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The influence of subthalamic nucleus stimulation on the pragmatic language production in Parkinson's disease

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As the dawn raises the day
The battle begins for me
To overcome my enemy

For all that I say
For all that I can be
The future I cannot see
To overcome my enemy

I work I train I fight
To try to fix what is not right
This fight I cannot see
I have learned about my enemy

What can I say
What can I do
When the enemy I see
My enemy is me

To override this fate
A fate I disagree
I summon all my strength
The better part of me

The future is told for all to see
I fear to become a shaky memory
How do I overcome my enemy
When my enemy is me

- Shaking Arts, a poet with Parkinson's disease

List of Abbreviations

5-HT	Serotonin
AD	Alzheimer Disease
BA	Brodmann's Area
BDAE	Boston Diagnostic Aphasia Examiniation
BG	Basal ganglia
CN	Caudate Nucleus
DA	Dopamine-agonist
DBS	Deep brain stimulation
dlPFC	Dorsolateral Prefrontal Cortex
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GLU	Glutamic Acid
GPe	Globus Pallidus externus
GPi	Globus Pallidus internus
HD	Huntington's Disease
H&Y stage	Hoehn and Yahr stage
HFS	High Frequency Stimulation
LSVT	Lee Silverman Voice Therapy
MDPDP+	1-methyl-1-4-phenyl-2,3-dihydropyridinium
MOA-B	Monoamine oxidase
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
NA	Noradrenaline
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron Emission Tomography
PoG	Postcentral gyrus
PPN	Pedunculopontine nucleus
PrG	Precentral Gyrus
QoL	Quality of life
rCBF	Regional Cerebral Blood Flow
RHD	Right-hemisphere damage
SAT	Speech Act Theory
SBL	Superior Parietal Lobe
SCOPA-COG	Scales for the Outcome of Parkinson's disease Cognition
SLI	Specific Language Impairment
SMA	Supplementary Motor Area

SN	Substantia Nigra
SNc	Substantia Nigra pars compacta
SNr	Substantia Nigra pars reticulata
SPES-SCOPA	Short Parkinson's Evaluation Scale /Scales for Outcomes in Parkinson's disease
STN	Subthalamic nucleus
TBI	Traumatic Brain Injury
UPDRS	Unified Parkinson’s Disease Rating Scale

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Introduction

Parkinson's disease (PD) is the second most prevailing neurodegenerative disorder of which an approximate 4 to 6 million people suffer worldwide (Bartels and Leenders 916; De Letter 15). In 2008, an estimate of 30.000 people were diagnosed with idiopathic Parkinson's disease in Belgium (De Letter 15). The disease is mainly defined by a gradual increasing degeneration of neurons located in the mesencephalon and a loss of dopaminergic neurons in the substantia nigra (SN), which ultimately results in a dysfunction of the intricate basal ganglia (BG) circuits (Bartels and Leenders 916). Bartels and Leenders (2008) note a prevalence of 1-2/1000, however, about '2% of the elderly are affected because the incidence increases above the age of 50.' While most patients suffer from idiopathic Parkinson's disease, first-degree relatives of patients suffering from PD 'have a two- to threefold increased relative risk to develop' the neurodegenerative disorder (Bartels and Leenders 916). Furthermore, epidemiological studies endorse the significance of genetic and environmental influences as conceivable causes of Parkinson's disease (Bartels and Leenders 916).

Generally, Parkinson's disease has an asymmetrical onset which results in an unsymmetrical degeneration of dopamine in the nigro-striatal pathway and the basal ganglia (De Letter 15). In other words, there is a noticeable difference between the dopaminergic levels of both hemispheres, which in a more advanced stage of the disorder ultimately leads to dysfunctions in the brain. 'Interestingly, the pathophysiological alterations are not clinically traceable "until

60 to 80% level of striatal dopamine loss is reached" (De Letter 15; Van Lier 2).' Once the brain can no longer cope and counterbalance this dopamine loss, motor deficiencies occur which can result in so-called 'gait disorders (shuffling, decreased arm swing, turning 'en bloc', gait freezing), speech and swallowing disturbances (hypophonia, festinating speech, drooling and dysphagia), micrographia, fatigue and impaired gross and fine motor coordination' (De Letter 15). However, apart from the aforementioned motor dysfunctions caused by the degeneration of dopamine, there are non-motor symptoms as well. Yet, while they were rarely the point of focus in studies in the past, recently there is an inclination in the number of researches attempting to elucidate the impact of the disorder on this less widely studied aspect of Parkinson's disease (De Letter 15).

Though PD is generally thought about as a movement disorder, a significant amount of studies have elucidated cognitive changes, such as an executive function deficit, language impairment, changes in memory, vision and psychomotor speed etc. (Halpern et al. 443-444). More specifically, studies have revealed a wide variety of 'language-related abnormalities', especially in word naming, word generation and verbal recall as noted by Illes et al. (Van Lier 3). The impact of Parkinson's disease on spontaneous language production, however, has not been adequately studied thus far and as such should receive more attention. Holtgraves and McNamara note that while 'the nature of the language-related deficits of PD have been hotly debated […], they are largely understudied. In particular, impairment in the domain of pragmatics has not yet been studied adequately (McNamara and Holtgraves 388).' McNamara and Durso's (2003) study revealed that patients with PD were indeed notably impaired when testing certain pragmatic communication proficiencies, more specifically the conversational appropriateness, prosodics and facial expression (McNamara and Durso 415). Furthermore, their results indicated that the patients were essentially unaware of their pragmatic deficits

(McNamara and Durso 422). As such, it is important to further study and elucidate the impact of Parkinson's disease on the pragmatic language proficiencies of patients as well as its impact on the patient's quality of life and eventually contribute to the 'development of an intervention program that can target pragmatic social communication skills and improve the quality of life for persons with Parkinson's disease (McNamara and Durso 422).'

This dissertation's goal is to participate and contribute to the existing discussion of the pragmatic impairments of PD patients and more importantly, the influence of deep brain stimulation of the subthalamic nucleus (STN) on pragmatic language production. Deep brain stimulation (DBS) as a treatment for PD has certain benefits over its older and more common alternative, namely levodopa medicinal therapies (Philips et al. 1). For example, stimulation of the internal pallidum (GPi) ameliorates the levodopa-induced dyskinesia and other side effects commonly associated with dopaminergic medication (Philips et al. 1; Santens et al. 253). Furthermore, Santens et al. (2003) note that the stimulation of the subthalamic nuclei (STN) has 'symptomatic benefits' surpassing those attained by GPi stimulation (Santens et al. 253). Moreover, several studies reported the effect of deep brain stimulation on all 'cardinal symptoms' of Parkinson's disease which resulted in a 'significant decrease of time spent in the off-state (Santens et al. 253).' Subthalamic nucleus stimulation also reduces the levodopa dosage needed pre-DBS, this subsides the prevalence of dyskinesia (Santens et al. 253).

The impact of DBS STN on language has not been thoroughly examined thus far, while it receives an increasing amount of attention from authors**,** only a small number of studies have examined the influence of subthalamic nucleus stimulation on lexical and grammatical processes in Parkinson's disease (Van Lier 2). This dissertation is based on a preliminary study which was conducted last year at the University of Ghent, however, whereas the former

research only studied the data of one patient, this current study will analyze the data of 18 patients receiving subthalamic nucleus stimulation in four different conditions. The analysis of the data of the preliminary study indicated that right hemisphere stimulation had a negative impact on the patient's linguistic abilities (Van Lier 33-34). Unilateral right hemisphere stimulation caused an increase in repetitions and reiterations as well as an increase in turn-taking which went hand in hand with a decreased coherence in the patient's utterances (Van Lier 27). However, no clear consensus could be reached as only one patient was analyzed, as such this paper will investigate whether right hemisphere stimulation - given that the left hemisphere is generally the language dominant one - consistently has a negative influence on the patient's linguistic pragmatic abilities or whether it is linked to the motor lateralization and the asymmetric dopaminergic levels in the mesencephalon (Van Lier 34).

Just like the preliminary study, no new data was recorded to avoid the toilsome process of receiving the Ghent University Hospital ethic committee's approval. Alternatively, the data was recorded in a clinical environment to examine and follow up how the patients responded to the different stimulation conditions which - probably - contributed to methodological flaws observed and contributing to limited results. Furthermore, similar to the pilot study, the data will be evaluated using the *Nijmeegse Pragmatiektest*, the only standardized Dutch test to assess pragmatic language abilities and as such the methodology of this paper will be very similar to that of the preliminary case-study.

The next section of this paper will present an overview of the pathology of Parkinson's disease as well as the motor and language impairments commonly observed in patients. Furthermore, deep brain stimulation and its benefits over the traditional medicinal therapies and how these treatments work, will briefly be addressed as it is necessary to fully comprehend what is explained in the discussion. Section 3 will cover the methodology, whereas section 4 and 5 will respectively present the results and the discussion. This will be followed by the last chapter which will present the conclusion to the research question.

Part 1

Chapter 1
Literature review

1.1 General introduction

This section of the dissertation will provide a fairly extensive introduction to the pathology and pathophysiology of Parkinson's disease and the motor and cognitive deficits caused by this neurological disorder. Furthermore, deep brain stimulation as a treatment will be explained as well as the benefits of this type of physiotherapy**.** Lastly, this section will describe what is generally understood under pragmatic language and underline the importance of it as an instrument of maintaining an endurable quality of life. The illustrations which are provided throughout the literature review serve as a visual aid and might facilitate to understand what is meant.

1.2 What is Parkinson's disease

Parkinson's disease was first identified by James Parkinson in 1817 under the name 'paralysis agitans', which was commonly referred to as 'Shaking Palsy (Bartels and Leenders 915).' He described the following symptoms: 'involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from walking to a running pace: the senses and intellects being uninjured (Bartels and Leenders 915).' However, medical knowledge has greatly improved and as such the pathology and pathophysiology has substantially evolved to a more exhaustive description (Bartels and Leenders 915). Today, Parkinson's disease is commonly characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta which results in disorganization and dysfunctions of the intricate basal ganglia (BG) structures (Bartels and Leenders 915). The involvement of the basal ganglia was first noted by Carlsson in the 1950s

(Bartels and Leenders 915). According to his research, he estimated that 80% of the dopamine in the mesencephalon is centered in the basal ganglia (Bartels and Leenders 915). Furthermore, he observed the correlation between the diminishing dopamine levels in the brain and Parkinson's disease; this so called 'dopamine-depletion theory' was later acknowledged by 'post-mortem biochemical studies showing decreased levels of dopamine and its metabolites in the nucleus caudatus, putamen, nucleus accumbens, SN and globus pallidus of PD patients (Bartels and Leenders 915).' Apart from the dopaminergic degeneration, Parkinson's disease is seen as a 'multicentric neurodegenerative disease' in which the various effects on parts of the basal ganglia during the neurodegenerative progression 'have consequences for motor and cognitive capacity and the performance of several skills (Bartels and Leenders 916).' Furthermore, Bartels and Leenders (2008) note that the pathology of Parkinson's disease evolves in a specific way, more precisely it commences 'in the dorsal motor nucleus of the vagus nerve and the olfactory bulbs and nucleus, followed by the locus coeruleus, after which neuron cell loss appears in the substantia nigra pas compacta (SNc) (Bartels and Leenders 916).' As the disorder progresses, less susceptible nuclei and cortical regions are slowly affected (Bartels and Leenders 916), this gradual degeneration leads to a variety of impairments which become more noticeable as the disease progresses (See figure 1).

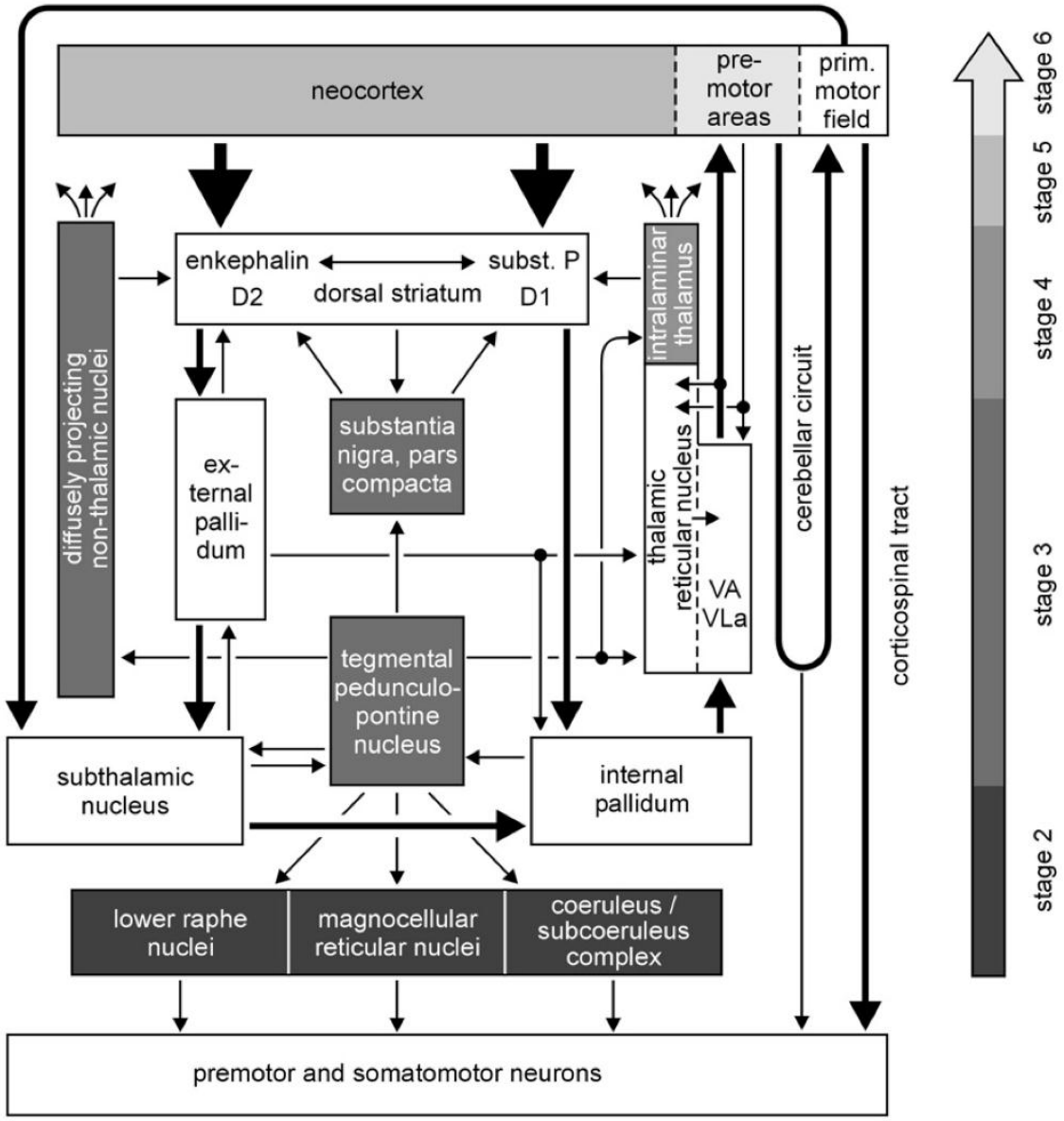

Figure 1: 'Amended version of the cortico-basal ganglia-cortical circuit. This model encompasses motor areas from the spinal cord to the neocortex and incorporates not only the consequences of dopamine depletion in the dorsal striatum but also additional non-dopaminergic somatomotor centers that become consecutively and severely impaired in PD. Cortical pathology most probably impairs the corticostriatal projection, whereas the corticosubthalamic connection remains intact. […] Neuropathological stages are indicated by various degrees of shading (Braak and Tredici 228).'

1.3 Ethiopathogenesis

While in most cases the disease is sporadic and referred to as idiopathic Parkinson's disease, first-degree relatives of patients, however, have a 'two- to threefold increase in risk to develop' the disorder (Bartel and Leenders 916). Bonnet and Houeto (1999) too observe a genetic predisposition to PD and base their observation on four types of studies, namely epidemiological studies, twin studies, 'analysis of large families with hereditary cases and studies of polymorphism of candidate genes (Bonnet and Houeto117).' However, like Bonnet and Houeto (1999), Bartel and Leenders (2008) note that the 'disease concordance rates' regarding monozygotic and dizygotic twins uncovered concordance rates equivalent of those 'when PD was diagnosed after the age of 50,' which suggests that heredity and genetic predisposition is not a key etiological element in the majority of cases as was previously thought (Bartels and Leenders 916). However, as it is difficult to determine concordance rates based on founded solely on clinical information, studies such as Bonnet and Houet's (1999) or Bartel and Leenders (2008) might be limited and should be approached and interpreted as such (Bartel and Leenders 916).[1]

Yet, epidemiological studies are of some importance as they endorse the value of genetic as well as environmental factors as likely causes of Parkinson's disease and as such help to establish the understanding of the pathogenesis of PD (Bartels and Leenders 916). While it is thought that several mechanisms, 'such as exogenous toxins, inflammation, genetic mutations and combinations of these factors' contribute to the emergence of Parkinson's disease, a widely acknowledged hypothesis is that it is the consequence of 'an interaction between genetic and environmental factors' which results in 'mitochondrial respiratory failure

[1] See appendix for a more in depth reference of genetic susceptibility in Parkinson's disease

and oxidative stress within nigral neurons, leading to cell death (Bartel and Leenders 916).' Bonnet and Houeto (1999) further strengthen the importance of environmental influence as illustrated in their study (Bonnet and Houeto 118). According to them, the frequency to develop Parkinson's disease is affected by four environmental factors, namely 'a more elevated frequency with rural living, well-water consumption, a more elevated frequency in industrialized countries; and, herbicide and pesticide exposure (Bonnet and Houeto 118).' The onset of Parkinson's disease thus appears to be complex with both genetic and environmental factors affecting the susceptibility (Bonnet and Houeto 118). It is worth mentioning that according to Bonnet and Houeto (1999) and other epidemiological studies, that there is a reverse relation between smoking and the recurrence of PD (Bonnet and Houeto 118). More precisely, these studies propose that 'compounds of cigarette smoke can protect dopaminergic neurons; in vitro, nicotine protects striatal neurons against apoptosis induced by free radicals. Dopaminergic neurons of SN contain sub-units of nicotinic receptors (Bonnet and Houeto 118).'[2]

Furthermore, Bonnet and Houeto (1999) their research observed that some non-dopaminergic neurotransmitters were also affected in Parkinson's disease (Bonnet and Houeto 118-119) . In what follows, a brief recapitulation of their findings will be put forth (Bonnet and Houeto 118-119). The following non-dopaminergic neurotransmitters are altered in PD (Bonnet and Houeto 118-119):

a) **Noradrenaline (NA):** Located in the locus coeruleus, treatments and medicines which reconstruct NA transmitters could also be potent for treating gait disorders, yet, this has not been acknowledged so far (Bonnet and Houeto 118).

[2] For a more in depth explanation of the MPTP-model, see appendix

b) **Serotonine (5-HT**): A reduced amount of serotonine could be (partially) responsible for depression in PD patients (Bonnet and Houeto 118).

c) **Glutamic acid (GLU):** 'Glutamatergic receptors are unchanged in PD, and GLU-antagonists may have a potential therapeutic effect on akinesia and rigidity, and may also potentiate the efficiency of L-dopa (Bonnet and Houeto 119).'

d) **Gamma-aminobutyric acid (GABA):** The GABAergic neurons are targeted by nigrostriatal dopaminergic neurons, a degeneration of these neurons results in a proliferation in activity of the GABAergic output (Bonnet and Houeto 119).

1.4 The importance of the basal ganglia

The importance of the basal ganglia in Parkinson's disease was first noticed by Carlsson who observed that almost 80% of the dopaminergic cells are located in the BG and this ultimately led to the association of the loss of dopamine and PD (Bartels and Leenders 915-916). Furthermore, Bartel and Leenders (2008) note that 'differential effects on regions of the BG during the neurodegenerative process in PD have consequences for motor and cognitive capacity and the performance of several skills (Bartels and Leenders 915-916).' As such, the basal ganglia have profusely been studied and because it is so important, a brief introduction to this complex structure is given in what follows.

The basal ganglia consist of subcortical nuclei that are actively engaged in the control of movement; the BG 'include the striatum (or caudate/putamen), the globus pallidus with external segment (GPe), and internal segment (GPi), the subthalamic nucleus (STN), the thalamus, the pedunculopontine nucleus (PPN), and the substantia nigra (SN) (Bonnet and

Houeto 119-120) (a representation of the connections and interaction between the nuclei is added below as a visual aid). It is generally suggested that the basal ganglia is involved in the instigation of voluntary movements, 'facilitation of some motion suppressing others, and comparison of motor commands with feedback from evolving motion (Bartels and Leenders 917).' Furthermore, apart from its role in motor control, the basal ganglia also participate in multiple emotional and cognitive functions (Bartels and Leenders 917).

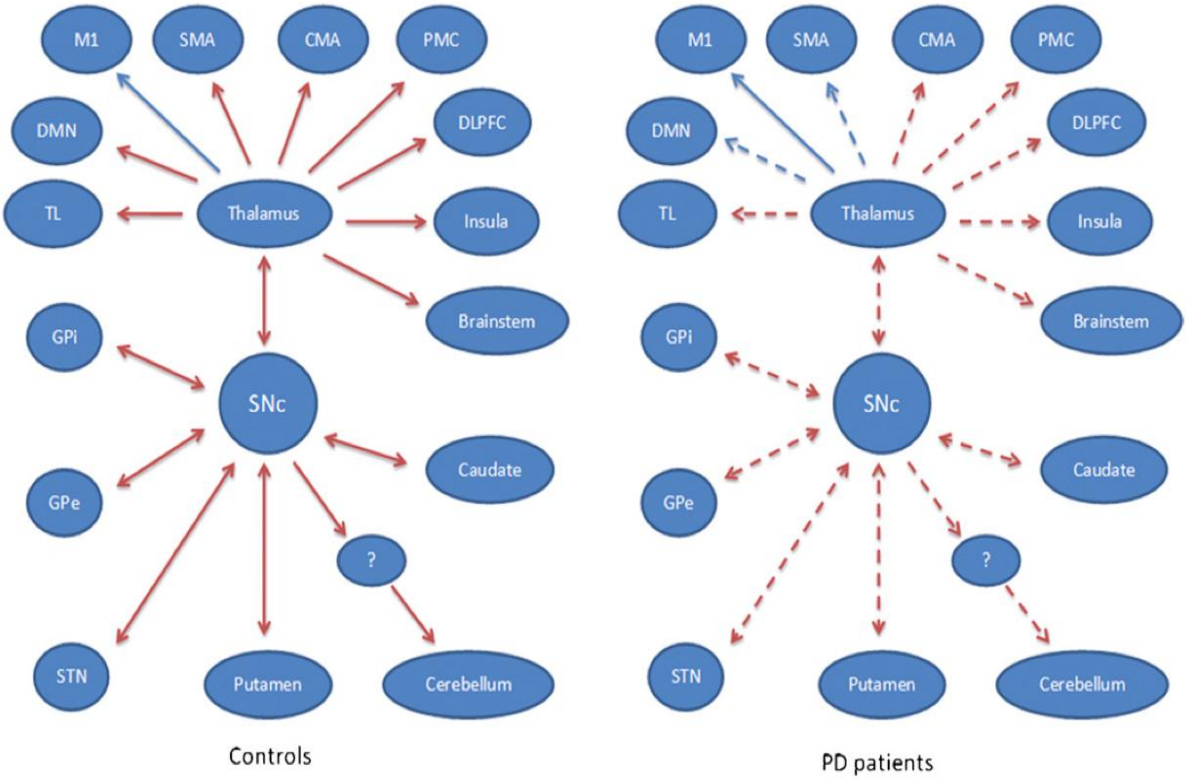

Figure 2: 'The different pattern of connectivity in the SNc, [one of the nuclei which is affected by the dopaminergic degeneration and depletion], in healthy controls and PD patients in the resting state. Red/blue lines indicate positive/negative influences of the SNc with other brain regions. The arrows indicate the directionality of influences between the SNc and other regions. The dotted lines indicate decreased connectivity from the SNc to the corresponding brain regions in PD patients compared to healthy controls. Abbreviations: CMA, cingulate motor area; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; GPe, external globus pallidus; GPi, internal globus pallidus; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TL, temporal lobe. The question mark indicates uncertain brain region (Tao Wu et al. 58).'

