Cognitive aspects of deep brain stimulation

A five-year follow-up study of patients with Parkinson’s disease

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Summary

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Abstract:

Parkinson’s disease (PD) is a progressive neurological disorder that influences a wide range of functions, including cognition. Over the past 30 years, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been successful in managing the neurological symptoms of PD. However, less is known about the cognitive consequences of this treatment method. This thesis aimed to investigate changes in cognition following STN DBS, and to identify pre-operative characteristics influencing these changes.

The current study is part of the NORSTIM study, a self-controlled single-center study of $n = 55$ PD patients treated at Oslo University Hospital (OUH) - Rikshospitalet. This thesis is mainly based on results from neuropsychological assessments that were carried out before, 1 year after and 5 years after STN DBS surgery. The significance of changes in cognitive functions across measurement points were analyzed using ANOVA for repeated measures, and pairwise comparisons were made using the paired-samples $t$-test. Exploratory correlation analysis and linear simple regression were used to identify predictors of change in cognitive function.

Overall, the decline of function in the years following DBS surgery was more rapid than that of the normative population. A more challenging question to answer was the degree to which the observed decline differed from the cognitive changes in normally developing PD. The results indicate that processing speed, executive functions (inhibition and switching), word generation and delayed verbal recall were negatively affected by STN DBS. The relationships between these functions are dynamic and complex, raising the question of which functions are directly affected by STN DBS, and which are indirectly influenced by the decline of other functions. It seems that executive functions play a central role in these interactions, consistent with theories of underlying mechanisms of change of cognition in PD. In addition, the current
study supports the recurring finding of reduced verbal fluency following STN DBS. Age and duration of disease were the strongest predictors of cognitive outcome, affecting change in motor function, attention/working memory, visual learning/memory and executive function in the year following STN DBS.

In conclusion, the results of the current study indicate that STN DBS treatment adversely affects some, but not all, domains of cognitive function. Further, results indicate that age and duration of disease are the most important pre-operative characteristics to take into account when considering patients for STN DBS treatment, from a cognitive point of view. However, further research is needed to separate the effects of STN DBS on cognitive function from normal progression of PD.
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1 Introduction

1.1 Background

1.1.1 The Shaking Palsy

Parkinson’s disease is a progressive neurological disorder that influences the lives of patients and caregivers to a large extent (Jankovic, 2008). In 1817, James Parkinson published a monograph called “Essay on the Shaking Palsy.” In it, he described the collection of symptoms that were to be known as Parkinson’s disease: “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured” (p. 225).

The motor symptoms described by Parkinson in 1817 are still regarded as cardinal features of Parkinson’s disease (PD), however the past 200 years have brought increased knowledge about the complex and diverse symptomatic picture of this disease. James Parkinson’s claim about “the senses and intellects being uninjured” is no longer supported in the medical community. Today, PD is known to have diverse clinical features, affecting a range of motor-, sensory- and cognitive functions, resulting in serious implications for daily functioning for affected individuals (Lezak, Howieson, Bigler & Tranel, 2012, p. 272; Jankovic, 2008). Nevertheless, the vast majority of research on PD so far has focused on motor function (Chaudhuri & Schapira, 2009).

Parkinson wrote that “the unhappy sufferer has considered it an evil, from the domination of which he had no prospect of escape” (1817, p. 223). Today, increased understanding of the underlying mechanisms of PD has led to the development of new treatment methods. Although there still does not exist a cure for the condition, methods have been developed that can alleviate symptoms and delay the progress of the disease (Hammond, Bergman & Brown, 2007). These methods largely aim at treating the motor symptoms of PD. In comparison, the effects of treatment on non-motor symptoms have received little attention (Chaudhuri & Schapira, 2009). Standard treatment for PD is pharmaceutical treatment with Levodopa, which alleviates motor symptoms by increasing the production of dopamine (LeWitt & Fahn, 2016). However, Levodopa is not able to alleviate the full spectrum of PD symptoms, and its
effect decreases over time, resulting in the need for gradually increasing doses as the disease progresses. Possible side effects of long-term use of Levodopa include disabling motor fluctuations and dyskinesias (Olanow & Stocchi, 2017), in addition to non-motor effects such as confusion, delirium and psychotic symptoms (Combs & Cox, 2017). One of the most promising alternatives to pharmaceutical treatment is surgical treatment with deep brain stimulation (DBS), the effects of which will be the focus of this thesis.

