). Even without external cues, physical therapy can be effective, but this is not specific for PD patients. External cues can also be delivered through a portable device (Fernandez del Olmo & Cudeiro, 2003; Nieuwboer et al., 2007; Wegen et al., 2006), but this has the disadvantage of burdening a sensory system and can be experienced as unpleasant (Thaut et al., 1996). A chronically implanted stimulation device may therefore be a more viable option. We investigated the physiological effect of external cues and the possibility of simulating the effect of an external cue by delivering electrical stimulation.

Based on the studies described here, we suggest several brain regions as targets for electrical stimulation. First is the mesencephalic locomotor region. Stimulation in this area has already been done with PPN-DBS and proven to be effective (Stefani et al., 2007). Based on the results from a motor imagery study (Snijders et al., 2011), however, we suggest that stimulation dorsomedial of the PPN may be more effective. Our second suggestion is the application of cortical stimulation. The lateral premotor cortex and supplementary motor cortex are believed to have a profound influence on gait disturbances (Hanakawa et al., 1999). We believe that increasing activity in these regions, and especially in the SMA, will ameliorate disturbances in gait patterns. Increasing SMA activity can be achieved by sub-threshold stimulation (1.8-8 Volt) of the motor cortex with frequencies ranging from low to high (20-130 Hz). This type of stimulation has been tried in several patients with promising results (Fasano et al., 2008; Pagni et al., 2005; Tani et al., 2007). But it may actually be more effective to directly stimulate the SMA or PMC. We further suggested several other brain areas as potential targets for electrical stimulation, such as the posterior parietal cortex, anterior cingulate cortex, and the cerebellum.

Much more research in this field is necessary to create a stimulation device that can improve gait disturbances by simulating the effect of external cues. There are also many parameters, such as stimulation frequency, that need to be optimized. Low frequency stimulation may seem the best option in this case, since we have only suggested brain regions that need to increase their activation and no regions that should be inhibited. However, optimal stimulation of the motor cortex was in the band between high and low frequencies. That the optimal stimulation frequency for a patient was in such a wide spectrum, suggests great differences between motor cortices of patients. There is also a great variation in the effectiveness of cortical stimulation on PD symptoms. Even though most patients experienced great improvements which seemed persistent (Pagni et al., 2005; Tani et al., 2007), one case was described as a complete failure (Pagni et al., 2005), and for one patient the improvements gradually disappeared after five months (Fasano et al., 2008). Cortical stimulation may thus prove more challenging than deep brain stimulation.

Another challenge will be to find the optimal stimulation treatment with multiple stimulation devices. The effectiveness of motor cortex stimulation was sometimes close to conventional DBS, but was in most cases less effective. We therefore do not propose these new targets as a replacement of DBS, but merely as an addition, especially to treat gait disorders. Multiple stimulation devices activated at the same time, have already proven to be effective (Mazzone et al., 2006; Stefani et al., 2007). But with multiple deep brain and cortical targets suggested in this review, finding the best combination with patient studies may prove to be almost impossible. Models of the basal ganglia and cerebello-thalamo-cortical circuit may provide a possible solution to this problem (Helmich, Hallett, Deuschl, Toni, & Bloem, 2012).

In short, with so much still unknown about the therapeutic effect of electrical stimulation on the brain, it is almost certain that a lot of development in this field will take place. We have suggested several new targets for DBS which may create a superior DBS treatment method. We analyzed the effectiveness of external cues on PD symptoms and suggested stimulation methods that can possibly simulate this effect. Hopefully this modulation of brain activity will ultimately make life with Parkinson's disease more bearable.

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