1.4.1 Classical model

In the classical model, the basal ganglia is part of an intricate system of loops that incorporates cerebral cortical regions (such as the associative, limbic and motor regions), the basal ganglia nuclei and the thalamus (Bartels and Leenders 917; Bonnet and Houeto 120). In the "direct pathway", 'GABAergic output neurons', which predominantly consist of D1 dopamine receptors, project directly from the putamen to the globus pallidus internus and the substantia nigra reticulata, also referred to as the 'output nuclei of the BG (Bartels and Leenders 917; Bonnet and Houeto 120).' The direct pathway produces a 'direct inhibitory [GABAergic] effect' on neurons located in the globus pallidus internus (GPi) and substantia nigra reticulata (SNr), resulting in a reduction of the inhibition of these nuclei on the thalamus and as such alleviating movement (Bartels and Leenders 917). In the "indirect pathway", on the other hand, the putamen interacts 'with the output nuclei - consisting of mainly D2 dopamine receptors - via the globus pallidus externus (GPe) and the subthalamic nucleus (STN) (Bartels and Leenders 917). Furthermore, when striatal projection neurons are stimulated in the indirect pathway, this results in an inhibition of the globus pallidus externus, a disinhibition of the subthalamic nucleus and excitation of the globus pallidus internus and substantia nigra reticulata, ultimately intensifying the inhibition on the thalamus and subduing movements (Bartels and Leenders 917). According to this "direct-indirect pathway-model", dopamine deficiency results in a reduced inhibition or hyperactivity of the indirect pathway, which leads to an unrestrained glutaminergic pressure to the GPi and SNr (Bartels and Leenders 917; Bonnet and Houeto 120). Moreover, there is an attenuated excitation of the 'inhibitory GABAergic direct pathway further disinhibiting the activity of the GPi and of the SNr (Bartels and Leenders 917; Bonnet and Houeto 120).' Since these output nuclei (GPi and SNr) utilize the neurotransmitter GABA, the augmented output of the BG results in an 'excessive inhibition' which leads to the closure of thalamic nuclei obtaining their "outflow"

(Bartels and Leenders 917; Bonnet and Houeto120). Furthermore, Bonnet and Houeto (1999) and other studies note that 'the excessive thalamic inhibition leads to inhibition of the cortical motor system, possible resulting in akinesia, rigidity and tremor, whereas the inhibitory descending projection to the brainstem is thought to contribute the abnormalities of gait and posture (Bonnet and Houeto 120; Wu et al. 55). However, Bartels and Leenders argue (2008) - while they acknowledging that this model functions as a decent starting point - that it yields no expertise and no acuity into the pathophysiology of certain motor impairments in Parkinson's disease (Bartels and Leenders 917). They write: 'Different aspects of parkinsonian motor symptoms and non-motor symptoms cannot be explained simply as a result of augmentation in the inhibitory output from the BG (Bartels and Leenders 917).' Yet, Bonnet and Houeto (1999) admit that this model can only to a certain degree account for the intricacy of the BG network, nevertheless, it provides a foundation for 'experimental, clinical, and therapeutical research (Bonnet and Houeto120).' In addition, apart from fine-tuning motor functions, the BG have been speculated to participate in the 'mediation of cognitive functions (Murdoch 28).' More specifically, studies observing lesions of the dorsolateral prefrontal basal ganglia circuit have elucidated cognitive deficits such as impaired spatial, episodic and semantic memory, common in patients suffering from Huntington's and Parkinson's disease (Murdoch 28). Furthermore, medicinal therapies with dopaminergic drugs (such as Levodopa) or high-frequency stimulation (HFS) of the globus pallidus internus or subthalamic nucleus could possibly suppress the 'synchronized oscillatory activity[3]' which occurs at 'low beta frequencies in BG circuits in PD' and eliminate the excitation of the basal ganglia output nuclei (GPi, SNr)(Bartel and Leenders 918). However, deep brain stimulation

[3] See appendix

has its limits and appears to exasperate cognitive or emotional symptoms, similar to dopaminergic drugs (Bartel and Leenders 918).

1.5 Motor impairments and clinical symptoms

Parkinson's disease is generally categorized as a hypokinetic movement disorder due to the neuronal degeneration within the basal ganglia, more specifically in the substantia nigra, which instigates a decline in the amount of dopamine secreted in the striatum (Murdoch 28). As the basal ganglia is involved in motor functions as mentioned above, pathology affecting the BG network is usually coupled with involuntary movement disorders, which are traditionally subdivided into either hyperkinetic and hypokinetic subcategories (Murdoch 28). Murdoch (2009) notes that 'hyperkinetic disorders (i.e. abnormal poverty of movement) arise as a consequence of damage to the basal ganglia (Murdoch 28).' Hyperkinetic disorders include 'conditions such as chorea, ballismus and athetosis[4] (Murdoch 28).' Chorea, for example, is characterized by fast involuntary movements which are 'jerky, irregular and non-repetitive in nature' and is often present in Huntington's disease (Murdoch 28). As mentioned above, Parkinson's disease is seen as a hypokinetic disorder with cardinal symptoms such as, resting tremor, righty, bradykinesia[5] [...] and postural disturbances (Murdoch 28).

Furthermore, dysarthria generally develops in idiopathic Parkinson's disease apart from the aforementioned motor impairments (Rusz et al. 319; Skodda et al. 1; Kyung Park et al. 358). According to Rusz et al. (2012) nearly 90% of the patients develop some form of 'hypokinetic dysarthria' (Rusz et al. 319; Skodda et al. 1; Kyung Park et al. 358). However, two large scale

[4] See appendix
[5] See appendix

speech studies yielded significantly different results, ranging from an approximate 49% to 70% of the patients suffering from speech impairment (Ho et al. 131). They observed that '89% experienced voice disorders, 45% experienced articulatory impairment and 20% experienced problems with fluency (Ho et al. 131).' Parkinsonian speech is commonly characterized by 'phonatory, articulatory and prosodic deviations which decline as the disorder progresses. The phonatory and articulatory deviation is defined by a 'breathy or hoarse voice, reduced loudness and restricted pitch variability (mono pitch and mono loudness), imprecise pronunciation and abnormalities of speech rate, and pause ratio (Rusz et al. 319; Skodda et al. 1; Kyung Park et al. 358).' These speech impairments are often related to the hypothesis of reduced cortical motor set due to basal ganglia (BG) dysfunction' (Ho et al. 132). Ho et al. (1999) note that the basal ganglia are most likely involved in the administration of internal cues which allows the 'sequential execution of sub-movements within a motor plan (Ho et al. 135).' Furthermore, 'defective internal BG cuing[6] in PD has been suggested to result in progressive decrements in amplitude over the duration of the motor sequence, a phenomenon known also as motor instability (Ho et al. 135).'

While these "abnormalities of voice and speech" are commonly seen as a result of the aforementioned dopaminergic deficit which leads to 'hypokinesia and rigidity of the laryngeal muscles' and are sometimes amended by dopaminergic treatment, other studies, however, have unsuccessfully attempted to elucidate a distinct causal relation 'between dopaminergic dysfunction and overall speech performance (Skodda et al. 1).' Hence, some studies propose that the modification of voice and speech can - at least partially - be explained as the consequence of non-dopaminergic processes 'with additional alteration of internal cueing, sensorimotor gating, scaling, and timing of speech movements (Skodda et al. 1).'

[6] See appendix

Furthermore, Skodda et al. (2013) note that the dysarthria worsens in the more advanced stages of Parkinson's disease, yet, admits, however, that 'data on development and progression of dysarthria in the individual patients are sparse (Skodda et al. 1).' Nevertheless, their study revealed deterioration of speech over time even though patients were taking dopaminergic medication which was honed for the best possible motor outcome (Skodda et al. 7). This, as a consequence, acknowledges the aforementioned hypothesis of non-dopaminergic processes involved in Parkinsonian dysarthria and dysarthrophonia (Skodda et al. 7). The therapeutic way of attempting to ameliorate the speech performance of PD patients is - according to Skodda et al. (2013) - still unsatisfactory, for example the Lee Silverman Voice Treatment (LSVT), which is regarded as the most efficient therapy, 'has its limitations by insufficient availability and prescription (Skodda et al. 7).'[7]

Another aspect of speech which is important in maintaining a quality of life (QoL) is emotional communication (Möbes et al. 824). This can be achieved either through gesture and mimics, but particularly through speech (Möbes et al. 824). However, as Parkinson's disease progresses, the nervous system becomes more and more deficient which could eventually have an impact on emotional speech (Möbes et al. 824). Indeed, as Möbes et al. (2008) observed, PD patients speak with a reduced 'modulation of pitch and intensity, i.e. reduced emotional prosody, making it more difficult to identify their emotional intention (Möbes et al. 824).' These alterations impair their social skills and pragmatic communication abilities, which will ultimately lead to a reduced quality of life (Möbes et al. 824). Furthermore, not only is the production of emotional speech impaired, studies illustrate that the 'perception of emotional prosody and facial gestures' too is deficient, which is exemplified by 'higher error rates in appreciation of emotionally spoken words and changes in event related brain

[7] See appendix for a more in depth description on how to treat hypokinetic speech impairment in PD

potentials in response to these words (Möbes et al. 824).' As such, "impairment of emotional processing" is seen as a component of parkinsonian speech alteration. Interestingly, Möbes et al. (2008) strengthen their argument by referring to comparable speech modifications observed in depressed patients and that PD patients recurrently experience depression, however, they do not further explain this link (Möbes et al. 824).

1.6 Non-motor impairments

As already mentioned above, Parkinson's disease is traditionally characterized as a hypokinetic movement disorder, however, recently a growing number of studies is meticulously elucidating the impact of the disorder on non-motor domains, such as cognition (Verbaan et al. 1182). Studying in which degree Parkinson's disease affects the cognition of the patient is important as cognitive degeneration is a forecast of dementia in PD (PDD); which again is essential for the clinical staff and patient management (Verbaan et al. 1182). Furthermore, the prevalence of PDD varies significantly from 2- 81% depending on the study; however, in general, it is assumed that on average 40% of the patients develop PDD (Verbaan et al. 1182). Possible factors contributing to the inconsistent results are 'sample characteristics (selection procedure, source population, sample size), applied criteria of dementia and cognitive impairment and the use of different methods for the evaluation of cognition in PD (Verbaan et al. 1182). These instruments, used to evaluate the cognition of patients, often contain items sensitive to motor symptoms seen in PD, thus influencing the outcome of the assessment (Verbaan et al. 1182). As such, new tools based on leading 'evidence that memory, attention and executive and visuospatial functioning are important aspects of cognitive impairment in PD, a reliable and valid quantitative PD specific instrument (Scales for Outcomes in Parkinson's disease-cognition (SCOPA-COG)) was developed in 2003

(Verbaan et al. 1182).' Verdaan et al. (2007) used this test on a large sample of patients and observed that patients were impaired on all four cognitive subdomains (namely memory, attention and executive and visuospatial functioning) (Verbaan et al. 1183). However, they admit that their study is limited and that it is a clinical study 'with a selection procedure based on age at onset and disease duration (Verbaan et al. 1182).' As such, they acknowledge that their results should not be generalized (Verbaan et al. 1182). Similar to other studies, they observed that the executive functioning was affected the most, seconded by memory (Verbaan et al. 1186). Furthermore, Verdaan et al. (2007) noticed that the age of the patient and the level of education were connected to the SCOPA-COG scores and, more importantly, that a more advanced stage of Parkinson's disease was related with decreased cognitive performance, which means as the disorder progresses, the cognitive impairment becomes more profound (Verbaan et al. 1186). Moreover, the dopaminergic drugs utilized to treat motor impairments repeatedly instigate 'non-motor side effects such as orthostatic hypotension[8], hallucinations, somnolence[9], insomnia [...], adding to the overall burden of the non-motor spectrum of parkinsonian morbidity (Poewe 14).'

1.7 Language

However, more important for this dissertation is the influence of Parkinson's disease on the language abilities of patients and which deficits commonly occur post onset. While it was generally thought that language skills were unaffected by PD, it soon became apparent that this was not the case. More precisely, since the end of the 1980s, a growing number of studies

[8] See appendix

[9] See appendix

observed that PD disrupts a variety of features of language processing (Lloyd 398). For example, 'Spicer, Roberts and Lewitt (1988) and Beatty and Monson (1989) reported evidence that PD patients were impaired at naming compared with matched controls. Illes, Metter, Hanson et al. (1988) and Cummings, Darkins, Mendez et al. (1988) observed that the speech of PD patients is less grammatically complex than age matched controls (Lloyd 389).' 'Lieberman, Friedman, Feldman et al. (1990) and Lieberman, Kako, Friedman et al. (1992)' on the other hand noted 'that this mild agrammatism can also be present in their speech comprehension (Lloyd 389).' Finally, 'Grossman, Carvel, Gollomp et al. (1991) and Grossman, Carvel, Stern et al. (1992) also found consistent evidence of a syntactic comprehension problem (Lloyd 389).'

According to Lieberman et al. (1990), these syntactic errors are not a consequence of the compensation of speech motor activity, instead they should be interpreted as a direct result of the disease itself as comprehension requires almost no motor participation (Lieberman et al. 364). Positron emission tomography (PET) studies[10] of PD patients propose a possible explanation for the linguistics deficits observed, more precisely they occur due to reduced frontal cortical activity (Lieberman et al. 364). Yet, before a detailed literature review regarding the language deficiencies which occur in Parkinson's disease is given, a brief introduction to how language is organized in the brain and subcortical participation in language processes is needed.

[10] See appendix

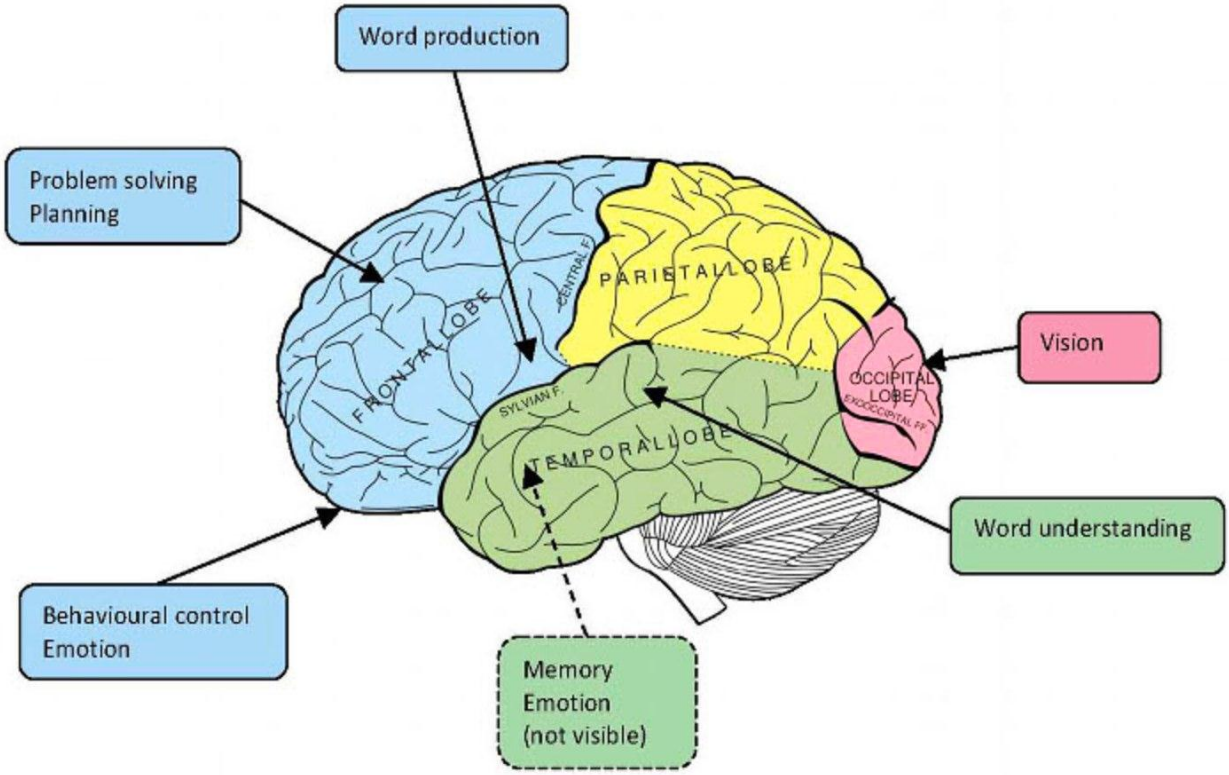

Figure 3: Simplified overview of the different brain regions and their role in language production and comprehension. (NeuRA, n.pag.)

Based on the models in which subcortical nuclei - more precisely the basal ganglia and the thalamus - participate in language processes, several studies anticipated language deficits in Parkinson's disease even before they were thoroughly studied (Altmann and Troche 2). One of the leading scholars on this subject, Crosson, hypothesized that disruption of the basal ganglia could develop both motor programming and language formulation impairments 'through their connections with the cortex (Altmann and Troche 2).' More specifically, already in the early stage in Parkinson's disease, the functions of the thalamus, putamen and caudate nucleus are dysfunctional which could contribute to the language impairments observed as 'these structures are hypothesized to integrate or control attention to input from

the superior and middle temporal gyri (Brodmann's Area 41,42, 21, 22[11]) and dorsolateral prefrontal cortex (dlPFC), especially BA 44, 45, and 47, during language processing (Altmann and Troche 2).' As such a dysfunction of these cortico-striato-pallido-thalamo-cortical circuits could damage some features of language production (Altmann and Troche 2). Moreover, imaging studies have observed that frontostriatal circuits are also activated during executive function tasks, which means that a disruption of these circuits could affect both language and cognitive functions (Altmann and Troche 2). It is clear that language - as well as cognitive - deficits as a result of a neurological disorder are not as easily explained as the origin is far less clear-cut compared to motor impairments. Furthermore, Altmann and Troche (2011) note that a delayed transmittal of information through these circuits as a result of the loss of connections due to PD related lesions, could as well partake in the disruption of the flow of information between different language areas (Altmann and Troche 2). This could result in the aforementioned deficits, such as 'impaired fluency of speech, if the language system has to wait for the next sentence elements to become available, or impaired computation of grammaticality if information necessary for computing agreement, for example, is no longer (or not yet) available when a verb is active (Altmann and Troche 2).' Likewise, deficits which affect the constant interaction between different language regions could reduce the 'information content in language output if the dynamics of conversational speech require a response to be started before specific conceptual information has been fully activated and made available to the language production system (Altmann and Troche 2).' As mentioned above, apart from PD's influence on subcortical nuclei, it also disrupts the functioning of the dorsolateral prefrontal cortex which 'plays an instrumental role in many aspects of language use and in the cognitive abilities that support language such as working

[11] See appendix

memory and executive function (Altmann and Troche 2).' Interestingly, Bastiaanse and Leenders claimed with certainty that cognitive impairments were entirely accountable for the language deficits observed in Parkinson's disease and as such there were no unique language impairments secondary to this disorder (Altmann and Troche 2). However, while it is likely - as it is still precarious to generalize certain studies and their conclusions - that several cognitive and linguistic functions employ the same underlying neural processes, it still remains plausible that there may also be neural circuits 'that are primarily used in language production that [are] independently damaged in PD (Altmann and Troche 2).' Lewis et al., for example, argued that the language functions of PD patients were intact; instead, they interpreted the language deficits as result of the cognitive impairment due to frontal lobe damage (Altmann and Troche 2). However, their claim was based on the validity of the tasks employed, namely patients scored the worst on language tasks which required 'organization, planning, abstract thought, and integration of information, functions associated with the frontal lobe (Altmann and Troche 2).' Furthermore, Berg et al. evaluated complex language production using a modified version of Lewis et al. their test battery which assessed 'sentence repetition, sentence production, and the ability to define words along with several receptive language (Altmann and Troche 2).' As expected, their observations of complex language production were very similar to those of Lewis et al. (Altmann and Troche 2). They noted that 'participants with cognitive dysfunction demonstrated significant impairments in the comprehension of metaphors and ambiguous sentences as well as in generating sentences; however, they performed similarly to controls when repeating sentences (Altmann and Troche 2).'