The primary aim of this thesis is to identify cognitive changes related to DBS of the subthalamic nucleus (STN). The thesis will focus on cognitive function investigated through neuropsychological methods. The association between Parkinson’s disease and other psychological phenomena is an important bordering field of research, however this aspect will not be reviewed in the current thesis. Clinical features of Parkinson’s disease, information about DBS STN and relevant research findings will be reviewed presently, followed by a presentation of the thesis’ research questions and hypotheses.

1.2 Parkinson’s disease

1.2.1 Etiology and epidemiology

Parkinson’s disease (PD) is the most common form of parkinsonism, a broader term used for conditions showing similar symptoms to PD. PD is an idiopathic disorder, meaning its cause is unknown. Other forms of parkinsonism can have known causes, such as toxic exposure or restricted blood supply to the brain (Dauer & Przedborski, 2003). This thesis will focus exclusively on PD.

In an extensive review of the epidemiological data on PD, de Lau and Breteler (2006) found that the prevalence of PD in industrialized countries is about 0.3% in the entire population, increasing to 1% when only considering those over 60 years of age. It is highly uncommon before the age of 50, and the prevalence increases sharply after the age of 60, ending at 4% in the highest age groups.

Although the underlying mechanisms of PD are not fully understood, it is broadly recognized that the condition is associated with depletion of dopamine in the basal ganglia and loss of cells in the substantia nigra, a small nucleus essential for the production of dopamine (Schapira, Chaudhuri & Jenner, 2017). The neuronal loss in brain stem nuclei in PD cooccurs
with the formation of Lewy bodies, a pathologic collection of intraneuronal proteins (Årsland, 2002; Walker, Possin, Boeve & Aarsland, 2015). Although PD is considered mainly to be associated with a disturbance in dopamine production, it involves several other neurotransmitters and pathological characteristics. Pathogenic mechanisms that have been suggested as contributing factors to the observed neurodegeneration in PD include genetic mutations, inflammation and mitochondrial dysfunction (Tekin & Cummings, 2002; Jankovic, 2008, p. 368; Dauer & Przedborski, 2003).

The underlying mechanisms of cognitive decline in PD seem to involve a group of brain circuits commonly called the frontostriatal circuits. The discovery of these circuits came from observations of similarities between neuropsychiatric symptoms emerging after damage to subcortical brain structures and frontal areas. Anatomical investigations later defined five parallel frontal-subcortical circuits. These connect specific areas of the frontal cortex to the striatum, the globus pallidus/substantia nigra, the subthalamic nucleus and the thalamus (Marceglia, Fumagalli & Priori, 2011; Alexander, DeLong & Strick, 1986). Two of the frontostriatal circuits are involved in motor functions, and two are believed to be associative, influencing executive functions and social behavior. The fifth is a limbic circuit, regulating emotional and motivational states. Neurotransmitters like dopamine, acetylcholine, glutamate and serotonin regulate the transmission of signals through these circuits (Tekin & Cummings, 2002). It appears that disruption of the frontostriatal circuits has a significant influence on behavior and cognition in patients with PD, especially on executive functions (Zgaljardic, Borod, Foldi & Mattis, 2003; O’Callaghan & Lewis, 2017). Lewy body degeneration and Alzheimer-type cortical changes have also been suggested as underlying mechanisms of cognitive dysfunction in PD (O’Callaghan & Lewis, 2017; Emre, 2003), in addition to inflammatory changes and genetic factors (Aarsland et al., 2017). However, a thorough review of the etiology and pathophysiology of PD is beyond the scope of this thesis.