However, the observations made by Lewis et al. and Berg et al. were generalized although they actually did not elucidate that much about the language output of PD patients as the standardized test did not allow to properly assess whether the language output was, for

example, coherent, grammatical, or syntactically complex (Altmann and Troche 3). Thus, while they might have correctly noted that complex language production and comprehension was indeed deficient in Parkinson's disease, such studies did not provide any information on how exactly the language deficits manifested (Altmann and Troche 3). Yet, this lack of a standardized test to apprehensively assess language was addressed and as such, 'several researchers have begun to measure more detailed characteristics of the language output of individuals with PD as well as the component cognitive abilities […] using tasks that provide a better estimate of different types of cognitive abilities (e.g., working memory, inhibition, set shifting, and speed of processing) (Altmann and Troche 3-4).'[12]

A study by Colman et al. (2009) studied the impact of cognition and task switching on language production of PD and compared them to age matched healthy participants (Altmann and Troche 4). The participants were asked to complete a set of cognitive tests as well as to fill in the appropriate form of an inflected verb in a specific sentence (Altmann and Troche 4). Colman et al. (2009) noticed that members of the PD group 'performed more poorly than healthy adults on cognitive measures of task switching and, marginally, on action fluency (P =.06), but not on tasks assessing sustained and divided attention, working memory, inhibition, semantic fluency, or phonemic fluency (Altmann and Troche 4).' For the "verb production task" they were given a picture which they needed to describe aloud with the appropriate inflected form of the given verb (Altmann and Troche 4). Additionally, they were asked to produce a past tense construction when the context contained a "time biasing adverb" (i.e. yesterday, last week) and a present tense verb if there was no adverbial cue present (Altmann and Troche 4). PD patients regularly produced a past tense verb even when there was no

[12] See appendix for a more in depth approach on the influence of PD on bilingual patients and its impact on implicit language processes

adverbial indicator present (i.e. they had to produce a regular present tense form) (Altmann and Troche 4). Colman et al. (2009) concluded that 'the verb production deficits in PD were due to cognitive deficits exaggerated by task specific demands, specifically having to switch from past to present tense when no cue appeared in the sentence (Altmann and Troche 4).' Moreover, Colman et al.'s (2009) study proposes that a higher experimental task demand can unveil weaknesses in language production in Parkinson's disease and, more importantly, increase awareness for the importance of a verb in a sentence: 'difficulties with verb access could seriously impact sentence production due to the centrality of the verb to the sentence construction process (Altmann and Troche 5). In fact, verb production in action fluency tasks seems to be particularly impaired in persons with PD whether they have dementia or not, while noun generation is relatively unimpaired (Altmann and Troche 5).' Other studies have indeed elucidated that people suffering from PD have more difficulty acquiring new verbs and producing the appropriate regular past tense forms of verbs (Altmann and Troche 5). However, as Colman et al. (2009) and Altmann and Troche (2011) note, the latter observations are difficult to reproduce and, in addition, 'the relationship between verb access deficits in PD and findings of diminished information content, impaired grammaticality, decreased syntactic complexity and impaired fluency has yet to be explored in the literature (Altmann and Troche 5).'

Altmann and Troche's (2011) noticed a 'significant predictive relationship' between on the one hand working memory and executive function and on the other hand different features of language production (Altmann and Troche 6). While this indicates a strong interaction of cognitive proficiency on "language production performance", these, however, cannot be fully held accountable for the deviations in PD patients' language performance (Altmann and Troche 6). As such, their study interestingly reveals an 'additional, unexpected possibility that the deficits in PD language production extend beyond what can be explained by standard tests

of working memory and executive function (Altmann and Troche 6).' Furthermore, the demand for new and improved statistical techniques specifically designed to determine 'whether the language impairments in PD are […] attributable to cognitive impairments, or whether deficits exist in PD […] are specific to language processing', is highlighted again (Altmann and Troche 6).

In short, the aforementioned studies meticulously examined different aspects of language production in Parkinson's disease and observed that there is a reduced information content across a range of different language tasks, such as 'conversational discourse, picture description tasks, and written sentences (Altmann and Troche 9). Secondly, several studies reported an impaired grammaticality of language production; more specifically they noticed a simplification of syntax in complex tasks (Altmann and Troche 9). Furthermore, most PD patients have a "fluency of production" deficit; however, this should be studied both 'as a language impairment as well as a motor speech impairment (Altmann and Troche 9).' Furthermore, several studies reported the importance and involvement of cognitive competency in language production and performance and, more importantly, some impaired features of language performance in Parkinson's disease have been associated - and susceptible - to cognitive deficits (Altmann and Troche 9).

Moreover, other studies have observed language-related abnormalities and have hypothesized as such that Parkinson's disease might indeed impair the patients' speech planning and lexical access (Illes 147). 'For example, on the naming section of the Boston Diagnostic Aphasia Examination, PD patients produced significantly fewer words than matched controls (Illes 147); in contrast, when tested for written descriptive ability PD patients used a greater number of words to identify the same number of themes described by normal control subjects (Illes 147).' Furthermore, when testing serial speech (for example naming the months of the year),

most of the patients were unable to stop at the end of the series (Illes 147). Illes (1988) hypothesizes that 'the relative reduction in the number of words produced per silent hesitation, the change in semantic form, and the eventual decrease in syntactic complexity with increasing severity are evidence that the linguistic changes are an intrinsic part of the disease process (Illes 156).' This suggestion is further strengthened by studies elucidating impairments of verbal generation and recall, and by cognitive assessments revealing 'deficits of concept formation and concept completion in PD (Illes 156).' However, inconsistent with his hypothesis and other studies, Illes (1988) observed that patients produced relatively more open optional phrases compared to normal speakers (Illes 156). Yet, while 'the production of superfluous referential utterances such as open class optional phrases may be consistent with patients' inability to exit from their cognitive loop, it is in direct contradiction to any intrinsic deficit of lexical access; a significant increase in the production of non-referential or automatic utterances such as interjection and moralizations would be the expected result (Illes 156-157).' Furthermore, the lack of any remarkable deviations in the prevalence of repetitions or aborted phrases is also proof that the digression from normal patterns - at least in spontaneous language production - is not caused by a 'primary deficit of lexical access or sentence planning and formulation in Parkinson's disease (Illes 156-157).' Illes (1988) also notes that the high number of 'open class optional phrases and the reduction in non-referential utterances in the PD samples' characterize a template of spontaneous language production which deviates from the spontaneous language observed in patients suffering from other neurodegenerative diseases, such as Alzheimer's disease (AD) or Huntington's disease (HD) (Illes 157). However, Illes (1988) interestingly provides an alternative analysis of the data which takes the patient's dysarthria into account, more precisely (Illes 157):

> 'As the severity of the disease and dysarthria increase, PD patients adopt a strategy to convey as much information about a concept as possible, as compactly as possible, in a

single sentence. It is not surprising that patients accommodate to or compensate for speech motor deficits by producing more open class optional phrases; moreover, the relative reduction in moralizations and interjections also favors the adaptation-hypothesis in that, because of their mechanical difficulty, it would be inefficient for PD patients to produce non-informative, extraneous speech (Illes 157).'[13]

1.7.1 Pragmatic language

More important for this dissertation is the impact of Parkinson's disease on patients' pragmatic language abilities and consequently its influence on their social environment. A dysfunction of these pragmatic communication proficiencies has far reaching consequences as they are 'essential skills to have if the brain-damaged individual is ever to integrate back into a job or personal social network as even the simplest tasks of daily life are undermined if an individual cannot effectively convey needs, desires and information to another' (McNamara and Durso 415). Monetta and Pell (2007) noticed that the comprehension of pragmatic language phenomena is affected if there was some kind of manipulation of information present within the working memory, thus acknowledging the influence of Parkinson's disease on the fronto-striatal circuitry and the dorsolateral prefrontal regions (Monnetta and Pell 81). Perkins (2013) describes pragmatics as 'a branch of linguistics which focuses primarily on the way in which language is used by actual speakers in real-life situations, rather than on its formal properties, which can be considered independently of speakers and hearers (Perkins 228).' He illustrates this with the example sentence "I've forgotten my umbrella" which can be examined in terms of 'its grammar, vocabulary, and phonology without the need to specify any actual context of use (Perkins 228).' However, if someone hears this sentence on a

[13] See appendix for a description of the impact of PD on patients' prosody as it is an important linguistic feature which conveys a lot of information. As this paper does not evaluate the prosody of the patients, we will not discuss this here.

specific occasion, uttered by a unique individual, we are inherently 'drawn to factors such as what other utterances and events (if any) precede and follow it, why the speaker chose this particular form of words, who the utterance is addressed to, its intended - and actual - effect on the addressee and other incidental hearers, where and when it was uttered, the speaker's facial expression, body posture and any accompanying gestures, the extent to which the utterance reflects or manifests a particular set of sociocultural parameters, and so on (Perkins 228).' Moreover, a patient who has a grammar, phonologic or semantic deficit will have a pragmatic impairment as well and as such their 'ability to produce or comprehend the requisite range of contextually appropriate utterances is limited (Perkins 228).' Furthermore, while the main focus of pragmatics is evidently on the use of language, it was originally more generally interpreted as the 'communicative use of all signs, not just linguistic ones (Perkins 228).' This broader view on pragmatics is particularly useful in the analysis of language deficits as a consequence of a neurological disorder or lesion 'where the use of non-linguistic signaling systems such as gesture and facial expression is commonly seen as a means of compensating pragmatically for language deficits (Perkins 228).'

Pragmatic impairment or deficiency is commonly used to refer to someone who has an impediment in language use; instead of relating to a single pragmatic disorder, it functions as an "umbrella term" pertaining to 'a wide range of disparate phenomena with no single underlying cause (Perkins 227).' Furthermore, a pragmatic deficit is often linked to or the consequence of a cognitive or neurological dysfunction (Perkins 227). It was first recognized and acknowledged in the early 1980s by theoretical pragmatists such as Austin and Searle ,whose Speech Act Theory (SAT) in particular was influential, and Grice known for his Co-operative Principle (Perkins 228). More recently, Discourse Analysis was postulated by the influential work of Halliday and Hasan (1976) which 'identified a range of means by which a

sequence of utterances - particularly in narratives -was able to form a coherent whole over and above its individual constituent sentences (Perkins 229).' Following Discourse Analysis, a more analytical method named Conversation Analysis has been progressively gaining influence and importance in clinical pragmatics by underlining and stressing the importance and contribution of both interlocutors as opposed to only focussing on the individual with the deficit (Perkins 229). Because of the multitude of influential theories and works, there is a vast diversity of symptoms commonly associated with the deficiency, for example: 'saying too little or too much; overuse of certain phrases; failure to initiate conversation; over-literalness; repetitiveness; problems with inference, topic maintenance, lexical retrieval, fluency, humor, figurative language, intonation; facial expression, tense use, eye gaze, intelligibility, event sequencing, physical proximity, politeness, and so forth (Perkins 229).' There are a number of tools available to assess pragmatic impairment, some of which focus on a wide variety of communicative behaviors, whilst others specifically focus on pragmatic aspects such as turn taking, topic management or cohesion (Perkins 229). However, as Perkins (2013) rightfully mentions, the characterizations of pragmatic deficits are but an 'artifact of the particular evaluation measure used' and should not be interpreted as an 'independent, pre-existing, discrete condition that was merely waiting to be discovered (Perkins 229).' Furthermore, as pragmatic impairments manifest in a wide variety of behaviors, it is obvious that it is unlikely that one single cerebral activity is responsible (Perkins 230). Instead "neuro-pragmatics" focus on the neuronal activities and processes observed in specific pathological conditions usually related to "pragmatically atypical behavior", 'such as damage to the right hemisphere, and Traumatic Brain Injury (TBI) in which the frontal lobes are most commonly affected (Perkins 230).' Moreover, Perkins (2013) notes that 'various pragmatically relevant cognitive functions have been linked to specific areas of the brain such as prefrontal cortex (cognitive control, memory for source of

information, meta-memory judgment, and the processing of novelty), orbito-frontal cortex (emotional and social control), right frontal lobe (awareness of others' - and one's own - mental states and retrieval of episodic memory), left frontal lobe (memory encoding), and ventromedial frontal lobe (social reasoning and empathy) (Perkins 230).'

As mentioned above, pragmatic deficits are often associated with a cognitive impairment, however, as Perkins (2013) righteously notes: 'there is more to pragmatics than just cognition; when interacting with others, even if we have a full appreciation of the context, the mental and emotional states of the participants and what is communicatively appropriate at any given moment, we are not going to be successful unless we also have the necessary ability to produce and understand language across its full range of complexity of subtlety (Perkins 233-234).' In what follows, a concise summary will be given of the pragmatic deficit which arises after the highlighted linguistic impairment.

- Syntax and morphology: A reduction in syntactic or morphological comprehension and the ability to process it will (a) decrease the morphosyntactic selections available for the appropriate structure to context, and (b) encroach an extra "processing burden" on the interlocutor (Perkins 234).

- Semantics: Difficulties with semantics, more specifically lexical selection are often related to pragmatic deficiency (Perkins 234). For example, word-finding problems are observed in patients suffering from aphasia and can also be pragmatically interruptive as it results in a prolonged endeavor at self-repair and circumlocution as is illustrated in following transcript presented by Perkins et al. (2006) where the patient attempts to retrieve the word "watch": 'it's er - (sigh) what I put on my hair on. er not my hair. er - (tuts) put it right er (sigh) dear dear dear get it. I'll get it in a minute (looks at watch and shakes his head) it's not going through. It's not getting it. It's not that one. It's easy that one. It's dead easy that is

(Perkins 234-235).' This perfectly illustrates the pragmatic impairment which accompanies a lexico-semantic deficiency following a lesion or a neurological disorder (Perkins 235).

- Discourse: Similar to pragmatics, discourse focuses on the linguistic context, however, it is different 'by highlighting in particular the way in which extended sequences of language mesh together (cohesion and coherence) (Perkins 235).' Individuals with aphasia or a Specific Language Impairment (SLI) tend to perform poorly on cohesion, in contrast with patients suffering from right-hemisphere damage (RHD), TBI, or Alzheimer disease (AD) are commonly associated with problems with social cognition and inference (Perkins 235).

- Phonology: Similar to the aforementioned deficits, difficulties with producing or perceiving phonological differences and distinctions results in concomitant pragmatic dysfunctions (Perkins 235). Perkins (2013) illustrates this with the following example: 'If one's attempts at producing "sit," "sick," "stick," and "tick" all result in the identical sound sequence [tIk]; in order to work out which word is intended, any interlocutor will need to rely on contextual inferences to a far greater extent than usual (Perkins 235-236). Yet, most commonly associated with pragmatic deficits, are the so-called "problems with non-segmental phonology" or prosody (i.e. intonation, pith, loudness, etc) (Perkins 236). Patients suffering from Parkinson's disease, as already mentioned, tend to speak very monotonously and have a reduced loudness of voice as a result of bradykinesia of the laryngeal muscles.

However, it should be mentioned that although they may very well have limited pragmatic competences, there is an inherent "compensatory adaption" present both 'within the individual [or intrapersonal]- e.g., compensating for a syntactic or lexical processing problem by using referentially opaque pronouns instead of more fully specified noun phrases - and

between individuals [or interpersonal] - e.g., using simplified syntax, gesture, and visual cues when talking to someone with poor comprehension (Perkins 241).'

1.7.2 Pragmatic language deficit in Parkinson's disease

Most studies on pragmatic communication deficits after brain damage focus on patients with a Traumatic Brain Injury (TBI), aphasics or patients with right-hemisphere damage (RHD) and as such there is not much literature available which specializes on pragmatic abilities in Parkinson's disease (McNamara and Durso 415). However, McNamara and Durso (2003) hypothesized that individuals with PD might also endure discordant difficulties with pragmatic and social communication (McNamara and Durso 415). They note that 'even before the disorder affects motor systems involving gesture and speech intelligibility, some persons with PD appear to experience inordinate difficulty in social conversation, turn-taking, staying on topic and appropriately conveying emotion (McNamara and Durso 415).' Furthermore, apart from the aforementioned study, neuropsychologic observations suggest that the "neuro-cogntive system" which sustains the pragmatic communication abilities - right hemisphere and frontal lobes -, is impaired in Parkinson's disease (McNamara and Durso 415). Their study acknowledged their initial hypothesis and found that PD patients were indeed significantly impaired on certain features of pragmatic communication abilities, more specifically 'in the realms of conversational appropriateness, prosodics, and gestures and facial expression (McNamara and Durso 418).' However, as they correctly note, the gestural, facial and prosodic deficits are indisputably mainly a consequence of motor impairments, nevertheless, they contribute to the patient's ability to communicate emotion and interest and thus should be interpreted as pragmatic as well (McNamara and Durso 418). The "conversational appropriateness deficit" (e.g. pauses, conciseness, etc.) is thought to be a consequence of a brain dysfunction related to Parkinson's disease, a hypothesis which is

further strengthened by ‘correlations of pragmatic performance with measures of frontal lobe performance (McNamara and Durso 418).’ Yet, as the patients did not - significantly - deviate from the healthy controls on tests of cognitive skills, McNamara and Durso (2003) did not link the observed pragmatic deficit to a general cognitive impairment (McNamara and Durso 418).

As dysarthria is present in nearly all cases of idiopathic Parkinson’s disease, a prosodic impairment is most likely to occur (McNamara and Durso 421). Moreover, according to their spouses, patients were impaired in conversational appropriateness, turn-taking, quantity conciseness and stylistics and, additionally, in ‘using/responding to speech acts (queries, comments, commands, etc.)’ (McNamara and Durso 421). However, these deficits could lead to communication difficulties and thus restrict their daily activities and impacting upon their QoL (McNamara and Durso 421). Interestingly, spousal ratings evaluating the pragmatic proficiencies indicated that the pragmatic impairment was seen as more severe than compared to the examiner’s assessment of the patients (McNamara and Durso 421). Yet, while McNamara and Durso (2003) claim the spousal ratings are more dependable, one should bear in mind that the spouses may be subjective, whereas the examiners utilize objective tools to assess pragmatic deficiencies (McNamara and Durso 421). McNamara and Durso (2003) based their thought on the fact that spouses interact and observe the patient daily, whereas the examiners assess the patients ‘from a single 10-15 minute conversation in a setting of formal neuropsychological testing; thus, the spousal ratings suggest that the examiner ratings […] may underestimate the degree of pragmatic deficit in PD patients (McNamara and Durso 421).’

Moreover, other studies too have previously found evidence for the unawareness of pragmatic impairment, yet, awareness of a particular deficit is a obligatory requirement for any successful treatment, as McNamara and Durso (2003) note: ‘The insight-impaired patient will

not consistently attempt compensatory cognitive strategies for higher-order social and cognitive skills when he does not realize he is deficient in these skills (McNamara and Durso 421). Alderman et al. (1995) have observed, when studying TBI patients, that a simple increase in the patient's perception of his 'inappropriate and impulsive behaviors can significantly decrease those behaviors (McNamara and Durso 421). McNamara and Durso (2003) argue that similar observations could be made with patients with PD as the origin 'of this unawareness deficit in PD may be the well-known frontal lobe dysfunction associated with PD (McNamara and Durso 421).'

However, not only pragmatic language production is important in a conversation, but recognizing and interpreting the speech act is essential as well (McNamara and Holtgraves 9). More importantly, in a more recent study McNamara and Holtgraves (2010) noticed that PD patients were selectively impaired in the recognition of the specific speech act (McNamara and Holtgraves 9). More specifically, 'people with Parkinson's disease did not demonstrate normal, automatic activation of speech act verbs and this deficit could not be ascribed to a general slowing of processing language materials (McNamara and Holtgraves 9).' While previous studies linked this deficit to the "Stroop performance[14]" which involves executive cognitive functions that support this specific system of pragmatic proficiency; McNamara and Holtgraves (2010) elucidated that it is in fact a 'previously undocumented language disorder […] in PD and that this disorder involves a selective deficit in speech act comprehension (McNamara and Holtgraves 9).' Moreover, evidence suggests that the ability to successfully interpret speech acts and to do so involuntarily declines as the disease progresses; this correlation between performance and disease progression indicates a possible neurobiological system which maintains speech act comprehension (McNamara and Holtgraves 9). However,

[14] See appendix

most commonly it is only in Braak stage five and six that cognitive - and thus language - deficits manifest as McNamara and Holtgraves (2010) note:

> 'In PD, the Braak six-stage descriptive system of pathologic Lewy Body[15] progression suggests that early stage disease begins in the brainstem and then ascends up the neuroaxis over several years until the cortex is affected. The first two Braak stages are presymptomatic while stages three and four involve pathology in the basal ganglia and neostriatum with onset and progression of motor symptoms, and the last two (cortical) stages are associated with cognitive impairment […]. Our patients were Hoehn-Yahr[16] stages II and III which corresponds roughly to Braak stages four and five, presumably indicating pathology in dopaminergic frontostriatal circuitry (McNamara and Holtgraves 9).'

Thus, according to this study, the pragmatic comprehension deficit occurs only in the more severe stages of the disease (McNamara and Holtgraves 10). Moreover, the results indicate that the reason for "the automatic speech act recognition deficit" is due to a decline of executive functions (McNamara and Holtgraves 10). This as well as the accompanying neurobiological background 'suggest that [the] speech act comprehension depends crucially on frontostriatal circuitry' which is impaired in later stages of the disease (McNamara and Holtgraves 10). Furthermore, similar to the aforementioned study of McNamara and Durso (2003), McNamara and Holtgraves (2010) observed 'that PD [patients] did not have awareness of their diminished communicative capacities […], they were just as confident when they were wrong as when they were right' during the experiments (McNamara and Holtgraves 10). Unlike Soroker et al. (2005) who noticed greater deficit after left-sided

[15] See appendix

[16] See appendix

lesions[17] compared to right-sided lesions, McNamara and Holtgraves (2010) were unable to assess the 'contributions of right [versus] left sided prefrontal function to speech act comprehension (McNamara and Holtgraves 10).'

The pragmatic impairment is without doubt related to the quality of life (QoL) of PD patients and their QoL could be ameliorated if their pragmatic abilities are treated as efficiently as possible (McNamara and Durso 418). However, 'the first step in such a program of remediation would be to assess awareness of deficit in these patients; self-awareness or self-monitoring may be fundamental for appropriate social communication (McNamara and Durso 418-419).' Moreover, self-awareness of communication abilities - as McNamara and Durso (2003) note - is indispensable for upholding 'sensitivity to social context and more generally for maintaining independence in routine activities of daily living (McNamara and Durso 418-419).

1.8 Treatments

1.8.1 Medicinal therapies

While there are a number of treatments available, the most extensively used form of intervention is still levodopa, a medicinal therapy invented by George Cotzias in the 1960s (Ho et al. 574). 'As dopamine cannot transverse the blood-brain barrier, a dopamine-insertion will backfire as a treatment (De Letter 29).' Alternatively, the 'dopamine precursor levodopa' is used since it has the ability to pass through the blood-brain barrier (De Letter 29). Furthermore, it still remains 'the most effective symptomatic therapy [as] it alleviates the

[17] And more specifically ,lesions close to the classical language areas in the perisylvian cortex of the temporal and parietal lobes (McNamara and Holtgraves 10).'

bradykinesia and rigidity and to a lesser extent also the tremor that are characteristic of Parkinson's disease (De Letter et al. 188),' yet, it should be mentioned that 'long-term use of levodopa may lead to dystonia[18], dyskinesia and on-off effects (i.e. unpredictable motor symptom fluctuations) (De Letter et al. 188).'

Yet, even when meticulously studying one patient, one will observe a switch from 'a stable to a fluctuating pattern of symptoms if given enough time (McColl et al. 1231).' According to McColl et al. (2002), the patients who display the most favorable initial levodopa response, are most likely to later 'develop symptomatic motor fluctuations and dyskinesia (McColl et al. 1231).' The "nonfluctuating cases", however, have a poor initial response to the dopaminergic therapy but display a 'gradual increase in response amplitude' and as such as the disorder progresses, will still benefit from levodopa therapy (McColl et al. 1231). The response of a patient to levodopa is reliant on the interaction of 'pathological and neurochemical factors: numbers of surviving substantia nigra neurons (roughly correlated with *off* phase score), preservation of striatal dopamine receptors (determines capacity to respond) and other degenerative or vascular changes in the motor system and elsewhere (that tend to blunt the L-dopa response and contribute to L-dopa-resistant problems with gait and cognition (McColl et al. 1232).' Yet, the degree of loss of cells of the substantia nigra and other nuclei varies from patient to patient and as such cannot be accurately defined resulting in speculation (McColl et al. 1232). The remainder of the nigral cells is essential and indicative for the initial L-dopa response, yet, when the first clinical symptoms manifest, an estimated 60% of the cells are already lost (McColl et al. 1232). Furthermore, evidence suggests that 'once the number of remaining nigral cells falls below a certain level, the L-dopa response becomes too unstable, too degraded by dyskinesia for prolonged patient survival (McColl et al. 1232).'

[18] See appendix

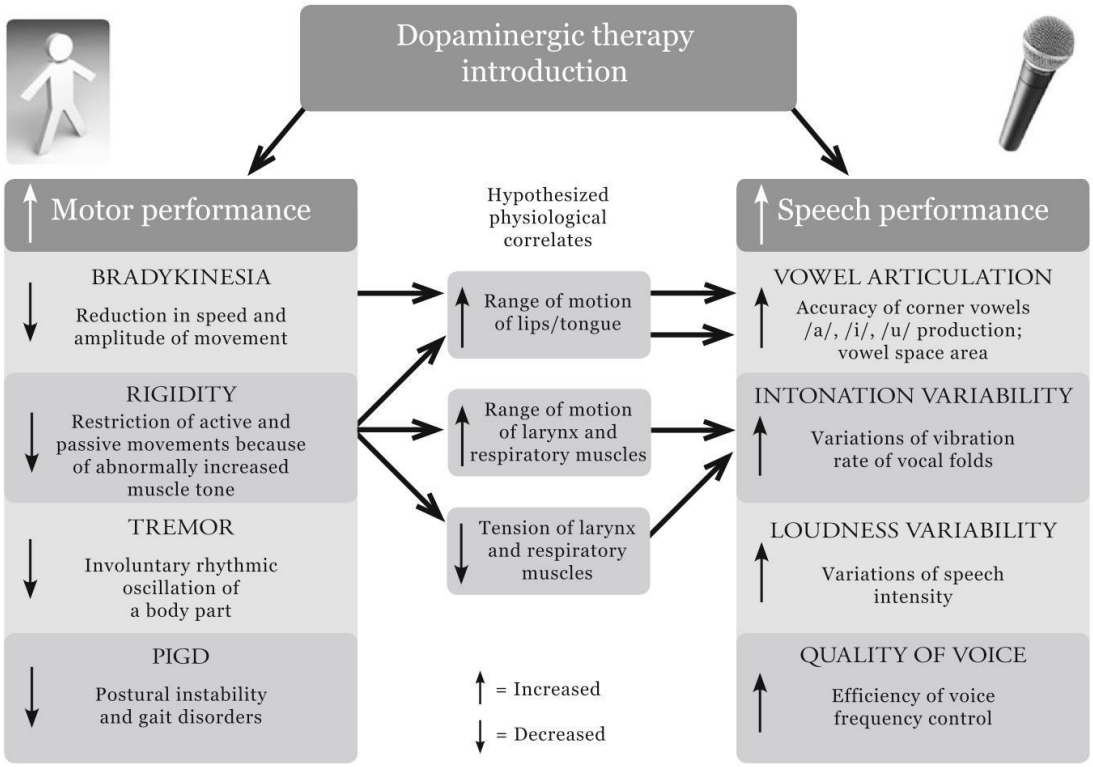

Figure 4: 'Diagram depicting speech changes after the introduction of treatment and relationships between speech and motor symptoms (Rusz et al. 326).'

More important, is the impact of L-dopa on speech (illustrated by figure 4). De Letter et al. (2005) note that the beneficent effect of levodopa on speech appears to fluctuate and as such some studies noticed improvements whereas others did not (De Letter et al. 188): 'While some studies reported positive effects on fundamental frequency (Sanabria et al., 2001) and on articulation, loudness, and persistence of phonation (Critchley, 1981; Wolfe, Garvin, Bacon, & Waldrop, 1975), others did not find significant changes on oral function (Gentil, Tournier, Pollack, & Benabid, 1999) or general speech performance (Poluha, Teulings, & Brookshire, 1998) (De Letter et al. 188).' Interestingly, one study even reported a 'worsening of speech with exacerbation of disfluencies' as a consequence of the levodopa therapy (De Letter et al. 188). Furthermore, De Letter et al. (2005) their results are in line with previous studies and noticed a significant increase in word intelligibility as a result of levodopa intake

(De Letter et al. 192). Yet, the influence of levodopa differs from patient to patient and some even scored higher intelligibility scores in the off-condition (De Letter et al. 192). Nakano et al. argued that some but not all PD patients have a 'subjective impression of speech improvement' and did not correct themselves 'when producing unintelligible speech fragments (De Letter et al. 192).' This can be linked to the hypothesis of a "defective auditory feedback system" in Parkinson's disease and was later acknowledged in De Letter et al.'s (2005) study where patients had difficulties monitoring and 'estimating their own articulatory speed (De Letter et al. 192).' This so-called defective auditory feedback system in Parkinson's disease could be associated with the neuro-chemical modification in the speech perception mechanism, which appears to be 'strongly lateralized to the left hemisphere, as demonstrated in a recent fMRI study (De Letter et al. 193).' Furthermore, it has not yet been adequately studied to what degree speech motor performance is linked to intelligibility in Parkinson's disease (De Letter et al. 193).[19] Moreover, studies indicate that 'measures of tongue strength and speech correlated such that the weaker the tongue, the greater the speech disorder (De Letter et al. 193).' The impact of levodopa on tongue strength and endurance was examined by De Letter et al. (2005) and elucidated a possible positive effect (De Letter et al. 193).

1.8.2 Deep Brain Stimulation (DBS)

1.8.2.1 General introduction to DBS

The second way to intervene in Parkinson's disease is deep brain stimulation (DBS) of - most commonly - the subthalamic nucleus (Bradberry et al. 607). Whereas levodopa therapy functioned as a 'direct-acting DA-agonist medication that stimulates DA receptors in the DA-

[19] See appendix regarding the link between speech and motor performance

depleted striatum', DBS is a 'reversible surgical intervention for advanced Parkinson's disease (Bradberry et al 607).' Figure 5 illustrates where the electrodes are implanted (A&B) while D depicts the influence-radius of the stimulation.

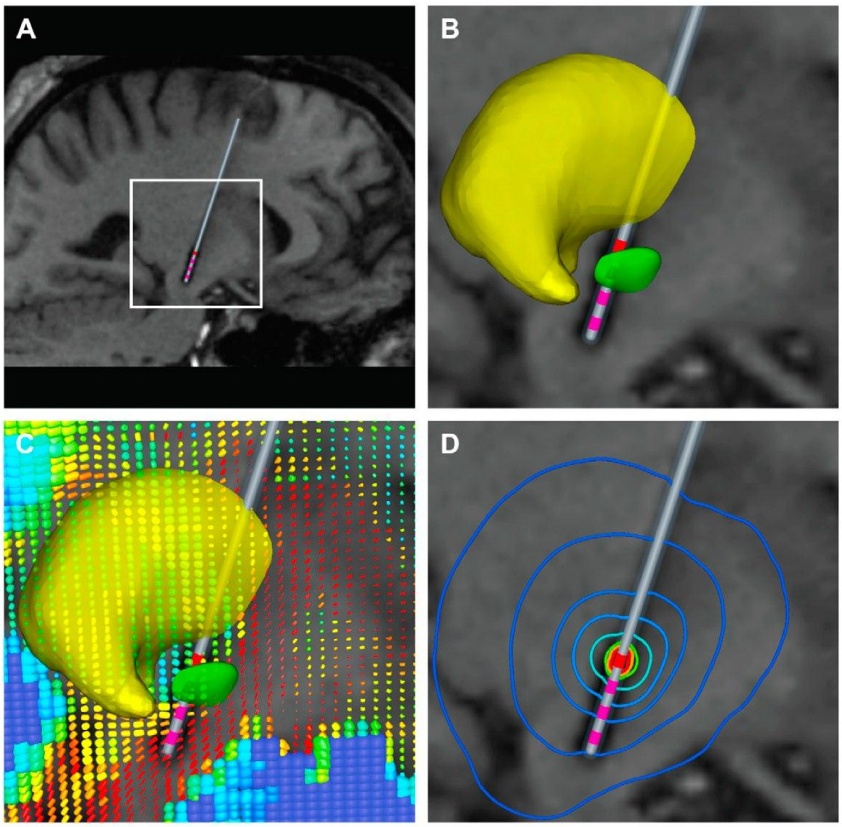

Figure 5: 'Patient-specific DBS model. (A) Sagittal view of the post-operative patient MRI with the patient-specific electrode location and trajectory determined by image-thresholding segmentation. Also shown is a white bounding box depicting the region of interest for panels B-F. (B) 3D nuclei placed within the same patient-specific modeling environment (thalamus – yellow volume; STN – green volume). (C) DTI tensors displayed as ellipsoids. The colors depict the individual fractional anisotropy values of the tensors (blue-0; red-1), while the shape describes both the magnitude and direction of water diffusion (spherical – isotropic; cylindrical – anisotropic). (D) Isolines depicting the potential distribution near the active contact 3 (blue – low voltage; red – high voltage) (Chaturvedi et al. 68).'

The choice for the subthalamic nucleus as the best potential target for deep brain stimulation is founded on the comprehension 'of the direct and indirect neural circuitry of the basal ganglia (figure 6) (Halpern et al. 444).'

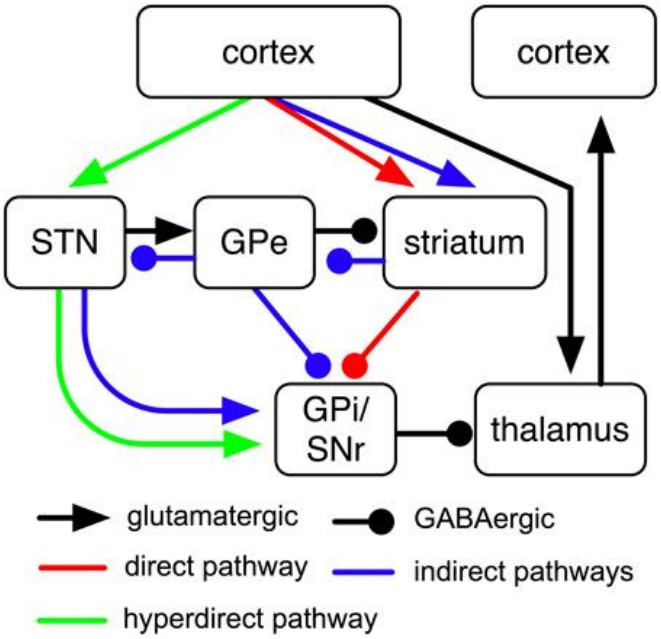

Figure 6: 'Sketch of cortico-BG-thalamic fiber tracts and their subdivision into direct, indirect and hyperdirect BG pathways. Of the "indirect pathway," two routes have been proposed), the short one of which passes from GPe directly to GPi, while the longer one additionally passes through STN (Schroll and Hamker 2).'

As illustrated in figure 6, there is a natural physiologic stability between 'indirect projections from the striatum to the globus pallidus internus (GPi) (via the external segment of globus pallidus and STN) and direct projections from the striatum to GPi (Halpern et al. 444). Final output from the BG is a modulated inhibition through GPi to the motor nuclei of the thalamus […] and then to motor and premotor cortex for execution of voluntary movement (Halpern et al. 444).' Under normal circumstances, the subthalamic nucleus' output to the GPi is excitatory, but in Parkinson's disease, however, the output is 'excessive secondary to upstream loss of inhibitory dopaminergic input' which results in an 'uncontrolled inhibitory output' from the globus pallidus internus to the thalamus (Halpern et al. 444; Mercado et al. 1458). Put differently, 'PD is a state characterized by hyperactivity of the glutaminergic excitatory action of the STN over the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) that propagate an excessive inhibitory influence in the thalamus, cortex and brainstem (Mercado et al. 1458).' Hence, the most obvious hypothesis is that deep brain

stimulation 'reduces or inactivates either the neurons of the STN or their excitatory glutaminergic projections (Mercado et al. 1458).'

Furthermore, the deep brain stimulation leads are implanted bilaterally in the subthalamic nucleus since high frequency stimulation (HFS) ameliorates 'predominantly contralateral motor functions (Novak et al. 12).' However, according to Novak et al. (2009), 'unilateral HFS of the STN provides bilateral clinical benefit although the ipsilateral[20] effect is much less prominent than its contralateral[21] counterpart (Novak et al. 12).' This means that the stimulation of the ipsilateral part influences not just the ipsilateral BG network but the contralateral side as well, including the contralateral STN (Novak et al. 12). Thus, as Bradberry et al. (2012) note 'the two different forms of treatment[22] act at different sites within the basal ganglia-thalamocortical circuitry that comprises the standard model of Parkinson's disease, but both show significant improvements in PD symptoms (Bradberry et al. 609).[23]

1.8.2.2 Impact of deep brain stimulation on motor impairments

However, the most important difference put forth in Bradberry et al.'s study (2012) is related to the motor consequence outcomes of both treatments (Bradberry et al. 614). As such deep brain stimulation of the STN increases -whereas DA agonist therapy decreases - activity in the ventrolateral thalamus and, more importantly, that this is associated with the unique impact of DBS STN on tremor and bradykinesia (Bradberry et al. 614). Bradberry et al. (2012) as well as several other studies reported that STN DBS remarkably ameliorated tremor more than

[20] Stimulating the most affected hemisphere

[21] Stimulating the least affected hemisphere

[22] Medicinal treatments and DBS

[23] See appendix for unique responses of DBS and what it has in common with medicinal therapies

dopamine therapy and that the significant increase in thalamic activity - as a consequence of STN DBS - was associated with an improvement of bradykinesia (Bradberry et al. 614).

Recent studies examining long-term influence of STN stimulation noticed a prolonged beneficial impact on motor deficits, nevertheless, the speech impairment and gait worsened as well as the cognitive deficiency and mood disturbances (Fraraccio et al. 400). Furthermore, DBS STN ameliorates bradykinesia as it inhibits or disrupts 'the abnormal and excessive neural outflow of the subthalamic nucleus (Fraraccio et al. 400).' However, STN stimulation might cause or worsen cognitive deficits as 'neural circuits [which originate] in the associative, prefrontal and limbic cortex also pass through the STN (Fraraccio et al. 400).'

1.8.2.3 Impact of deep brain stimulation on cognition

Yet, while the beneficial influence of DBS STN on motor impairments has been successfully replicated, not all studies examining the effect of STN stimulation on cognition observed a dissentious impact and as such there is no clear consensus (Fraraccio et al. 400). To illustrate this, 'two recent long-term follow-up studies demonstrated general as well as frontal cognitive decline 5 years after surgery'; however this could be related to the normal disease progression (Fraraccio et al. 400). Yet, two other researches noticed remarkable improvements in cognition as a result of DBS, however, at the moment of evaluation, the patients were not on medication which as a consequence resulted in 'severe bradykinesia, apathy, anxiety or fatigue' when in *OFF*-stimulation condition and may have influenced patients' performance (Fraraccio et al. 400). Moreover, other studies elucidated that when patients maintain their regular doses of dopaminergic medication, deep brain stimulation of the subthalamic nucleus induces almost no alteration in cognitive functioning, however, these observations were again contrasted by another study which argued that 'STN stimulation improved non-declarative

memory while simultaneously causing impairment in declarative memory (Fraraccio et al. 406).' Based on their results, they hypothesized that an 'improvement in one domain may be accompanied by impairment in another,' however, this has not been acknowledged so far (Fraraccio et al. 406). While it may not yet be fully elucidated whether or not STN stimulation indeed has an impact on a patient's cognition, nevertheless, one should keep in mind that as the disease progresses, a cognitive impairment is more likely to occur (Mercado et al. 1459).

Moreover, Mercado et al. (2006) interestingly distinguished that DBS STN in Parkinson's disease is related to a placebo effect, more specifically that 'the clinical benefit given by the information about the condition of the stimulation enhanced the final clinical effect in opposite directions (Mercado et al. 1459).' In short, they observed that the 'clinical benefit was heightened when the patients were advised that the stimulation was ON, whereas clinical worsening was further potentiated when the patients were advised that the stimulation was OFF, a response modulated by a nocebo effect[24] (Mercado et al. 1459).'

1.8.2.4 Impact of deep brain stimulation on speech and language

However, more important is the fact that STN stimulation has a remarkably beneficial effect on all cardinal symptoms of Parkinson's disease which contributes to a reduced amount of time in the *OFF*-state (Santens et al. 253). Moreover, as Santens et al. (2003) note, 'STN stimulation allows reduction of the levodopa dosage, which decreases the occurrence of dyskinesia (Santens et al. 253).' Yet, just like dopaminergic therapy incites adverse side

[24] See appendix

effects, STN stimulation has unwanted repercussion too, for example 'transient confusion, apraxia of eyelid opening, apathy and equipment-related problems (Santens et al. 253) .' Whereas some studies observed an improvement of speech after bilateral stimulation, others have noticed an increase of dysarthria and proposed that it is an underrated problem (Santens et al. 253). Most studies examining the 'stimulation-induced speech alterations' have focused on the bilateral *ON* vs *OFF* condition, while laterality effect studies on patients' speech has been studied but a few times (Santens et al. 253). Santens et al. (2003) elucidated that speech is differently influenced by left and right STN stimulation conditions; more specifically 'it seems that right STN stimulation has little effect compared to bilateral stimulation off, irrespective of the status of the left-sided stimulation (Santens et al. 256).' 'However left-sided stimulation negatively influences speech when right-sided stimulator is off (Santens et al. 256).' A possible reason for this negative impact of left STN stimulation is that it may generate an imbalance; however, it seems that bilateral stimulation evens out this disparity and mends the intelligibility (Santens et al. 256). Santens et al. (2003) conclude in their study that 'some aspects of speech are highly dependent on a balanced tuning of bilateral basal ganglia circuits, of which the STN is a crucial part (Santens et al. 257).' Furthermore, there is no clear cause for the negative impact of left side STN on speech, especially when comparing it to motor improvements in the limbs (Santens et al. 257). A more recent study conducted by Wang et al. (2006) too revealed a negative impact of left subthalamic nucleus stimulation, especially on articulatory accuracy and syllable rate (Whitehill 110). However, while there is no general consensus about the impact of unilateral STN DBS, Wang et al. (2006) argued that there were distinct 'hemisphere-specific effects on speech' and that this was 'presumably related to language dominance also being located in the left hemisphere (Whitehill 110).'

Deep brain stimulation of the subthalamic nucleus does not only affect motor and speech of a patient, some authors have found a neuropsychological impact on cognition and language

(Bordini et al. 118). A number of studies observed a category fluency and word fluency decline after bilateral stimulation, tasks which 'represent a specialized lexical/semantic store search and retrieval task, dependent upon attention, vigilance, and working memory (Bordini et al. 118).' As such Bordini et al. (2007) conclude that bilateral stimulation has a profound negative influence on particular language functions (Bordini et al. 118). As the word fluency impairment has also been observed after pallidotomy[25] and GPi-stimulation, the deterioration of language has been hypothesized to be an 'adverse effect of the bilateral frontal lobe trajectory used to access the basal ganglia or an effect of stimulation on the physiological pathways in basal ganglia circuitry (Bordini et al. 118).' However, contrary to Bordini et al.'s (2007) observations, another study noticed a gradual linguistic improvement over 12 months of bilateral STN stimulation, yet, 'factors such as a small sample size (n = 2) and high degree of inter-subject variability could have affected the findings and thus limit the generalizability of such findings (Bordini et al. 118).' As a concluding remark, they correctly note that it is conceivable that there are still unknown effects which 'underlie the etiology of cognitive sequelae in DBS of the STN, and that factors such as patient age, preoperative neuropsychological function, surgical trauma, electrode placement within subdivisions of STN, and natural history of PD interact in a complicated manner to influence the outcome (Bordini et al. 119).'

Apart from its impact upon speech and cognitive functions, it has been acknowledged that STN stimulation influences language processing in one way or another. However, the impact of DBS STN on language, and more specifically on lexical and grammatical functions, in Parkinson's disease has only been studied by a few scholars and as such the full extent has yet to be discovered (Philips et al. 2). As already briefly mentioned above, 'the results of STN

[25] See appendix

stimulation are variable and as such lexical knowledge and retrieval tests have shown inconsistent patterns after stimulation occurred, resulting in improvements, degeneration and even no alteration after a treatment' (Van Lier 13). One of the studies attempting to elucidate the impact of STN DBS on grammar, was conducted by Zanini et al. (2008) and found a gradual grammar improvement as well as a reduction in grammatical errors following STN DBS (Zanini et al. 608). Interestingly, they observed no amelioration of 'speech complexity (number of utterances) and speech fluency (speech blocks), nor phonology (phonological paraphasias) or lexical semantics (lexical access[26] and verbal/ semantic paraphasias) (Zanini et al. 608).' However, regarding the grammar improvement, these results cannot be generalized as a consequence of the small sample size (n = 5) (Zanini et al. 609). Furthermore, they tried to explain their results 'in terms of PD pathophysiology and restoration of basal ganglia functional equilibrium following DBS (Zanini et al. 609).' As Zanini et al. (2008) note that while 'language improvement should not be a surprise as [the] basal ganglia are known to be involved in grammar processing, [stating, however,] that the PD-related basal ganglia functional disequilibrium is corrected by the DBS of subcortical nuclei - be it STN or PPN[27] - with a consequent correction of the disequilibrium of basal ganglia-frontal cortex pathways, and therefore, of language processes mechanisms, does not explain the pathophysiology of these phenomena' and hence why an improvement is observed (Zanini et al. 609).'

[26] See Appendix

[27] Stands for pedunculopontine nucleus

1.9 Pilot study

A preliminary study evaluating the pragmatic language abilities of one patient was conducted prior to this dissertation. Similar to this paper, the pilot study assessed the spontaneous language production using the *Nijmeegse Pragmatiektest,* a test designed by Embrechts et al. which is the only Dutch test available to evaluate pragmatic language. The patient was a woman who had been diagnosed with PD over 15 years ago and who has been receiving deep brain stimulation for 87 months (Van Lier 17). She had a left motor lateralization which means that there was a reduced dopaminergic activation in the right hemisphere (Van Lier 17). Her cognition was not severely impaired by the disease as she had a decent score on the moca-test (Van Lier 17). The data was analyzed without any pre-knowledge of which condition corresponded with the specific situations to prevent a biased analysis (Van Lier 17). The results indicated that some parameters of the test were more important than others as the four different stimulation conditions had a more significant impact on them (Van Lier 33). Remarkably, the right-sided hemisphere stimulation condition commonly had a negative effect upon the patient's pragmatic language abilities and as such it appeared that - at least for the patient evaluated in the pilot- right hemisphere stimulation worsens the communicative abilities (Van Lier 33). Furthermore, when the right hemisphere was stimulated, an increase in the number of repetitions was observed as well as an increase in turn-taking. Yet, this proliferation is accompanied by a decreased coherence in the patient's utterances which indicated that right hemisphere stimulation had a negative impact on the patient's linguistic pragmatic abilities (Van Lier 33).