1.2.2 Clinical features

The four motor symptoms bradykinesia (slow movement), tremors, postural instability and rigidity are recognized as cardinal symptoms of PD (Schapira, Chaudhuri & Jenner, 2017). Other common motor symptoms include flexed posture and freezing (Limousin et al., 1998; Jankovic, 2008). Cognitive impairment is an important group of non-motor symptoms, and is discussed in depth below. The most common neuropsychiatric symptoms associated with PD
are depression, apathy, anhedonia and fatigue (Jankovic, 2008). Some patients experience sensory symptoms such as disturbed sense of smell, taste or touch, or pain in the back and shoulder. In addition, autonomic dysfunction and sleep disorders sometimes occur in PD (Chaudhuri & Schapira, 2009). There is no definitive diagnostic test for PD. Diagnosis is therefore based on clinical criteria (Postuma et al., 2015).

**Cognitive dysfunction in Parkinson’s disease**

It is estimated that 25-30% of PD patients have some degree of cognitive impairment. However, estimates vary with the use of different assessment tools, levels of medication at the time of assessment and variations in disease progression among the patients studied (Lezak, 2012). For instance, the Sydney Multicenter Study of PD reported that 84% of evaluated patients showed cognitive decline when following the same group of patients for 15 years (Hely, Morris, Reid & Trafficante, 2005).

When discussing cognitive decline in PD it is important to distinguish between the cognitive impairments associated with a PD diagnosis and the global impairments seen in Parkinson’s disease dementia (PD-D). The former is considered to be caused mainly by dopaminergic disruptions of frontostriatal networks, while the latter is associated with more posterior cortical deficits and impaired daily functioning (O’Callaghan & Lewis, 2017). Structural and functional imaging studies, as well as electrophysiological studies, have found differences between PD and PD-D (Emre et al. 2007). PD-D shares many pathological and clinical features with Dementia with Lewy bodies, and some consider the two to be part of a spectrum of Lewy body disease (McKeith & Burn, 2000). With old age and advanced progression of PD, it becomes more difficult to differentiate normal cognitive decline from PD-D (Hely et al., 2008). This thesis will focus on the normal cognitive decline seen in PD.

**Executive functions**

Executive functions (EFs) are a group of top-down processes that regulate goal-directed behavior and cognition (Diamond, 2013; Dirnberger & Jahanshahi, 2013). Based on factor analyses of test methods assessing EF, Miyake et al. (2000) postulated three dimensions of core EFs within the cognitive domain; mental set shifting (shifting), information updating and monitoring (updating/working memory), and inhibition of prepotent responses (inhibition). The three domains are not completely independent from each other, but still clearly
distinguishable. When combined, they make up higher order EFs such as strategic planning, reasoning and problem solving (Diamond, 2013).

Impairment of executive functions is the most common and prominent type of cognitive deficit seen in the PD population (Zgaljardic et al., 2003). These impairments typically appear in the early stages of the disease, commonly considered to be caused by depletion of dopaminergic cells in the substantia nigra, which affects executive functioning by reducing the connectivity between the striatum and dorsolateral prefrontal cortex (O’Callaghan, Bertoux & Hornberger, 2014; Schapira, Chaudhuri & Jenner, 2017).