However, the outcomes of the tests and the hypotheses formulated based on these results could not be generalized as the preliminary study only examined the data of one patient. Since language is an important factor for creating an enjoyable quality of life for the patients,

further research is required to elucidate the full impact of DBS STN on the pragmatic language abilities of patients suffering from Parkinson's disease. To conclude, this dissertation will study whether right hemisphere stimulation always has a negative impact on the linguistic pragmatic abilities or if it is linked to the motor lateralization of the patient and the asymmetric dopaminergic activation in the brain.

Chapter 2
Methodology and results

2.1 Methodology

Similar to the pilot study, this dissertation did not gather new data from patients suffering from Parkinson's disease to avoid the tenuous process of receiving the ethics committee of the Ghent University Hospital's approval. Instead, the analyses were again made based on data which was clinically recorded in the UZ Ghent to see how the patients reacted on the STN stimulation. Furthermore, the methodology of this dissertation coincides with the preliminary study's methodology. The data was examined using the Embrechts et al.'s *Nijmeegse Pragmatiektest*, which is the only Dutch test available to evaluate pragmatic language, however, this test was not designed for this target group and as a consequence this could causes some methodological issues which will be discussed more in depth later.

2.1.1 Patients and methods

As already mentioned above, this paper analyses the data of 18 patients which were already recorded for clinical evaluation. All patients suffered from levodopa-responsive PD (De Letter 120). The patients were thoroughly assessed before the operation which included 'neurological assessment in ON and OFF-stages with video-taping, neuropsychological testing, psychiatric evaluation, cerebral MRI and flow-SPECT, neuro-ophthalmological[28] and neurolinguistic testing' (De Letter 120). The examination revealed that none of the patients had any other unstable medical diseases other than Parkinson's disease (De Letter 120). 'Cognitive dysfunction exceeding the well-known deficits of PD and major psychiatric problems were absent in all' (De Letter 120). No anti-parkinson medication was given to the patients at least 24 hours before the surgery to assure a stabilized off-situation resembling the 'worst-off' as possible (De Letter 121). Furthermore, each time a new stimulation condition

[28] See appendix

was programmed, the investigators partook in 10 minutes of free conversation 'to allow adaptation to the new condition (De Letter 122),' as such, there was no influence of the prior stimulation settings. The speech samples were recorded in a quiet room with without any background noise, and most of the sample files were afterwards transcribed by 'two speech-language pathologists with experience in neurogenic speech and language disorders (De Letter 122). I transcribed the remaining audio files (six patients). With regards to the impact of DBS STN on the pragmatic language, patients' were asked to answer spontaneously on standardized questions (as put forth by the Spontaneous Speech Evaluation of the Aachen Aphasia Test.) (De Letter 122).

The data samples were analyzed blindly to prevent a biased examination. Afterwards, Dr. De Letter conferred the patients' characteristics and the stimulation parameters, as well as which condition corresponded with which situation. See section 5.2.4 for the individual patient characteristics and stimulation parameters.

2.1.2 Language evaluation

Similar to the preliminary study, the data was examined using the *Nijmeegse Pragmatiektest* designed by Embrechts et al. as this is the only available Dutch test to study pragmatic language. The test is based on Roth and Spekman's model of pragmatic competences (1984) (Belling et. al 56). The *Nijmeegse Pragmatiektest* consists of three categories: Communicative Functions (CF), Conversational Skills (CS) and Story-telling Skills (SS). The test's original target group are children ranging from 4 to 7 years whom attend the regular primary school (Belling et al. 56). However, while we are aware of this limitation that we cannot use the norms, this does not pose a problem was we compare the patients with themselves throughout the four different stimulation conditions The purpose of this test is to evaluate the production of pragmatic language and to locate and diagnose when problems arise (Belling et al. 56).

However, the test is not a means on its own and serves as a complementary tool to be used for further treatment (Belling et al. 56)

2.1.3 Communicative Functions (CF)

Similar to the other parts of the test, this section consists of a checklist which allows the examiners to see which parameters the patient uses. As the name suggests, this part focuses on communicative functions and skills such as asking a question, whether the patient describes his emotions, gives new information, etc. Furthermore, akin to the pilot study, not everything on the checklist is of use for this paper or is shown in the data, for example 'negotiating' is not present in the language samples of any of the patients.

Furthermore, when analyzing, difficulties arose whether certain utterances were indicative of communicative functions (as described in the *Nijmeegse Pragmatiektest*). As such, decisions were made as to include them or not. For example, in situation A of patient 18, the utterance '*dat vond ik prima hé toch'* was seen as a question, absent the question mark in the transcription. However, because of the large amount of data processed, it is impossible to present a full list of utterances which deviated from standard language use and were or were not interpreted as belonging to a specific parameter.

2.1.4 Conversational Skills (CS)

The second section evaluates the conversational abilities such as repeating something when the interlocutor does not fully understand an utterance or whether or not. Unlike the first part, this one concentrates on the conversation as an action by focusing on the turn-taking during a discourse and how they maintain and end a turn. Most of the patients used words such as '*euh,*','*ja', 'nou',* etc. which were not seen as a repetitions and thus were not counted.

Furthermore, similar to the previous section, some parameters were not utilized by the patients, e.g. 'opening [or closing] a conversation'.

2.1.5 Story-telling Skills (SS)

The last section focuses on the content of what is being said by the patient, for example if it is clear when or where the event takes place[29], if the interlocutor can distinguish the main idea or whether the patient uses discourse connectives such as 'and' or 'but'. In some instances, several patients' use of the orientational parameters was not counted as they were too vague (e.g. '*vroeger*').

2.1.6 Methodological issues

Since deep brain stimulation of the subthalamic nucleus and its influence on language - and more specific pragmatic language - has not been thoroughly studied yet, finding usable literature was a challenge. The interaction of the interviewer was left out in some transcriptions; however, the recorded files are available University Hospital of Ghent and can be consulted (after approval). Some parameters of the test itself were not sensitive enough which resulted in less interesting outcomes. Furthermore, the only Dutch standardized pragmatic test was optimized for children. A more indepth approach to the methodological issues will be given in the 'Discussion' section.

[29] In the discussion, these parameters will be referred to as the "orientational parameters", namely orientation of person, place and time

2.2 Results

This section will present the statistical results of each individual section of the *Nijmeegse Pragmatiektest* and whether or not there were any significant outcomes. As mentioned in the previous section, the results presented in the tables were obtained by through a Friedman non-parametric test in the latest version of SPSS statistics (22.0). The tables are presented in section 5.2.2.

2.2.1.1 Communicative functions (CF)

The statistic analysis of the first section of the test of the entire sample size did not yield any significant result.

2.2.1.2 Conversational Skills (CS)

As presented in table 2, the second part does not yield significant outcomes when comparing the entire sample size (n = 18).

2.2.1.3 Story-telling Skills (SS)

Table 3 illustrates the statistical outcome of the analyses after applying a Friedman non-parametric statistical test. When analyzing the general sample size, i.e. not making a distinction between the motor lateralization of the different patients, there are no significant parameters according to the statistics. However, there are 2 parameters which yield a somewhat better score; whether or not these are influenced by the different stimulation conditions or due to a methodological flaw will be discussed in the next section.

2.2.1.4 Communicative functions (CF) of motor lateralization subgroups

As mentioned above, the sample group has been divided into 2 different subcategories; table 4 presents the results after applying another Friedman non-parametric test on the analyses of the patients with a right side motor lateralization. Compared to table 1, there are some remarkable differences and even a parameter which scores lower than the significance level of 0,05. More specifically, parameter "giving an explanation (K)" scored lower (0,023) than the proposed significance level and both "request of a certain action (H)" and "talking about other people's activities (I)" scored remarkably better (respectively 0,112 and 0,092) than in the previous table. In the following table, a closer look is presented of parameter K: "giving an explanation."

The outcomes which are presented table 5 are the result of a Wilcoxon non-parametric test and offer a closer examination of the aforementioned parameter compared throughout the different stimulation conditions. Again, there are two instances in which there a significant values, more specifically when comparing the scores of left ON versus bilateral ON (0,005) and left ON versus bilateral OFF (0,014). While left ON versus right ON has a low score, it does not, however, transgress the significance level of 0,05. Furthermore, right ON versus bilateral ON/OFF does not yield any strikingly low results, nor does bilateral OFF vs ON.

Similar to table 5, table 6 presents the results after applying a Friedman test on the second subgroup, more precisely on the patients with a left side motor lateralization. Akin to the results of the patients with a right motor lateralization, the same parameter "giving an explanation (K)" scored lower (0,014) than the significance level (p = 0,05). Furthermore, some parameters, such as "describing emotions (C)" and "talking about other people's activities (I)" yielded notably lower results, yet were not significantly important enough.

Analogous to when examining the first subgroup of lateralized patients, table 7 allows a closer examination of the parameter throughout the different stimulation conditions.

Identical to the results presented in table 5, table 7 illustrates the outcome of a Wilcoxon test of the same statistically important parameter K. Interestingly, similar to the results of the first Wilcoxon test, left ON versus bilateral ON and left ON versus bilateral OFF again yield scores lower (respectively 0,020 and 0,034) than the significance level of p=0,05. Furthermore, left ON versus right ON scores remarkably low, yet not low enough to be statistically significant. Right ON versus bilateral ON/OFF and bilateral OFF versus bilateral ON did not reveal anything statistically remarkable.

2.2.1.5 Conversational Skills (CS) of motor lateralization subgroups

Table 8 and 9 present the results of the Friedman test performed on the analyses of the two subcategories of patients, respectively those with a right motor lateralization (n = 10) and those with a left motor lateralization (n = 8). However, there were no parameters which were significantly important.

2.2.1.6 Story-telling Skills (SS) of motor lateralization subgroups

Table 10 and 11 illustrate the outcomes of the Friedman non-parametric test of both subgroups, respectively patients with a discernible right motor lateralization (n = 10) and patients with a left motor lateralization (n = 8). Furthermore, apart from one parameter, "the number of discourse connectives (J)", there are no remarkable differences between the subdivisions of patients as the other parameters are more or less the same regardless of the lateralization

Chapter 3
Discussion

Similar to the pilot study, only a small part of the *Nijmeegse Pragmatiektest* was applicable for people suffering from Parkinson's disease. This part of the dissertation will discuss the results presented in the previous section and relate them to the literature mentioned in the literature review section. Each part of the test will be individually addressed and extra attention will be given to the statistically significant parameters. Furthermore, the methodological issues and shortcomings which occurred during the analyses will be discussed with regards to the necessity of a proper test to assess the pragmatic language production not only of patients suffering from Parkinson's disease but neurodegenerative or lesion patients in general.

3.1 Communicative functions

3.1.1 Parameter: Emotional language use

As put forth in the results section, there were no significant outcomes when the entire sample size was examined as one group, yet, there were some parameters which scored remarkably lower compared to others. Interestingly, while the pilot study noticed an increase in emotional language when both hemisphere were stimulated (especially compared to the bilateral OFF-stimulation) (Van Lier 20), no significant levels were found after a statistical analysis. However, there are some patients whose emotional language use notably varies throughout the four stimulation conditions. Unfortunately, as the examples below will illustrate, there is no consistency amongst the patients and the stimulation conditions which - as well as the absence of statistically significant results - imposes us to properly propose a valid reason. While patient 3 produces a 'normal' amount of emotional language during left ON and bilateral OFF, as soon as the right hemisphere is stimulated his use of emotional language

declines to either a point where he either produces no emotional language (right ON) or very little (bilateral ON). However, while the aforementioned patient both saw an increase while under left hemisphere stimulation, the opposite is observed in patient 4 who produced more emotionally loaded utterances when the right hemisphere was being stimulated. Furthermore, this seems to be the case for patient 14 as well as his use of emotional language increases when being unilaterally stimulated (right ON). However, not only are there examples where unilateral stimulation (i.e. either left OR right ON) has a negative impact on the patient's emotional language use, patient 12 displays a negative influence of bilateral stimulation whereas the remaining stimulation conditions have a comparable effect. Lastly, another patient 17 reveals no difference between either left ON, right ON or bilateral ON but the aforementioned stimulation conditions notably improve his emotional language use when compared to bilateral OFF. Our data can be related to some hypotheses which claim that 'the right hemisphere is dominant over the left hemisphere for all forms of emotional expression and perception (Achuff, n. pag.)' and as such unilateral right hemisphere stimulation should theoretically - according to this theory - result in more linguistically noticeable emotional language. The analyses of the data aid this hypothesis as 10 out of the 18 patients produced more emotional language under right hemisphere stimulation (versus three which produced more under left hemisphere stimulation and five which did not yield any differences).

Furthermore, when comparing the statistical analysis of the subgroups, i.e. left motor lateralization versus right motor lateralization, there is a prominent difference in the scores of the parameters i.e. a score of 0,178 for the left motor lateralization subgroup versus 0,818 for the patients with a right motor lateralization. However, there is no trend observable that could explain the difference between the stimulation conditions and the emotional language use of

the patients. Thus, based on our results, it appears that no clear connection between the stimulation conditions and the motor lateralization.

3.1.2 Parameter: Giving a suggestion

In the pilot study, this parameter was not seen as important as it did not yield anything interesting which could be discussed. The statistical analysis, however, of the sample data revealed a notable difference between either the left motor lateralization subgroup and the patients with a right motor lateralization (0,194 versus 0,801 respectively). The original description of the parameter as found in the *Nijmeegse Pragmatiektest* reads '*aandragen van ideeën waardoor een oplossing gevonden wordt* (Embrechts et al., n. pag.)' and was changed to suit the clinical examination of the patients and the data itself. For this study, the parameter was altered to a broader meaning of 'giving a suggestion' which could lead to a solution or a new topic in the conversation with the examiner. However, while there is a remarkable difference in the statistical outcomes between the subgroups, examples in the data do not occur frequently, more specifically, there are only four patients of which an example of this parameter can be found. Moreover, the statistical difference between the subgroups can merely be a consequence of the fact that the patient who displayed the most instances of this parameter - namely 6 versus the observed maximum of 1 in other patients' data - belonged to the left motor lateralization subgroup. Nevertheless, the parameter covers an essential part of pragmatic language, namely the ability to solve problems which occur during a conversation, giving advice to the person you are talking to and could even aid with topic management. As such, it could be due to methodological issues[30], i.e. there were no standard questions, nor

[30] A more in depth analysis of the methodological issues will be given in the last part of this section

questions which involved problem solving. Hence, a set of questions which encompasses problem solving, decision making, etc. and other (communicative) functions monitored in the frontal lobe could elucidate a possible dysfunction of the patient's communicative abilities. Moreover, Bernicot and Dardier (2001) observed communication deficits in patients with frontal lobe damage (Bernicot and Dardier 246), which would indeed strengthen our claim for the need of a fixed set of questions which entail, amongst other things, problem solving. However, as Bernicot and Dardier (2001) note that 'the [communicative] difficulties […] are not necessarily rooted in linguistic dysfunction, but may stem from general problems in extracting and inferring information from the context.' Yet, while the frontal lobe may not be directly responsible for language processes, it still remains crucial for our communicative abilities as it 'requires the implementation of specific cognitive capacities and executive functions ensured by the frontal lobe (Bernicot and Dardier 249).' As indicated in the literature review, language and cognitive processes are inherently related to each other, hence, utilizing parameters such as these which encompass both, could require specific communicative strategies[31] to elucidate a possible influence of STN DBS.

3.1.3 Parameter: Talking about other people's activities

Before moving on to the parameter which yielded statistically significant results, a last "second grade parameter" will be looked at more in depth, namely "talking about other people's activities. In the pilot study conducted last year, unilateral stimulation appeared to influence the number of times the patient referred to other people, more specifically left ON-stimulation produced the most results while 'bilateral ON and OFF stimulation conditions

[31] Bernicot and Dardier (2001) propose three types of strategy, namely structured, unstructured and alternating. For a full description of these strategies, the reader is referred to Bernicot and Dardier's article.

yielded remarkably less results (Van Lier 25).' As the pilot study only examined the data of one patient, we were unable to postulate a hypothesis regarding these results (Van Lier 25). As already mentioned, the sample data (n = 18) did not present a significant result, nor did the statistical analysis of both the left motor lateralization and right motor lateralization subgroups (respectively 0,156 versus 0,092). Comparing the analyses of the entire sample size, during unilateral hemisphere stimulation, some of the patients refer to other people's activities the most (12 out of the 18 patients, see table 12 below), more specifically - similar to the observation made in the pilot study - left hemisphere stimulation yielded the most results in the majority of cases (namely 58% versus 33%) where unilateral stimulation scored higher than bilateral stimulation. Furthermore, while in the pilot study the patient referred most often to her husband or family, this is not found to be the case in the analyses of these data samples. As such, the data does not support the observation made in the previous research where STN-stimulation affected the patient's referrals to people closest to him/her.

3.1.4 Parameter: Giving an explanation

In the preliminary study, this parameter did not yield discussable results as there were no remarkable differences throughout the four stimulation conditions. While the statistical analysis of the entire sample size was not significant (0,076), the analyses of the subgroups, however, both presented results below the significance level of p = 0,05. More specifically, the right motor lateralization subgroup scored 0,023 and the left motor lateralization subgroup 0,014; both remarkable outcomes as the parameter was previously found to not be affected by STN DBS[32]. As Embrechts et al. describe the criterion as '*de gevolgen van iets duidelijk*

[32] Based on the data of the case-study

maken (Embrechts et al. n. pag.)', it is evident that it is in fact a cornerstone of pragmatic language as it allows speakers to explain what happened next in a chain of events or to validate why they made a certain decision. Furthermore, as the ability of produce and comprehend pragmatic language is inherently linked to cognitive functions, various pragmatic functions have been linked to the same areas of the brain such as 'prefrontal cortex (cognitive control, memory for source information), orbito-frontal cortex (emotional and social control), right frontal lobe (awareness of others' - and one's own - mental states and retrieval of episodic memory); left frontal lobe (memory encoding), and ventromedial frontal lobe (social reasoning and empathy) (Perkins 230).' Based on this, the parameter could be argued to most likely involve the prefrontal cortex as it is responsible for cognitive control, the orbito-frontal cortex, the right frontal lobe and the ventromedial frontal lobe. Yet 'there is more to pragmatics than just cognition, [...] we are not going to be successful unless we also have the necessary ability to produce and understand language across its full range of complexity and sublety (Perkins 233-234).'

Furthermore, Mitchell and Crow (2005) highlighted 'the importance of full access to right hemisphere language functions to ensure successful social communication', in other words, according to them, pragmatic language functions are inherently linked to the right hemisphere and any damage or dysfunction would automatically result in pragmatic deficiencies (Champagne-Lavau et al. 67). However, Champagne-Lavau (2007) notes that the right hemisphere (RH) 'cannot be viewed as nesting "pragmatics" per se; many different cognitive processes are required for such a complex social behavior, some of them possible depending upon RH-based neural networks (Champagne-Lavau et al. 67).' Yet, evidence which supports a central role for the right hemisphere in pragmatic functioning remains inconclusive and is subverted to debates (Champagne-Lavau et al. 67).

However, neuropsychologic observations of PD patients suggest that the neural substrates which sustain the cognitive system and more particularly the pragmatic communication abilities were disrupted in the right hemisphere and frontal lobes and as such contributed to the pragmatic deficiency commonly observed in Parkinson's disease (McNamara and Durso 415). This lends support for Mitchell and Crows (2005) study of right hemisphere dominance in pragmatic language. Interestingly, when most patients of the left motor lateralization subgroup are stimulated on their most affected hemisphere, i.e. right ON, this generally results in patients no longer giving an explanation for something. Based on the results, it appears that when the right hemisphere is affected most by Parkinson's disease, patients tend to perform worse throughout the four different stimulation conditions. Yet, there are some instances, albeit sparse, in which the left hemisphere seems to compensate which manifests in improved results when the left stimulator is active. This pragmatic deficit strengthens Mitchell and Crow's hypothesis that argues for right hemisphere dominance in pragmatic language abilities. It appears that - in this sample size - unilateral subthalamic nucleus stimulation of the right hemisphere does not appear to restore the disequilibrium in the brain when the right hemisphere is most affected by the loss of dopaminergic cells. This is illustrated by the negligible difference between right ON and bilateral OFF, i.e. no stimulation. Thus, based on the data presented here, DBS STN does not seem to ameliorate - nor worsen - the pragmatic impairment of this subgroup of patients. Perhaps it could be related to the individual patient characteristics as pragmatic functioning relies on a set of cognitive functions as well (e.g. attention, memory or his/her executive functioning). As the prefrontal cortex and right frontal lobe might be affected, this could – based on Perkins (2013) – influence the patient's pragmatic proficiency. Pragmatic language production is of a higher order compared to other language processes and whilst the right hemisphere might be dominant, it is possible that the left hemisphere is involved as well.

Moving on to the second subgroup, namely patients with a right motor lateralization, we immediately notice that they score better on the parameter and as such that their pragmatic skills could either be less affected by Parkinson's disease or restored by the subthalamic nucleus stimulation. The statistical analysis yielded significant results when comparing the left ON stimulation condition and the bilateral ON and OFF conditions and after a more in depth assessment it seems that during the bilateral ON condition, various patients of the subgroup performed better and gave more explanations than when they weren't being stimulated (bilateral OFF). This contributes to the hypothesis that, while the observations made of the first subgroup could (partially) be attributed to the (pragmatic) dominance of the right hemisphere and the neuronal degeneration of regions in the right hemisphere, the left hemisphere does partake in pragmatic functions too. More specifically, as (some) patients perform better during bilateral ON versus OFF, the active state of the left stimulator could balance and restore certain disruptions in the left hemisphere as the difference in results might not be fully attributable to the dominance of the right hemisphere. Yet, there is the possibility - however remote or less likely - that, when the right hemisphere stimulator is active, certain pragmatic functions are further strengthened, however, this is not observed when evaluating the results of the right motor lateralization subgroup.

In short, based on the data of this study, patients with a left motor lateralization are more impaired and perform worse on this parameter most likely due to the neuronal degeneration of the pragmatically dominant hemisphere. Nevertheless, the left hemisphere is thought to participate in these kinds of processes as well based on the results of the bilateral ON stimulation condition of patients with a right motor lateralization.This could mean that the pragmatically dominant right hemisphere needs or is supported by the left hemisphere, yet, further research on this topic is still needed.