Studies using neuropsychological testing have shown that PD patients struggle with several aspects of EFs, including strategy shifting, performance maintenance, self-monitoring, dual task performance, inhibition, strategic planning, decision making and problem solving (Robbins & Cools, 2014; Dirnberger & Jahanshahi, 2013; Papagno & Trojano, 2017). Some argue that the executive deficits seen in PD are made up of more pronounced impairments in attentional aspects than in abstract reasoning and problem solving. For instance, patients often struggle with internally cued behavior and shifting attention to novel stimuli (Emre, 2003; Kudlicka, Clare & Hindle, 2013). A proposed explanation for the observed executive dysfunction in PD is frontostriatal networks failing to maintain the underlying balance between inhibition and facilitation, thus affecting response thresholds of higher order executive functions (Jahanshahi, Obeso, Rothwell & Obeso, 2015). Different conceptualizations of EFs complicate the understanding of the specific pattern of executive dysfunction in PD (Papagno & Trojano, 2017; Kudlicka, A., Clare, L. & Hindle, J. V., 2011).

**Attention**

Attention can be defined as the differential allocation of information processing resources, with allocation taking place on different levels of awareness. Underlying functions include covert and overt attention to space, sensory modalities, tasks and other external and internal stimuli (Klein & Lawrence, 2012). Attention is a basic cognitive function which is necessary for optimal performance of other cognitive functions. The relationship between attention and executive function is particularly complicated. Some see the two as separate cognitive functions (e.g. Diamond, 2013), while others see attention as a subcategory of executive function (e.g. Sheree & Thomas, 2013). Certain attention-related functions are more closely related to executive function than others, for instance selective attention, suppression of stimuli and working memory (Miyake et al., 2000; Lehto, Juujärvi, Kooistra & Pulkkinen, 2011).
2003). In this thesis, memory span and working memory are classified as attentional functions, while selective attention and shifting are classified as executive functions.

Neuropsychological studies on attentional functioning in the PD population have found impairments in visuospatial attention, though it is uncertain whether these impairments reflect disruptions in oculomotor or higher-order cognitive processes (Norton et al., 2016). Memory span and working memory are often assessed using different conditions of digit span tests. Most studies assessing memory span have found performances within normal limits for the PD patient population. However, performance on reversed digit span seems to be poor relative to the original condition, suggesting difficulties in working memory function (Whitehead & Brown, 2009). A study on working memory in PD found impairments on both spatial and verbal working memory in patients with severe clinical symptoms. Unmedicated patients with mild clinical symptoms performed within normal limits, while comparable medicated patients showed reductions in performance on spatial working memory (Owen et al., 1997). Another study showed impairments of both spatial and verbal working memory. In addition, the types of errors that were made were affected by test subjects being on or off medication (Levodopa), suggesting influence by dopamine depletion in the striatum on working memory function in PD (Uitvlugt, Pleskac & Ravizza, 2015; Papago & Trojano, 2017).

Memory and Learning
Neuropsychological studies on memory and learning in the PD population have yielded inconclusive results, and researchers have suggested that this could be a particularly heterogeneous area of cognitive function within this patient population (Lezak, 2012). Impaired episodic memory is common in early PD, and a possible risk factor for future cognitive decline (Papago & Trojano, 2017). In some studies, free recall seems to be impaired relative to cued recall, recognition, learning and long-term retention (Costa et al., 2014; Whitehead & Brown, 2009). This could indicate a specific problem with the retrieval process. It has been suggested that deficits in executive functions could explain the observed difference in performance on memory tasks (Dubois & Pillon, 1997). Specifically, some argue that the inability to generate retrieval strategies or initiate retrieval processes could explain the improvement of results when using cues (Whitehead & Brown, 2009). However, other studies have found no improvement of performance when using cueing (Ding et al., 2015; Massman, Delis, Butters, Levin & Salmon, 1990).
**Verbal functions**

Several aspects of verbal functions, such as syntax, grammar and vocabulary, show little decline in PD patients, although the general amount of verbal communication is often reduced. A possible explanation is that neurological symptoms of PD lead to issues with pronunciation, speech volume and emotional communication (Barnish et al., 2017). In addition, PD patients can have difficulties understanding complex sentences, which has been attributed to impairments in working memory (Lezak, 2012).