3.2 Conversational skills

3.2.1 Parameter: Reiterations

In the preliminary study, the bilateral ON-stimulation appeared to have the most notable negative impact on the number of reiterations, followed by right hemisphere stimulation (Van Lier 26). However, when no stimulation occurs, the patient produced fewer flaws (Van Lier 26). This led to the idea that while deep brain stimulation might have a beneficial influece on language production, it has a negative impact as well, albeit of a lesser extent and importance (Van Lier 26). As the higher number of repetitions occurs both in bilateral on and right on (left off), this could mean that whenever the right stimulator is active, it negatively influences certain language abilities, however, as only one patient was analyzed, this could not be be generalized to the entire population. Furthermore, the examination of the pilot's study's data revealed that the majority of reiterations were function words and that the content words appeared to be far less subsequent to flaws.

The statistical analysis of the entire sample size did not display a significantly important result, nor did the evaluation of the subgroups; however, as it was an important parameter in the previous study, a more in depth qualitative approach will assess the data and compare them with the aforementioned observations. In the data, unilateral stimulation generally appears to affect the number of repetitions produced in a negative way (i.e. a higher number), more specifically in 12 out of the 18 patients, either unilateral left (7) or right (5) stimulation notably influenced the number of reiterations.The results of the data do not seem to correspond with the initial observation were right hemisphere stimulation had a negative impact on the parameter.

However, the motor lateralization which occurs in Parkinson's disease where one hemisphere's dopaminergic activity is remarkably lower should be taken into account. It is possible that there is a relation between the observed impact of unilateral stimulation and the motor lateralization which manifests in the patients, yet, this was not reflected in our data as only 50% indicated a concordance between their worst performance and contralateral stimulation.

Interestingly, there are cases where unilateral, e.g. right or left, stimulation and bilateral ON stimulation negatively impact the patient's number of repetitions, but where respectively - in these examples - left or right stimulation notably decreased the extent of reiterations. And, more importantly, this difference between unilateral stimulation conditions appeared to affect the bilateral ON stimulation condition as well. For example, patient 14 reiterated more during right ON-stimulation and bilateral ON-stimulation, but repeated remarkably less during left ON-stimulation, and it seems that when the left stimulator is active (i.e. during bilateral ON) there is a decrease is the number of reiterations. Interestingly, he scored worst during right hemisphere stimulation which is the same hemisphere which is most affected by the dopaminergic degeneration. In this example, contralateral stimulation, i.e. stimulating the hemisphere which is most affected by neuronal degeneration, yields the worst outcome and appears to be mediated by ipsilateral stimulation, in this case the left hemisphere. However, as the aforementioned relationship only occurs in three patients, it remains unclear whether or not this is related to the motor lateralization of the patients and the impact of contralateral stimulation which according to the preliminary study and the example above negatively impacted the pragmatic language production of patients. Yet, as our data is inconclusive, we cannot - with certainty - rule out the aforementioned hypothesis. More specifically, only three

out of the seven patients revealed a relation between their contralateral stimulation and their worst performance[33] and a slightly lower number of repetitions during bilateral ON-stimulation which would suggest some sort of balancing when the least affected hemisphere is stimulated.

Secondly, compared to bilateral ON, the bilateral OFF-stimulation condition appears to increase the number of repetitions made, namely out of the 18 patients, bilateral ON (14 patients) scored the best. This means that in this sample size, the majority of patients benefit from bilateral stimulation compared to the OFF-stimulation condition which improves their pragmatic language abilities - at least regarding the number of repetitions - and might even ultimately contribute to an increase in self-esteem and awareness that they are still able to properly communicate despite their disease.

Furthermore, there were three patients which did not display any remarkable differences between the different stimulation conditions which is - most likely - due to individual characteristics as the remaining fifteen patients did indicate notable differences throughout the stimulation conditions. However, further research with a larger sample size is preferred to further examine whether or not this is really due to individual characteristics (e.g. disease progression, DBS-treatment cycle, etc.). In addition, the results of this parameter are probably not affected by the lack of a fixed set of questions, in contrary, the spontaneous language production[34] of these patients is most likely at its best (i.e. closest to daily life and unrestricted by questions) which would de facto mean that a free conversation is the best way to evaluate the impact of STN DBS on the number of reiterations (and the conversational fluency that goes hand in hand with it).

[33] For this parameter and where the performance is mediated by bilateral stimulation

[34] Spontaneous language production is also differently organized in the brain

Lastly, similar to the preliminary study, it seems that the majority of repetitions are function words rather than content words. More specifically, it appears that patients - regardless of the stimulation condition - have difficulties uttering or recalling the appropriate use of certain pronouns and adverbs. Based on this, it seems that in these patients, deep brain stimulation of the subthalamic nucleus does not seem to affect the type of word which is reiterated. However, we cannot generalize this observation due to the limited amount of patients and the lack of a clear trend throughout the entire sample size and as such further research is needed.

3.2.2 Remarks

The statistical analysis of the data did not yield any significant results, nor was there any remarkable difference between the left motor lateralization and right motor lateralization subgroups. In the pilot study, the higher number of repetitions was accompanied by a decrease in coherence and overall comprehensibility. This further strengthened the hypothesis that the observed pragmatic deficiency could either be linked to the stimulation of the right hemisphere, which is responsible for the pragmatic communicative abilities, or to the motor lateralization of the patient and the stimulation of the hemisphere most affected by dopaminergic degeneration. Unfortunately, we were unable to meticulously examine the impact of deep brain stimulation on the turn-taking of some patients. However, a qualitative approach of randomly selected patients indicated that there was indeed a connection between the stimulation of the hemisphere which is most affected by the dopaminergic loss (i.e. so-called “contralateral stimulation”) and on the one hand a decrease in coherence and on the other an increase of shorter sentences. In addition, a higher amount of interaction was needed by the interviewer to keep the conversation going.

Furthermore, apart from the parameters which are explained above, the data revealed no remarkable impact of subthalamic nucleus stimulation on the patients' conversational skills. However, some of the parameters - while still essential conversational skills – did simply not apply in this kind of setting, for example none of the patients open or close the conversation but that does not necessarily mean that they are incapable of doing so, in contrary, most of the data is transcribed or recorded at a point during which a consensus of conversation has already been established. This means that both the interviewer as well as the interviewee already acknowledged the situation that they are in and thus do not need to open nor close the interviews. Additionally, the parameter 'grabbing the attention of somebody' does not apply in these types of interview settings either as in most of the recordings there are only two people present or taking part in the conversation, namely the patient and the interviewer. Similar to difficulties encountered with another parameter, it is complicated to evaluate the parameter 'meaning of preceding sentences' as some transcriptions do not clearly distinguish between the different utterances or do not include all interactions from the interviewer. The inability to correctly assess certain parameters contributes to the overall difficulty of thoroughly studying the impact of the four different stimulation conditions on the conversational skills of the patients. Hence, as studying pragmatic language deficiency is becoming more important, there is a need for a new and standardized test which allows studies to fully expose the extent of the pragmatic impairment encountered in, for example, a neurodegenerative disease or after a traumatic brain injury (TBI). Nevertheless, the *Nijmeegse Pragmatiektest* is an adequate tool to evaluate the pragmatic lanuge production, yet, some of the parameters are seen as less sensitive for these kinds of studies. However, this will be discussed in the last part of this section.

3.3 Story-telling Skills

Similar to the previous section of the *Nijmeegse Pragmatiektest,* this part did not yield any significant results either; however, some parameters will be discussed more in depth from a more qualitative point of view. With regards to the observations made in the preliminary study, the results of the so-called "orientational parameters" (i.e orientation of person, place and time) did not change much throughout the four different stimulation conditions and as such no trend was noticed, nor did it matter which hemisphere was most affected by the dopaminergic degeneration of cells. This could mean that the episodic memory of these patients is not affected by subthalamic nucleus stimulation. 'Episodic or implicit memory is the recollection of an event or episode (UCSF, n. pag.). It is part of the declarative memory [instead of procedural] and 'is relevant both to recent and remote events (UCSF, n.pag.).' Furthermore, it can be seen as a 'process with several different steps, each of which relies on a separate system of the brain (UCSF, n.pag.).' Interestingly, based on our results, it appears that STN DBS does not affect the retrieval process where the information is accessed which is commonly thought to take place in the frontal lobe and the lateral temporal lobes. However, when describing the aforementioned communicative functions, we ascribed the impairment to be related to a frontal lobe dysfunction, yet according to neuroanatomical studies, damage to these regions could result in a disorganization of memory encoding but not necessarily to a disorganization of memory retrieval (yet the inability to recall certain memories can still occur) (UCSF, n.pag.). Furthermore, it should be mentioned that while the different stimulation conditions of STN DBS do not appear to affect the patients' episodic memory, neurodegenerative diseases - such as Parkinson's disease - might have a negative impact and cause a dysfunction of the aforementioned regions responsible for encoding and retrieving memories (UCSF,n.pag.).

On the other hand, the results could - be influenced by a lack of a fixed set of questions, namely, in a free conversation where the interviewer barely guides the patient, the topics change throughout the different patients and even within the same situation. Some individuals tell an anecdote (e.g. working abroad or traveling, etc.) or events regarding their own lives (e.g. his time at university, etc.), while others narrate about their family. Thus, the results are influenced by the topic of the conversation, for example, a patient talking about his hobbies (e.g. cycling) will utilize less "orientational parameters" than someone who used to work abroad. However, we should not overstress this either as spontaneaous language production is the best way to evaluate a patient's pragmatic language ability as it is differently organized in the brain. This means that a conversation which is guided too much by questions will produce results which are biased or influenced. The main reason for this is – as already mentioned – the different language organizations within the brain itself, spontaneaous language production may entail different regions or circuits.

3.3.1 Parameter: Discourse connectives

Based on the results, this is the only interesting parameter of the last section to explore more in depth as there is a distinctive difference between the two motor lateralization subgroups. Discourse connectives are seen as linking devices within the coherence theory framework, whereas in the relevance-theoretic framework they are analyzed as a unit of discourse which connects an utterance to a specific context (Rouchota 1). However, while there is not a single right approach, this paper favors the 'coherence theory' and as such will focus more on interpreting the results according to that framework. Generally, within the model of coherence theory, there are a set of shared ideas, e.g. 'that texts are coherent, that there is a definable set of coherence relations, and that the recovery of such coherence relations are essential for

comprehension (Rouchota 2).' Yet, as Rouchota (1996) notes that these relationships can be implicit or explicit (Rouchota 3), we will focus only on the explicit and how a higher or lower number of discourse connectives influences the coherence of the patients' utterances.

Most patients use discourse connectives to explicitly connect two utterances which are interpreted as 'belonging together' or 'pertaining to the same topic' (i.e. the linked sentence is an elaboration or extension of the topic). Yet, there are instances in which the conjunctions do not serve a real purpose. More specifically, while they do connect two utterances, the link between them is unclear; in other words, the discourse connective is used to relate two different topics that should not be linked. Additionally, in other cases they are used too such an extent that they create a feeling of enumeration, a list of sentences placed after each other with or without a clear link. This is illustrated in the following extract in which a patient (patient 16 situation A) talks about how she felt about living in Belgium (she was born in the Netherlands):

> ja maar ja maar nu niet meer hoor maar in het begin heb ik het echt moeilijk me gehad (ja) met de taal
> maar toen was er nog niet zoals nu
> want nu zijn er veel meer buitenlanders die daar wonen
> en toen was ik waren er eigenlijk maar een paar Nederlanders
> en daar was ik dan ook bij
> dus ik ging dan naar de winkel om boodschappen
> er was één supermarkt
> en de rest waren allemaal kleine kruidenierswinkeltjes
> en euh ik ging dan in die kleine kruidenierswinkeltjes want ik vond dat wel leuk maar ze verstonden me dan niet
> en dan werd ik zo kwaad hé
> en zei ik
> en nu ga ik er niet meer naartoe he
> en dus ja
> en toen ben ik dan maar naar de supermarkt
> maar ja daar moest ik eigenlijk niets zeggen
> dus dan ik kon ik da zo pakken hé
> en van lieve lee is dat zo begonnen
> en toen kreeg ik dan een kind
> en toen was het over (Extract patient 16, situation A)

In the first sentences, the discourse connectives are utilized correctly, however, as she keeps using them, they lose their function at a certain point, and from then onwards she appears to be merely listing events that more or less relate to one another (but which is 'lost' due to the "enumeration-effect"). Nevertheless, despite the language flaws (repetitions, grammatical errors), the extract seems coherent, yet deviates from normal language use due to the high number of discourse connectives.

Furthermore, when comparing unilateral stimulation versus bilateral ON stimulation, it seems that both left ON and right ON hemisphere stimulation affect the use of discourse connectives, more specifically 15 patients (n = 18) used more conjunctions during unilateral STN DBS. However, as illustrated by the excerpt above, an increased use does not necessarily enhance the coherence of the patients' discourse. Interestingly, when linking the unilateral stimulation results to the motor lateralization subgroups, we observe a - albeit small - correlation, more precisely stimulating the STN of the hemisphere which is most affected by the dopaminergic degeneration appears to increase the use of discourse connectives. Thus it appears that for some patients, stimulating the hemisphere most affected by Parkinson's disease has a beneficial[35] effect regarding the use of discourse connectives and as such contributes to amelioration of the pragmatic deficit commonly observed in the disease. However, a high number of discourse connectives could have a negative influence on the patient's coherence as well as was illustrated above. Nonetheless, this minor improvement cannot compete with the various negative consequences noticed in some patients when stimulating the most affected hemisphere. Yet, due to the small sample size and the fact that some patients' results do not correlate with the observation, we cannot generalize this hypothesis and as such further research is needed. Lastly, it is worth mentioning that -apart

[35] However, there were cases were there was a negative effect as well

from a few instances - there are no remarkable differences between the three ON-conditions and the bilateral OFF stimulation condition, this could be ascribable to for example individual patient characteristics or, as Mercado et al.'s (2006) observed as well, a placebo-effect. They noticed a 'significant worsening when the patients were advised that the stimulation was OFF, in comparison with the blinded OFF condition (Mercado et al. 1460),' yet their findings are only based on observed motor improvements and may not be applicable to cognitive functions such as language.

3.4 Concluding notes

As reported by several studies, deep brain stimulation of the subthalamic nucleus influences PD patients' language processes. However, as the disease progresses a 'worsening of motor symptoms was observed both in 'medication-ON' condition and in stimulation-ON' condition, with a parallel reduction in the synergistic effect of medication-ON/stimulation-ON' condition (Merola et al. 2074). As such neuropsychological examinations indicate a 'gradual decline in the performances of all main cognitive domains, with an initial involvement of executive functions, followed by the impairment of language, reasoning and memory (Merola et al. 2074).' Nevertheless, longitudinal studies reveal that DBS STN still appeared to significantly ameliorate the 'main disease cardinal features (Merola et al. 2074).' Thus, based on data presented in neuropsychological researches, it is possible that as the disease develops (e.g. 30 years post onset), the pragmatic language production further deteriorates as cognitive and language processes are more affected by the neuronal loss. Yet, this is merely a hypothesis as there is no conclusive data available at this time.

With regards to the studies presented in the literature review, the patients examined for this study concord with the observation made by, for example, McNamara and Durso (2003). Indeed, patients appeared to 'experience inordinate difficulty in social conversation, turn-taking, staying on topic and appropriately conveying emotion (McNamara and Durso 415). Yet, based on the results, some patients' inability to disclose emotion appears to be affected by STN DBS. However, this study only examines pragmatic language production and as such does not take into account the gestures of the patients which - according to some authors - form part of the patient's ability to communicate emotion and hence should be interpreted as pragmatic as well (McNamara and Durso 418). Nevertheless, 10 out of the 18 patients produced more 'emotional language use' during unilateral right hemisphere stimulation, i.e. the hemisphere which is responsible for all forms of emotional expression (Achuff n. pag.). Furthermore, similar to other studies, some of the patients were unaware of their pragmatic impairment and as such they did not utilize 'compensatory cognitive strategies' (McNamara and Durso 421); this caused some of the patients to perseverate when they were unable to pronounce or recall a certain word or to continue making the same grammatical errors

As already mentioned several times above, we suggested that the results could have been influenced by methodological limitations. However, our methodology itself[36] is actually not to 'blame' and as such arguing that it is liable, would not be correct. The reason why this dissertation did not succeed in fully elucidating the impact of STN DBS on the pragmatic language production in Parkinson's disease is far more complicated. As pragmatic language production consists of a complex network of circuits which probably involve multiple cognitive functions as well as diffuse neuroanatomical regions, evaluating this is challenging and complicated task. It is generally accepted that pragmatic language production is most

[36] With that I mean the way we conducted the actual research, not the tools available

likely differently organized in the brain, more specifically – as mentioned above – it does not only consist of language processes but may require the participation of certain cognitive functions as well. Thus it could be that the test which is used to evaluate the pragmatic production abilities is not sensitive enough and, hence, inadequate[37] and unsatisfactory. However, the *Nijmeegse Pragmatiektest* will be discussed more at length later.

Secondly, as the data was clinically recorded to see how the patients reacted on the DBS, the interviews itself were not guided by a fixed set of questions. This has its advantages as well as disadvantages, for example, as it is a free conversation (with minimal interaction of the interviewer), the patient can talk about whichever he or she pleases and feels comfortable about, which benefits the outcomes of certain parameters. Furthermore, spontaneous language production is crucial when studying the pragmatic language proficiency of patients as it is differently organised in the brain. When the patient is guided too much by questions, their language production could rely on other neural circuits and as such we would not be assessing their actual pragmatic language proficiency.

Nevertheless, we still argue that the lack of a fixed set of questions could have contributed to the fact that some parameters of the test were either undiscussable in this paper as they were never found in the data or were influenced by the conversation itself. An example of the former are the parameters '*eind resultaat (i.e. vertellen van de afloop van sen verhaal)*', '*afronding (i.e. aangeven dat het verhaal ten einde is).*' A consequence of the latter is that some parameters might be influenced by a certain conversational topic, namely a patient talking about his/her family results in the use of more parameters (for example we get an increase use of the "orientational parameters (person, place and time)" or an increase of the

[37] They are inadequate to evaluate the pragmatic language production as they insufficiently take the neuroanatomical correlations into account

communicative function parameter 'talking about other people's activities'). However, these conversational influences will probably always occur so their impact should not be overstressed either. Hence, one should take these variables into account, but not in such a way that they are interpreted as restricting or distorting the influence of STN DBS.

Ideally, the best way to study the influence of subthalamic nucleus stimulation on the pragmatic language production - or the pragmatic language deficiency in general - is to achieve a feeling of free conversation, yet, somewhat 'guided' by a fixed set of questions which evaluate specific pragmatic abilities. This method should result in a more unified outcome which is less affected by the situation itself. However, based on the previously mentioned hypothesis which highlights the complex nature of pragmatic language production, we suggest that the pragmatic language should be divided even further into subcomponents and, additionally, to include the cognitive functions which are involved.

While the *Nijmeegse Pragmatiektest* undoubtedly fulfills its goal as a complementary tool to be used alongside a patient's treatment, it is still designed to evaluate the pragmatic language abilities of children. This does not mean that the test cannot be utilized in these kinds of studies but, unfortunately, some parameters are found lacking to properly assess the pragmatic language abilities of PD patients.[38] As this is the only Dutch test available to evaluate the severity of a pragmatic language production deficiency and as studies elucidating the impact of a pragmatic impairment on the QoL of a patient are becoming more important, the need for a new test specifically designed for people with a neurodegenerative disease or a lesion grows. This would not only make it easier for the medical staff and researchers to properly assess a patient's abilities, the patient him- or herself would intrinsically benefit as well, as

[38] Some parameters were seen as less sensitive

his/her treatment can focus on deficits observed in the test. Based on our prior thoughts and ideas, a test which evaluates the pragmatic language production should first subdivide the pragmatic language into smaller components as it is a highly complex process which consists of a number of minor functions.[39] Moreover, it should take into account – or, ideally, include – the possible cognitive activity[40] which is essential in the production of pragmatic language. Lastly, the new test should be designed in such a way that it would allow the examiners to standardize their observations for the healthy and pathological population.

[39] Similar to the *Nijmeegse Pragmatiektest* but with specific parameters which are all sensitive

[40] As well as the different neuroanatomical regions which possibly participate

Chapter 4
Conclusion

This paper studies the influence of subthalamic nucleus stimulation on the pragmatic language production of patients suffering from Parkinson's disease, a progressive neurological disorder characterized by an asymmetric dopaminergic degeneration in the brain (Verreyt al. 405-406). While the disease is predominantly known for its motor symptoms, 'already in the very early stages of PD, the majority of patients often develop cognitive impairments such as selective attention and working memory deficits (Van Lier 31).' Yet, while speech motor deficiencies such as dysarthria have already been thoroughly studied, the impact of Parkinson's disease on various language processes still remains fairly unstudied compared to motor impairments (Skodda et al. 606). Furthermore, the observed language deficits are often related to the cognitive impairments, for example verb production deficits are often linked to cognitive processes. While this could be indicative for a strong interaction of cognitive proficiency on "language production performance", these, however, cannot be fully held accountable for the deviations in PD patients' language performance (Altmann and Troche 6). Until now, authors have observed that there is a reduced information content across a range of different language tasks, such as 'conversational discourse, picture description tasks, and written sentences (Altmann and Troche 9).' Individuals suffering from Parkinson's disease have an impaired grammaticality of language production, namely there is a simplification of syntax in complex language tasks (Altmann and Troche 9). Moreover, most PD patients have a "fluency of production" deficit; however, this should be studied both 'as a language impairment as well as a motor speech impairment (Altmann and Troche 9).' Some authors noticed language-related abnormalities and argued that Parkinson's disease might impair the patients' speech planning and lexical access; however, this is not the case (Illes 147). More specifically, while 'the production of superfluous referential utterances such as open class optional phrases may be consistent with patients' inability to exit from their cognitive loop, it is in direct contradiction to any intrinsic deficit of lexical access (Illes 156-157).

Unfortunately, the impact of Parkinson's disease on the pragmatic language proficiencies of patients still remains rather unstudied, as there is almost no literature available. Some authors observed 'that the comprehension of pragmatic language phenomena were affected if there was some kind of manipulation of information present within the working memory, thus acknowledging the influence of Parkinson's disease on the fronto-striatal circuitry and the dorsolateral prefrontal regions (Van Lier 3).' Furthermore, McNamara and Durso (2003) note that PD patients seem to have difficulties with 'social conversation, turn-taking, staying on topic and appropriately conveying emotion (McNamara and Durso 415).' Neuropsychologic observations on the other hand suggest that the 'neuro-cognitive system' which sustains the pragmatic communication abilities - i.e. right hemisphere and frontal lobes -, is impaired in Parkinson's disease (McNamara and Durso 415). As PD patients were significantly impaired on certain features of pragmatic communication such as 'conversational appropriateness, prosodics or gestures,' this could lead or contribute to communication difficulties, thus limiting their daily activities and affecting their quality of life (QoL) (McNamara and Durso 418-421).

Most of the cardinal symptoms, however, are ameliorated by medicinal therapies which contain the dopamine precursor levodopa since a dopamine-insertion will backfire as it cannot transverse the blood-brain barrier (De Letter 29). However, while it still remains the most effective and used therapy, there are adverse side effects, namely 'long-term use of levodopa may lead to dystonia, dyskinesia and on-off effects (i.e. unpredictable motor symptom fluctuations (De Letter et al. 188).' Moreover, as the disease further develops, 'the efficiency of the medication lessens, which leads to an increased daily dose requirement (Van Lier 11, Philips et al. 1).' As a result, there is an increased interest towards deep brain stimulation of

the subthalamic nucleus. Apart from the improvements of cardinal motor impairments, the impact of STN DBS on speech remains inconclusive as some studies observe an improvement, while others noticed an increase of dysarthria (Santens et al. 253). Some authors argued that left side STN stimulation had a negative impact on speech, which was supported by Wang et al. (2006) who observed distinct 'hemisphere-specific effects on speech' which were 'presumably related to [the] language dominance also being located in the left hemisphere [...] (Santens et al. 256, Whitehill 110).' Moreover, some authors observed that bilateral subthalamic nucleus stimulation had a negative impact on certain language functions, such as category fluency and word fluency (Bordini et al. 118). Yet, whether the pragmatic language production deficit is affected by subthalamic nucleus stimulation remained unclear.

As such a preliminary study was conducted which evaluated the impact of subthalamic nucleus stimulation on the pragmatic language production of one PD patient. Similar to this paper, the pilot assessed the spontaneous language production using the *Nijmeegse Pragmatiektest* designed by Embrechts et al. which is the only Dutch test available to evaluate pragmatic language use. The analysis of the data indicated that right-sided hemisphere stimulation could have a negative impact upon some of the patient's pragmatic language abilities (Van Lier 32-33). However, as the data of only one patient was examined, it remained unclear whether the negative effect of right-ON stimulation could be related to the motor lateralization of the patient, i.e. the hemisphere which is most affected by the dopaminergic degeneration (Van Lier 33). And since language is an important factor for creating an enjoyable quality of life for the patients, further research was required to elucidate the full impact of DBS STN on the pragmatic language production of patients suffering from Parkinson's disease.

This study's goal is to further evaluate the ideas and hypotheses which arose in the pilot. The first parameter discussed was the impact of STN stimulation on the emotional language use of patients. The statistical evaluation of the data did not reveal a significant outcome, nor was there a distinct trend observed either. Our obversations argue in favor of the theory which claims that the right hemisphere is dominant for emotions and emotional expression as unilateral right hemisphere stimulation resulted in more emotionally loaded utterances. When comparing the results of both subgroups, there is a notable statistical difference in the scores. This difference could be due to various reasons, it could, for example, be related to the topic of the conversation or perhaps to the neuronal degeneration as a result of the pathology itself. The absence of a significant result and the lack of a trend throughout all patients means that we cannot present clear evidence of the impact of STN DBS on the emotional language use of the patients. Furthermore, the other so-called second grade parameters[41] which were discussed, did not indicate a clear trend and thus there was no evidence of STN DBS' impact on those abilities in our data.

The results of both subgroups scored below the significance level of p = 0,05 for the parameter 'giving an explanation'. The outcomes were linked to neuropsychologic observations of PD patients which suggested that the neural substrates, which sustain the cognitive system and more particularly the pragmatic communication abilities, were disrupted in the right hemisphere and frontal lobes and as such could contribute to the pragmatic deficiency commonly observed in Parkinson's disease (McNamara and Durso 415). When most patients of the left motor lateralization subgroup are stimulated on their most affected hemisphere, i.e. right ON, this generally resulted in the patients no longer giving an

[41] i.e. parameters which did not yield a significant result but which were nonetheless considered interesting to discuss

explanation for something. Based on the results, it appears that when the right hemisphere is affected most by Parkinson's disease, patients tend to perform worse throughout the four different stimulation conditions. It seems that - at least for the left motor lateralization subgroup - unilateral subthalamic nucleus stimulation of the right hemisphere does not restore the disequilibrium in the brain when the right hemisphere is most impaired by the loss of dopaminergic cells. Thus, based on the data presented here, DBS STN does not appear to ameliorate - nor worsen - the pragmatic impairment of this subgroup of patients. Patients with a right motor lateralization scored better on this parameter, which could mean that their pragmatic language abilities could either be less affected by Parkinson's disease or restored by the STN stimulation. However, with regards to the first subgroup, the findings of the second group contributed to the hypothesis that the left hemisphere might participate in pragmatic functions too. In short, based on our observation, we conclude that the usage of this parameter could be affected by both the pathology of Parkinson's disease (i.e. the hemisphere which is affected the most) and STN stimulation as was illustrated by the results of the second subgroup. More specifically, as (some) patients perform better during bilateral ON versus OFF, the active state of the left stimulator appears to balance and restore certain disruptions in the left hemisphere as the difference in results might not fully be attributable to the right hemisphere.

The statistical analysis of the results of the second section of the *Nijmeegse Pragmatiektest* did not yield any significant outcome. The results of the first parameter, the number of reiterations, indicated that unilateral stimulation appeared to increase the numbers of repetitions. It seemed that the initial observation where right hemisphere stimulation had a negative impact on the parameter, is not reproduced by the larger sample size of this study. Furthermore, there was no clear evidence for a correlation between the impact of unilateral

stimulation and the motor lateralization of the different patients as only half of the patients indicated a link between their worst performance and the stimulation of their most affected hemisphere. Moreover, when comparing the bilateral stimulation conditions, bilateral OFF-stimulation resulted in an increase in the number of repetitions made and as such the majority of patients seemed to benefit from bilateral stimulation compared to the OFF-condition and thus improving their pragmatic language production.

Similar to the previous section, the statistical analysis of the data of the last component of the test did not indicate any significant outcomes. It seemed that the results of the three orientational parameters (eg. person, place and time) were not remarkably influenced by the different stimulation conditions, nor which hemisphere was most affected by Parkinson's disease. It was hypothesized that the episodic memory of the patients was not affected by STN DBS, however, as this is still precarious to conclude, further research is needed to verify this.

The last parameter which was discussed, was the use of discourse connectives. When closely examining the results of the different stimulation conditions, it appeared that unilateral STN stimulation had a beneficial effect on the use of discourse connectives. Moreover, when the STN of the hemisphere which was most affected by the dopaminergic degeneration was (unilaterally) stimulated, an increase in the use of discourse connectives was noticed. Based on the data, we concluded that the stimulation of the most affected hemisphere appeared to have a positive impact regarding the use of conjunctions and thus seemed to contribute to the improvement of the pragmatic deficit of the patients. However, because of the lack of a statistically significant result and the fact that the trend was not observed throughout all the patients, the aforementioned observation cannot be generalized.

Furthermore, we argued that the results of some could have been influenced by methodological limitations; however, as already explained this was not entirely the case. While some of the parameters of the test were seen as insensitive and thus might not yield (usable) results, we should not hold our own methodology accountable. In addition, it became clear that evaluating pragmatic language production is far more complex as it involves participation of certain cognitive functions.

Moreover, it was suggested that the optimal way to study the impact of STN stimulation on the pragmatic language production is to make the interviewee feel comfortable (i.e. feeling of 'free conversation'), but nevertheless guided by a set of questions which assess specific pragmatic proficiencies. Yet, not too much either, as this might influence the language organisation and thus could involve other neural circuits than those used in spontaneous language production.

Lastly, this paper argues for the need of a new test which is specifically designed to evaluate the pragmatic language production of, for example, individuals with a neurodegenerative disease. As mentioned in the discussion, both the medical staff and researchers as well as the patients themselves would benefit from a new and specifically designed test.

To conclude, this paper studied the influence of subthalamic nucleus stimulation on the pragmatic language production of 18 individuals suffering from Parkinson's disease. Based on our results, we hypothesize that there could be a relationship between the stimulation of the hemisphere which is most affected by PD and the pragmatic language production of the patients. However, as it was unclear whether STN ameliorated or worsened the pragmatic proficiency, hence, we argue that there is no such thing as "an influence" but that organisation and evaluation of pragmatic language production is far more complex than initially thought.

Furthermore, in the discussion, we speculated that while the right hemisphere may be dominant for the pragmatic proficiencies, it appears that the left hemisphere is involved as well. Yet, to verify hypotheses like these, further research is essential. However, as the existing tests are not sensitive enough and not as adequate to assess the pragmatic language production as they do not take the neuroanatomical correlations into account, we believe that a new test is long overdue.

Chapter 5
Bibliography and appendix

5.1 Bibliography

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5.2 Appendix

5.2.1 Footnotes

- *Footnote 1*: Another research studying the genetic susceptibility in Parkinson's disease illustrates the importance of genetic studies as the investigation of 'monogenic forms of parkinsonism with a clear Mendelian pattern of inheritance' has contributed to the 'discovery of mutations in SCNA (α-synuclein), PARK2, PINK1, PARK6 and LRRK2 as causes of primary parkinsonism and/or PD (Bras and Singleton 597).' However, these mutations will not be discussed in detail in this paper, for a full overview, the reader is referred to Bras and Singleton's (2008) *Genetic susceptibility in Parkinson's disease*.

- *Footnote 2*: Epidemiological studies studying the etiopathogenesis of Parkinson's disease often stress the importance of toxins as a possible influence and instigator (Bartels and Leenders 916; Bonnet and Houeto 117). The MPTP-model in particular - and toxins similar to MPTP - has often been the subject of various studies and has repeatedly been linked to Parkinson's disease (Bonnet and Houeto 117). MPTP or 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine is a so-called tetrahydropyridine which incites an irreversible parkinsonian syndrome similar to Parkinson's disease (Bonnet and Houeto117). Neuropathological studies illustrate that MPTP damages the 'nigrostriatal dopaminergic pathway' equal to that monitored in Parkinson's disease (Przedborski 190). Furthermore, there is a resemblance that goes further than the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Przedborski 190). Similar to the degeneration in Parkinson's disease, there is a great loss of dopaminergic neurons located in the SNc than in the ventral segmental area (Przedborski 190). However, it is not MPTP itself that causes

the dopaminergic neuronal loss; after it crosses the blood-brain barrier, it is metabolized into MDPDP+ (1-methyl-1-4-phenyl-2,3-dihydropyridinium) and ultimately into MPP+ by the monoamine oxidase B (MOA-B) formed in the glial cells (Przedborski 190-191; Bonnet and Houeto 117). After the formation of MPP+, it is transported into dopaminergic cells by dopamine DA transporters and as it has a strong chemical attraction for neuromelanin of dopaminergic cells, it might ultimately contribute to the onset of Parkinson's disease as it is linked to oxidative stress which could no longer be alleviated by neuromelanin (Bonnet and Houeto 117). 'Oxidative metabolism of dopamine by monoamine-oxidase (MAO) leads to the formation of peroxide, which is normally cleared by glutathion (Bartels and Leenders 916). As glutathion is decreased in PD SN more toxic free oxygen radicals may be formed (oxidative stress), which damage the dopaminergic neurons (Bartels and Leenders 916).' These consecutive events eventually result in the loss of dopaminergic neurons in the substantia nigra (Bonnet and Houeto 117).

- *Footnote 3*: 'The oscillatory activity is usually identified and studied in cortical local field potentials (LFPs) and EEG, and reflects local rhythmic synchronized subthreshold activity in presynaptic terminals and the postsynaptic neurons. [...] Oscillatory activity in the basal ganglia (BG) has attracted a great deal of interest in the past few years as it is thought to be important in both the normal functioning of the system and the pathophysiology of Parkinson's disease. [...] Studies of neuronal firing in both humans with Parkinson's disease and animal models of Parkinson's disease provide evidence for an increase in oscillatory activity in the external and internal segments of the globus pallidus (GPe and GPi), and the subthalamic nucleus (STN) [...]. Such changes in the patterns of firing of STN and GP neurons may be very important in causing the motor symptoms of PD and perhaps of other BG-mediated movement disorders (Dotrovsky and Berman 721).'

- *Footnote 4*: Chorea, ballismus and athetosis: “Chorea is a condition that causes involuntary, unpredictable body movements that do not have a pattern. Chorea symptoms can range from minor movements such as fidgeting to profound, uncontrolled movements of the arms and legs. Medical expers consider chorea to be one of three types of hyperkinetic disorder. Chorea causes rapid involuntary motions. Ballismus (or choreoballismus) causes more-severe jerking motions that are more likely to cause injury. Athetosis (or choreoathetosis) causes slow, writing movements (Nall, n.pag.).”

  (Source: Nall, http://www.healthline.com/symptom/chorea)

- *Footnote 5*: “Bradykinesia means slowness of movement and is one of the cardinal manifestations of Parkinson's disease. Weakness, tremor and rigidity may contribute to but do not fully explain bradykinesia. We argue that bradykinesia results from a failure of basal ganglia output to reinforce the cortical mechanisms that prepare and execute the commands to move. The cortical deficit is most apparent in midline motor areas. This leads to particular difficulty with self-paced movements, prolonged reaction times and abnormal pre-movement EEG activity (Berardelli et al. 2131).”
  (Source:http://brain.oxfordjournals.org/content/124/11/2131.full)

- *Footnote 6*: ‘This cue deficit is seen in the gradual reduction of movement amplitude [...]; articulation impairment could be compared to the lower and upper limb demonstration of cue deficit over a sequence of sub-movements and could likewise be attributed to defective internal BG cueing in PD (Ho et al. 135).’ The “pattern of prevalence” observed in patients with speech impairments suggest that the pathophysiology on speech deficits in Parkinson’s disease may be similar to that seen in other motor deficiency (Ho et al. 135).

- *Footnote 7*: The most common way of treating the hypokinetic speech impairment found in Parkinson's disease is a dopaminergic therapy using 'dopamine precursor' levodopa (Rusz et al. 320; De Letter 29). While beneficial effects on the cardinal motor impairments of PD have been observed, the impact of the therapy on the general speech parameters still needs to be elucidated as contemporary studies disclose contradictory results (Rusz et al. 320). Rusz et al. (2013) studied the influence of pharmacotherapy on speech and revealed that after a therapy of 1-2 years, most of their patients' speech ameliorated or uphold their initial speech performance; hence, their results concord with other studies which showed an overall improvement in speech (Rusz et al. 325). Furthermore, 'kinematic and electromyographic studies found treatment-related improvements in articulatory performance, including normalization of abnormal lip muscle activation, and improvement of mandibular movements (Rusz et al. 325).' Unlike previous (and older) researches which in general only exhibited improvements of speech performance as a result of dopaminergic therapy, more recent studies, however, presented no 'significant treatment effect on speech intensity, phonatory parameters, pitch variability, articulation, and overal intelligibility (Rusz et al. 325).' As a result, there is no clear consensus as of yet; however, a possible explanation for the inconsistency of the former studies could be related to a number of individual-participant related variation or the methodology (Rusz et al. 325). Rusz et al. (2013) argue that the majority of the studies indeed only concentrated on selective aspects of speech and did not attempt to review complex speech manifestations, whereas patients suffering from Parkinson's disease may exhibit diverse speech 'deficits across individual measures and characteristics (Rusz et al. 325). In particular, in early PD patients with little perceptible dysarthria, effects of medication on speech production can hardly be detected by a single UPDRS speech item (Rusz et al. 325).' Furthermore, Rusz et al. (2013) observed an improvement of 'speech intensity, quality of voice, intonation variability and

articulation' following the dopaminergic therapy, whereas 'speech fluency and sustained phonation time were changed rather individually', which could be due to a 'high initial inter-individual variability (Rusz et al. 326).'

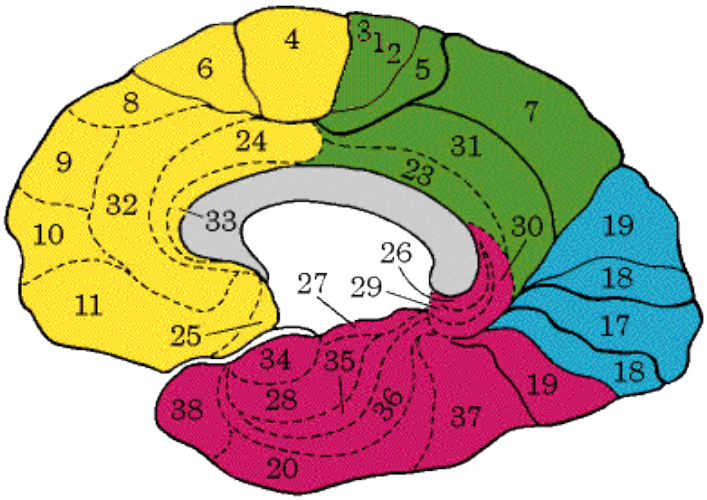
- *Footnote 8*: 'Orthostatic hypotension — also called postural hypotension — is a form of low blood pressure that happens when you stand up from sitting or lying down. Orthostatic hypotension can make you feel dizzy or lightheaded and maybe even faint. Orthostatic hypotension is often mild, lasting a few seconds to a few minutes after standing. However, long-lasting orthostatic hypotension can be a sign of more-serious problems, so talk to your doctor if you frequently feel lightheaded when standing up. It's even more urgent to see a doctor if you lose consciousness, even momentarily.' (Mayo Clinic Staff, n. pag., Source: www. Mayoclinic.org)

- *Footnote 9*: 'Sleepiness, the state of feeling drowsy, ready to fall asleep. A person experiencing somnolence is somnolent and is acting somnolently' (MedicineNet, n.pag. Source: www.medterms.com).

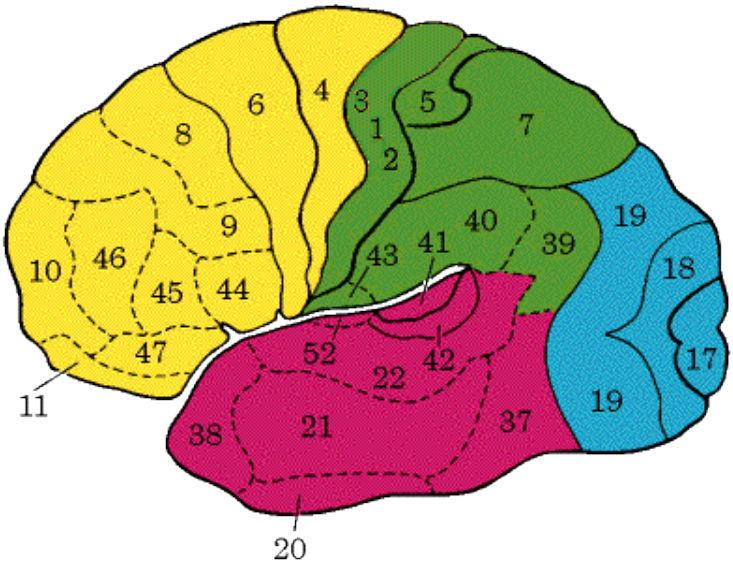
- *Footnote 10*: PET-scan: 'A positron emission tomography (PET) scan is an imaging test that uses a radioactive substance called a tracer to look for disease in the body. A PET scan shows how organs and tissues are working. This is different than magnetic resonance imaging (MRI) and computed tomography (CT), which show the structure of and blood flow to and from organs (MedlinePlus, n.pag.).' (Source: www.nlm.nih.gov)

- *Footnote 11*: Brodmann areas:

Mid-sagittal view:



Sagittal view:



Yellow: **Frontal lobe**: 'thinking, planning, & central executive functions; motor execution (University of Michigan, n.pag.)'

Green: **Parietal lobe**: 'somatosensory perception, integration of visual & somatospatial information (University of Michigan, n.pag.)'

Purple: **Temporal lobe**: 'language function and auditory perception involved in long term memory and emotion (University of Michigan, n.pag.)'

Blue: **Occipital lobe**: 'visual perception and processing (University of Michigan, n.pag.)'

Images were taken from the website of the University of Michigan, www.umich.edu.

- *Footnote 12*: Furthermore, Altmann and Troche (2011) refer to an interesting study by Zanini, Tavano and Fabbro (2010) which assesses spontaneous language production of bilingual PD patients and observed a significantly higher grammatical error rate compared to the age and education matched control group; however, the impairment was restricted to L1 performance of patients (Altmann and Troche 4). Several linguists suggest that early acquisition of language (someone's native language or L1) is mainly 'implicit/ procedural and supported by the cerebellum (i.e. the right hemisphere), the left neostriatum and other basal ganglia [nuclei], and circumscribed to the perisylvian cortex and as such the acquisition is incidental (Zanini et al. 84).' Linguistic proficiency is supported implicitly, employed instinctively and involuntarily, and involves 'components of language that can be described in terms of rules (i.e. phonology, morphology, syntax, and the morphosyntactic properties of lexicon) (Zanini et al. 84).' This model is often referred to as the Procedural or Declarative model of language acquisition and was proposed by Ullman (Zanini et al. 84). Moreover, according to Ullman's model, neurological disorders such as Parkinson's disease which involve the basal ganglia (which starts in Braak's stage 3 classification when only the midbrain is affected) were hypothesized to impact bilingual

patients' linguistic proficiencies in L1 vs L2 differently (Zanini et al. 84-85). More precisely, Zanini et al. (2010) note 'L1 impairments should be predominant, particularly as far as phonology, morphology and syntax are concerned (Zanini et al. 84-85).' However, other authors proposed that L1 and L2 share a large number of neural circuits and brain areas, yet, some minor peculiarities occur in the activity of cortical and subcortical regions when processing a native language versus a second language 'which have been attributed to variables such as degree of mastery, age of acquisition and level of exposure (Zanini et al. 85).' This hypothesis eliminates a selective involvement of basal ganglia in the L1 language, as they are all 'processed within a cortical-subcortical language brain network (Zanini et al. 85).' Moreover, according to this theory of "shared brain networks for language processing", neurological disorders which cause a dysfunction of the basal ganglia circuitry might not evoke distinct impairments between L1 and L2 language proficiencies (Zanini et al. 85). However, as mentioned above, Zanini et al. (2010) observed that patients' native language (Frulian) was more impaired than their L2 (Italian) which was illustrated by more severe errors, more precisely patients conferred 'with a simplified syntax and morphological and syntax deficits, particularly in the use of closed-class words and inflectional morphology (Zanini et al. 86).' Zanini et al. (2010) their findings supported Ulman's Procedural/ Declarative model where lesions or neurodegenerative pathology disrupt neural substrates and circuits (e.g. basal ganglia) of "implicit memory processing" and would cause a deficit of implicitly acquired proficiencies (Zanini et al. 87). Moreover, PD patients did not reveal the same L1 advantage as the control group when producing different words which can 'be explained by the fact that, during lexical retrieval grammatical properties are also accessed and such properties are part of the implicit system (Zanini et al. 87).' No semantic L1 deficit (verbal or semantic paraphasias) was observed in PD patients, 'which would be expected if the

lexical semantics of a native language expanded mainly following the development of the declarative memory system (Zanini et al. 87).'

- *Footnote 13*: Other studies report altered prosody in Parkinson's disease; 'prosody is a term used to cover features of speech such as the emphasis placed on certain syllables, changes in tempo or timing and differences in pitch and intonation (Lloyd 390).' Because prosody involves speech characteristics, it is unclear whether it is a subdomain of speech or language, however, most studies - and this dissertation as well - tend to interpret it as a language characteristic. Additionally, it is utilized to 'convey a great deal of semantic, syntactic and affective information (Lloyd 390).' Studies elucidated that prosody can be deficient 'independently of other language functions' because the processing is 'dissociated from other language processes and [because it] is a right hemisphere function (Lloyd 390). The prosody of PD patient is often described as discerning from the normal prosodic variation and is commonly characterized as dysprosodic (Lloyd 390). While the production can be related to the dopamine depletion in the basal ganglia as speech motor functions are involved, some authors, however, observed that PD patients had difficulties 'recognizing and processing prosody in the speech of others (Lloyd 390).' A study of Scott, Caird and Williams conducted in 1984 evaluated the understanding of prosody in 28 patients and observed that while they could 'discriminate sentences with prosodic contrasts (e.g. "I can run" vs. "I *can* run"), they were impaired at judging whether the pairs of sentences had the same meaning or not (Lloyd 390).' Moreover, PD patients displayed an inability of assessing the emotional dimension of different utterances (Lloyd 390). However, not all studies yield comparable results and as such there is no consensus in the literature on the subject of comprehension deficits in Parkinson's disease (Lloyd 398). While Lloyd (1999) did not observe any comprehension impairment, Scott et al. (1984) on the other hand did notice a deficit in the comprehension, yet patients could still 'discriminate between pairs of

stimuli as well as controls (Lloyd 391).' This could mean that the impairment is not due to a deficit at the 'level of early auditory processing, but rather may affect the mapping between prosodic processing and affective/semantic representations (Lloyd 391).' In addition, the fact that PD patients are impaired in both prosodic comprehension and production further endorses the hypothesis that 'it is caused by cognitive rather than motor deficit (Lloyd 399).' As mentioned above, it has been hypothesized that the basal ganglia are involved in the processing of prosody; more specifically, Starkstein et al. (1994) noticed that the right basal ganglia in particular were involved (Lloyd 399). Moreover, this was supported by a study conducted by Folstein et al. (1990) who examined the comprehension of prosody in patients suffering from Huntington's disease (HD), a neurological disorder characterized by 'selective atrophy of the caudate nucleus of the basal ganglia' and as such its pathology is similar to Parkinson's disease (Lloyd 399). HD patients performed remarkably worse at 'recognizing and discriminating propositional (question, statement or command) and affective prosody when compared to matched controls (Lloyd 399-400).' As such, a dysfunction of the basal ganglia's associative role results in the patients' inability to correctly 'map the auditory input onto affect and linguistic representations (Lloyd 400).'

- *Footnote 14*: 'The instrument most often used for attention was the Stroop Test (ST) [...]. This test, developed by John Ridley Stroop in 1935, is aimed at evaluating selective attention, inhibitory capacity and concentration.This test has some variations, but the full format has the following stages. Scores may be defined according to test performance time, number of errors or both, or according to the number of items read or named within a given timeframe (Romann et al. 4).'

- *Footnote 15*: 'In the early 1900s, while researching Parkinson's disease, the scientist Friederich H. Lewy discovered abnormal protein deposits that disrupt the brain's normal functioning. These Lewy body proteins are found in an area of the brain stem where they deplete the neurotransmitter dopamine, causing Parkinsonian symptoms. In Lewy body dementia, these abnormal proteins are diffuse throughout other areas of the brain, including the cerebral cortex. The brain chemical acetylcholine is depleted, causing disruption of perception, thinking and behavior (Lewy Body Dementia Association Inc., n.pag. Source: www.lbda.org).'

- *Footnote 16*: 'The Hoehn and Yahr scale is a system commonly used for describing, in broad terms, how Parkinson's symptoms progress and the relative level of disability. It was originally published in 1967 in the journal *Neurology* by Melvin Yahr and Margaret Hoehn, and included stages one to five. Since then, stage 0 has been added and stages 1.5 and 2.5 have been proposed and are widely used (European Parkinson's Disease Association, n.pag., Source: www.epda.eu.com).'

Stage 0	No signs of disease
Stage 1	Symptoms on one side only (unilateral)
Stage 1,5	Symptoms unilateral and also involving neck and spine
Stage 2	Symptoms on both sides (bilateral) but no impairment of balance
Stage 2,5	Mild bilateral symptoms with recovery when the 'pull test is given'
Stage 3	Balance impairment, mild to moderate disease. Physically independent
Stage 4	Severe disability, but still able to walk or stand unassisted
Stage 5	Needing a wheelchair or bedridden unless assisted

(Source table: European Parkinson's Disease Association, www.epda.eu.com)

- *Footnote 18*: ‘Dystonia is a medical term that describes a range of movement disorders that cause muscle spasms and contractions**.** The spasms and contractions may either be sustained or may come and go. Movements are often repetitive and cause unusual, awkward and sometimes painful postures. Tremor (shaking) can also be a characteristic of some types of dystonia. Dystonia is thought to be a neurological condition (caused by underlying problems with the brain and nervous system). However, in most cases brain functions such as intelligence, memory and language remain unaffected (NHS Choices, n.pag., Source: www.nhs.uk).’

- *Footnote 19*: More recently, Ho et al. (2007) studied the effect of levodopa on speech, and more particularly, the idea that a parallel impact occurs on the speech and skeletal motor system (Ho et al. 5). During the “on phase”, they observed an increase in UPDRS motor performance score, which ‘was accompanied by an increase in the overall level of speech intensity (Ho et al. 5).’ Yet, while Ho et al. (2007) and other studies noticed a positive ‘dopaminergic effect on overall speech intensity’, other authors do not acknowledge this (Ho et al. 5). This discrepancy, however - as Ho et al. (2007) argue - could perhaps be partially due to ‘individual patients characteristics and as such it is therefore important to recognize the different speech profiles of PD patients, beyond that which can be captured in the UPDRS speech item (Ho et al.).’ Interestingly, they noticed a parallel between speech and limb motor control which was strengthened by the remarkable inverse reciprocity between speech rate and UPDRS (Ho et al. 6). As their results suggest, levodopa might ameliorate fluency problems yet only if the (“pre-intake”) speech is slow enough and an increase in intelligibility could be due to an augmented speech intensity, ‘but if compounded with a “festinating” fluency problem (which may be exaggerated by even greater intensity decay), there may not be a perceptible net improvement (Ho et al. 6).’

- *Footnote 23*: Both treatments have common effects, for example the ‘bilateral STN DBS and apomorphine injection each deactivated rCBF (regional cerebral blood flow) in sensorimotor areas of the neocortex, basal ganglia and cerebellum (Bradberry et al. 609).’ ‘The deactivated neocortical areas were the supplementary motor area (SMA), pre central gyrus (PrG), post central gyrus (PoG), and the deactivated basal ganglia structure was the putamen (Bradberry et al. 609).’ ‘Each treatment also increased regional cerebral blood flow (rCBF) in the superior parietal lobule (SBL) and midbrain (Bradberry et al. 609).’ However, Bradberry et al. (2012) report that each treatment has unique effects as well (Bradberry et al. 609). While they both decrease the regional cerebral blood flow of the aforementioned areas, deep brain stimulation ‘exhibites more widespread decreases, whereas the dopamine agonist (DA) therapy, in contrast, activates portions of these neocortical sensorimotor regions (Bradberry et al. 609-610).’ Furthermore, a subcortical activation of the globus pallidus as a consequence of DBS was observed, opposed to DA-therapy which deactivated comparatively wider regions of the putamen and cerebellum (Bradberry et al. 609-610). Interestingly, Bradberry et al. (2012) noticed that ‘DA-therapy and DBS had several reciprocal effects: in the posterolateral cerebellum, rCBF was increased by DBS but decreased by apomorphine, activity of the ventrolateral thalamus followed the same trend where it was increased by DBS but decreased by DA-therapy (Bradberry et al. 609-610).’
-
- *Footnote 24*: ‘A negative placebo effect as, for example, when patients taking medications experience adverse side effects unrelated to the specific pharmacological action of the drug. The nocebo effect is associated with the person's prior expectations of adverse effects from treatment as well as with conditioning in which the person learns from prior

experiences to associate a medication with certain somatic symptoms (MedicineNet, n.pag., Source: www.medterms.com).'

- *Footnote 25*: 'A surgical operation performed on the globus pallidus to destroy it. The purpose of this operation is to relieve involuntary movements or muscular rigidity, as, for example, in Parkinson's disease. [...] The globus pallidus is specifically part of what is called the lentiform nucleus which, in turn, is part of the striate body. The striate body is a component of the basal ganglia that can be seen as large masses of gray matter at the base of the cerebral hemispheres of the brain (MedicineNet, n.pag., Source: www.medterms.com).'

- *Footnote 26*: Auriacombe's study to check whether PD patients are impaired in the retrieval of semantic information or not, demonstrated that they have a retrieval deficit, not an alteration of the semantic memory itself (Colman 31). This means that PD patients have difficulties retrieving the underlying phonological form (Colman 31). These semantic processing deficits are related to a striatal dopamine deficiency (Colman 36). (This extract was taken from my bachelor paper but was originally written by Katrien Colman.)

- *Footnote 28*: 'The neuro-ophthalmology exam begins with a careful history of the patient's problem and a review of any neurological or medical problems that could be relevant. This is followed by an evaluation of the patient's vision and eye movements and typically includes testing of the visual acuity, color vision and visual fields. The eye will be examined under the microscope (slit lamp) with special attention paid to the optic nerve and retina in the back of the eye. In most cases, dilating drops will be administered to allow easy viewing of these important structures. The pressure and size of each eye may be

checked as well. Eye movements will be evaluated, which may include the use of prism lenses and special charts. In cases of unequal pupils, certain drops may be administered which help identify the cause of the problem. Visual field testing is conducted at a machine which displays lights in various parts of the visual world while the patient presses a button to acknowledge each light. In this way, patterns of visual field loss may emerge that can help lead to a diagnosis (Weill Cornell Medical College, n.pag., Source: http://weillcornelleye.org/services/neuro.html).'

5.2.2 Tables42

5.2.2.1 Table 1: Communicative functions (n = 18)

	A	B	C	D	E	F	G	H	I	J	K	L
CF	0,084	0,640	0,440	0,468	1,000	0,300	0,393	0,572	0,340	0,392	0,076	1,000

CF: Communicative functions, A: Request for an explanation, B: Request for a clarification, C: Describing emotions, D: Giving suggestions, E: Giving information, F: Giving instructions, G: Request information, H: Request of a certain action, I: Talking about other people's activities, J: Enquiring the wish of somebody, K: Give an explanation, L: Negotiate

5.2.2.2 Table2: Converstaional Skills (n = 18)

	A	B	C	D	E	F	G	H	I
CS	0,517	1,000	0,330	0,367	0,641	0,392	1,000	1,000	1,000

CS: Conversational Skills, A: Repeating (when unclear), B: Grabbing the attention of somebody, C: Reason of value judgement, D: Meaning of preceding sentences, E: Taking the foreknowledge into account, F: Talking outside of the conversation, G: Turn-taking, H: Opening a conversation, I: Closing a conversation

[42] Note: the parameters are translated into English

5.2.2.3 Table 3: Story-telling Skills (n = 18)

	A	B	C	D	E	F	G	H	I	J
SS	0,883	0,668	0,09	1,000	1,000	1,000	1,000	0,682	1,000	0,153

SS: Story-Telling Skills, A: Orientation of person, B: Orientation of place, C: Orientation of time, D: Structure, E: Core, F: End result, G: Ending a narrative, H: Causal connection, I: Reference[43], J: Discourse connectives

5.2.2.4 Table 4: Communicative functions of patients with a right motor lateralization (n =10)

	A	B	C	D	E	F	G	H	I	J	K	L
CF	0,284	0,701	0,818	0,8011	1,000	0,300	0,572	0,112	0,092	1,000	0,023	1,000

CF: Communicative functions, A: Request for an explanation, B: Request for a clarification, C: Describing emotions, D: Giving suggestions, E: Giving information, F: Giving instructions, G: Request information, H: Request of a certain action, I: Talking about other people's activities, J: Enquiring the wish of somebody, K: Give an explanation, L: Negotiate

5.2.2.5 Table 5: Statistical analysis of the parameter 'giving an explanation' of patients with a right motor lateralization (n= 10)

Parameter 'giving an explanation'	
Left on vs Right on	0,107
Left on vs Bilateral on	0,005
Left on vs Bilateral off	0,014
Right on vs Bilateral on	0,655
Right on vs Bilateral off	0,257
Bilateral off vs Bilateral on	0,414

[43] Parameter I: References was not examined in this paper as another study was conducted at the time

5.2.2.6 Table 6: Communicative functions of patients with a left motor lateralization (n = 8)

	A	B	C	D	E	F	G	H	I	J	K	L
CF	0,392	0,719	0,178	0,194	1,000	0,300	0,468	0,300	0,156	0,392	0,014	1,000

CF: Communicative functions, A: Request for an explanation, B: Request for a clarification, C: Describing emotions, D: Giving suggestions, E: Giving information, F: Giving instructions, G: Request information, H: Request of a certain action, I: Talking about other people's activities, J: Enquiring the wish of somebody, K: Give an explanation, L: Negotiate

5.2.2.7 Table 7: Statistical analysis of the parameter 'giving an explanation' of patients with a left motor lateralization (n= 8)

Parameter 'giving an explanation'	
Left on vs Right on	0,058
Left on vs Bilateral on	0,02
Left on vs Bilateral off	0,034
Right on vs Bilateral on	0,655
Right on vs Bilateral off	1,000
Bilateral off vs Bilateral on	0,564

5.2.2.8 Table 8: Conversational Skills of patients with a right motor lateralization (n = 10)

	A	B	C	D	E	F	G	H	I
CS	0,600	1,000	0,526	0,348	0,392	1,000	1,000	1,000	1,000

CS: Conversational Skills, A: Repeating (when unclear), B: Grabbing the attention of somebody, C: Reason of value judgement, D: Meaning of preceding sentences, E: Taking the foreknowledge into account, F: Talking outside of the conversation, G: Turn-taking, H: Opening a conversation, I: Closing a conversation

5.2.2.9 Table 9: Conversational Skills of patients with a left motor lateralization (n = 8)

	A	B	C	D	E	F	G	H	I
CS	0,881	1,000	0,492	0,525	0,370	0,368	1,000	1,000	1,000

CS: Conversational Skills, A: Repeating (when unclear), B: Grabbing the attention of somebody, C: Reason of value judgement, D: Meaning of preceding sentences, E: Taking the foreknowledge into account, F: Talking outside of the conversation, G: Turn-taking, H: Opening a conversation, I: Closing a conversation

5.2.2.10 Table 10: Story-telling Skills of patients with a right motor lateralization (n=10)

	A	B	C	D	E	F	G	H	I	J
SS	0,852	0,922	0,115	1,000	1,000	1,000	1,000	0,899	1,000	0,778

SS: Story-Telling Skills, A: Orientation of person, B: Orientation of place, C: Orientation of time, D: Structure, E: Core, F: End result, G: Ending a narrative, H: Causal connection, I: Reference[44], J: Discourse connectives

5.2.2.11 Table 11: Story-telling Skills of patients with a left motor lateralization (n=8)

	A	B	C	D	E	F	G	H	I	J
SS	0,767	0,551	0,276	1,000	1,000	1,000	1,000	0,530	1,000	0,190

SS: Story-Telling Skills, A: Orientation of person, B: Orientation of place, C: Orientation of time, D: Structure, E: Core, F: End result, G: Ending a narrative, H: Causal connection, I: Reference[45], J: Discourse connectives

[44] Parameter I: References was not examined in this paper as another study was conducted at the time

[45] Parameter I: References was not examined in this paper as another study was conducted at the time

5.2.3 Nijmeegse Pragmatiektest (Copied from original textbook)

I COMMUNICATIEVE FUNCTIES	
VERZOEK OM UITLEG	Vragen om een verklaring waardoor iets duidelijk wordt
VERZOEK OM VERDUIDELIJKING	Vragen om een nadere verklaring
BESCHRIJVEN VAN GEVOELENS	Verwoorden van emoties en gevoelens
SUGGESTIE GEVEN	Aandragen van ideeën waardoor een oplossing gevonden wordt
INFORMATIE GEVEN	Geven van nieuwe inlichtingen om een beeld van iets te krijgen
INSTRUCTIE GEVEN	geven van opdrachten die opgevolgd moeten worden
VRAGEN OM INFORMATIE	Vragen om inlichtingen om bepaalde zaken uit te sluiten en een helder beeld te krijgen
VRAGEN OM ACTIE	Verzoek tot het uitvoeren van een handeling
PRATEN OVER WAT ANDEREN DOEN	Praten over de bezigheden van anderen
VRAGEN NAAR WENS	Vragen naar de wens van een ander
VERKLARING GEVEN	De gevolgen van iets duidelijk maken
ONDERHANDELEN	Proberen het met elkaar eens te worden

(Embrechts et al. n. pag.)

II CONVERSATIEVAARDIGHEDEN	
HERHALING BIJ ONDUIDELIJKHEID	Iets opnieuw zeggen of verduidelijken
GERICHT ROEPEN OM AANDACHT	Expliciet roepen van één persoon van wie men aandacht wil
REDEN GEVEN M.B.T WAARDEOORDEEL	Motiveren van een mening over iets
BETEKENIS VOORAFGAANDE ZINNEN	Hetgeen verteld wordt heeft een logisch verband met voorafgaande zinnen
REKENING HOUDEN MET VOORKENNIS VAN DE LUISTERAAR	Wanneer iets ter sprake wordt gebracht wat bij de luisteraar niet bekend is, wordt een toelichting gegeven
PRATEN BUITEN HET HIER-EN-NU	Praten over iets dat niet in de situatie aanwezig is
BEURTWISSELING	Om de beurt reageren (verbaal)
OPENEN VAN CONTACT	Groeten of zich voorstellen waardoor een gesprek wordt begonnen
BEËINDIGEN VAN CONTACT	Groeten of afscheid nemen waardoor een gesprek wordt beëindigd

(Embrechts et al. n. pag.)

III VERHAALOPBOUW	
ORIËNTATIE VAN PERSOON	Aangeven over welke hoofdfiguur het verhaal gaat
ORIËNTATIE VAN PLAATS	Aangeven waar het verhaal zich afpseelt
ORIËNTATIE VAN TIJD	Aangeven op welk tijdstip de gebeurtenis plaatsvindt
STRUCTUUR	Aangeven van de opbouw of de lijn van het verhaal, waardoor het geheel logisch en duidelijk wordt
KERN	Aaangeven wat het belangrijkste deel van het verhaal is
EINDRESULTAAT	Vertellen van de afloop van het verhaal
AFRONDING	Aangeven dat het verhaal ten einde is
CAUSAAL VERBAND	Aangeven van een oorzakelijk verband tussen twee aspecten
REFERENTIE	Verwijzen naar een ander woord uit de context
CONJUNCTIE	Verbinden van zinnen door middel van een voegwoord

(Embrechts et al. n. pag.)

5.2.4 Individual patient characteristics

5.2.4.1 Table 12: Patient characteristics

Patient	Motor lateralization	Age	PD duration (years)	Time after DBS (months)	Moca-test	Lanugage dominant hemisphere
1	Right	66	13	6	23	Left
2	Right	71	19	35	27	Left
3	Right	71	15	40	23	Left
4	Left	57	14	7	25	Left
5	Left	47	12	5	25	Left
6	Left	53	16	80	28	Left
7	Right	46	13	6	28	Left
8	Right	62	12	3	28	Left
9	Left	66	8	6	28	Left
10	Right	69	10	12	25	Left
11	Right	56	16	12	25	Left

12	Right	57	16	93	27	Left
13	Right	54	10	20	21	Left
14	Left	41	13	106	23	Left
15	Right	58	10	37	21	Left
16	Left	60	14	36	26	Left
17	Left	57	14	65	22	Left
18	Left	73	15	87	21	Left

5.2.4.2 Table 13: Stimulation parameters

Patient	Left stimulator				Right stimulator			
	Pole combination	A	Pulse width (µs)	Freq (Hz)	Pole combination	A	Pulse width (µs)	Freq (Hz)
1	1-case+	1,80	90,00	130,00	9-case+	2,20	90,00	130,00
2	3-case+	3,70	90,00	130,00	10+11-	2,50	60,00	130,00
3	0+1-2-3+	3,10	60,00	130,00	10-case+	3,10	60,00	130,00
4	1-case+	3,00	60,00	130,00	9-case+	3,00	60,00	130,00
5	0-1-	2,20	90,00	130,00	10-11-	2,60	90,00	130,00
6	2-case+	3,50	60,00	160,00	11-case+	2,00	60,00	160,00
7	2-	2,30	90,00	130,00	10+,11-	2,90	90,00	130,00
8	1-	3,70	90,00	130,00	9+,10-,11-	4,00	90,00	130,00
9	1-,2+	3,30	60,00	130,00	9-,10-	2,50	90,00	130,00
10	1-	1,50	90,00	130,00	10-	0,90	90,00	130,00
11	2-3-	2,50	90,00	130,00	9-10-11+	2,70	90,00	130,00
12	1-2+	5,30	90,00	130,00	9-10-11+	5,00	90,00	130,00
13	2-3-case+	1,80	90,00	130,00	8+9-10-11+	3,00	90,00	130,00
14	1-2+	2,00	90,00	130,00	10-case+	1,10	60,00	130,00
15	1-2+	4,50	90,00	130,00	9-case+	4,00	90,00	130,00
16	1-case+	2,30	90,00	130,00	9-10-	2,30	90,00	130,00
17	3+2-	4,00	90,00	130,00	9-11+	4,30	90,00	130,00
18	1-2-	2,90	60,00	130,00	10-case+	3,30	60,00	130,00

A: amplitude (Volt), Freq: Frequency (Hertz)

5.2.4.3 Table 14: Speech intelligibility (NSVO test results)

Patient	Bilateral ON	Bilateral OFF	Left ON	Right ON
1	95%	98%	98%	93%
2	100%	98%	96%	99%
3	92%	98%	95%	91%
4	98%	94%	97%	99%
5	96%	95%	100%	99%
6	88%	87%	91%	85%
7	100%	98%	99%	100%
8	95%	92%	98%	95%
9	93%	99%	97%	96%
10	97%	98%	98%	100%
11	98%	98%	93%	97%
12	83%	76%	83%	80%
13	98%	98%	97%	97%
14	86%	94%	94%	93%
15	99%	97%	100%	99%
16	90%	90%	98%	95%
17	83%	81%	71%	80%
18	98%	98%	100%	97%

Part 2: Transcriptions and data

The transcriptions and other data such as the rough results (before statistical analysis) are included on a separate CD.