An exception to the relatively intact cognitive verbal functions in PD seems to be verbal fluency. A meta-analysis of verbal fluency performance in PD patients compared to healthy controls showed moderate impairment of both phonemic and semantic fluency, with significantly more impairment of semantic relative to phonemic fluency (Henry & Crawford, 2004). Many argue that word generation has a strong executive component, and therefore categorize these functions as part of the executive domain (Whiteside et al., 2015). The phonemic condition of verbal fluency is considered to have a stronger executive component than the semantic condition (Lezak, 2012). Keeping this in mind, the finding of semantic fluency possibly being more impaired than phonemic fluency in the PD population is surprising, as executive impairments are common in this group. The authors attribute this finding to impairments of semantic memory (Henry & Crawford, 2004).

**Visuospatial functions**

Visuospatial impairments are established findings in PD patients, including problems with spatial orientation, construction, analysis and discrimination (Seichepine, Neargarder, Davidsdottir, Reynolds & Cronin-Golomb, 2015). Visuospatial dysfunction is more common in later stages in PD, and it has been postulated that early emergence of these symptoms is an indicator of more serious cognitive decline as the disease progresses (Mills et al., 2016; Dubois & Pillon, 1997). Findings of visuospatial impairments in PD are complicated by motor function, perceptual defects and executive components such as strategic planning when copying a complex figure (Papagno & Trojano, 2017). It is challenging to control for these components, and therefore it is uncertain how much of the task performance can be attributed to visuospatial impairment (Dubois & Pillon, 1997; Whitehead & Brown, 2009).
1.3 Deep brain stimulation (DBS)

1.3.1 Background

In 1870, Fritsch & Hitzig challenged the established notion that the cortex was non-excitable by physiological stimuli. By stimulating the motor cortex in dogs, they demonstrated localization of functions in the cortex, and the usefulness of electrical stimulation in affecting these functions (Carlson & Devinsky, 2009). Since then, electrical stimulation has been used to map cognitive functions in the brain, both in order to increase our general understanding of brain-behavior relationships and to improve the precision of neurosurgery using pre-operative brain mapping (Perlmutter & Mink, 2006). The development of methods to treat neurological conditions by stimulating deeper brain structures began in the 1960’s (Pollak et al, 2002). Since then, DBS has been used to alleviate symptoms in neurological disorders such as dystonia, essential tremor, Tourette Syndrome and PD, but also in other types of conditions such as treatment-resistant depression and Obsessive Compulsive Disorder (Mayberg et al. 2005; Perlmutter & Mink, 2006).

The surgical treatment of Parkinson’s disease through DBS has become increasingly established as a recommended form of treatment for patients not benefitting sufficiently from pharmacological treatments (Levodopa). The surgical procedure consists of electrodes being
placed deep within the brain, continually emitting high-frequency stimulation and regulating the activity of the targeted nuclei (Mosley & March, 2015). DBS was first applied mainly to the ventral intermediate nucleus of the thalamus (Vim), as this was considered the most promising target for alleviation of tremors (Pollak et al., 2002). Later, in the 1990’s, the subthalamic nucleus (STN) and the internal globus pallidus (GPi) became more common targets for stimulation, as research showed that stimulation of the STN or GPi resulted in alleviation of the main parkinsonian motor symptoms; bradykinesia, tremors and rigidity (Limousin et al., 1998; Siegfried & Lippitz, 1994). Improvement and management of these motor symptoms is still the main aim of treatment with DBS (Foltynie & Hariz, 2010).

1.3.2 The subthalamic nucleus

This thesis will focus on bilateral DBS of the STN, which is now the most frequent target of DBS surgery in PD (Foltynie & Hariz, 2010). The STN mainly consists of excitatory projection neurons, and it has an anatomically central position within the basal ganglia (Fife et al., 2017; Temel et al., 2005). In the 1980’s, it was believed that the STN was simply a relay station for basal ganglia thalamocortical circuits, however it later became known as an important regulator of these circuits (Temel, Blokland, Steinbusch & Visser-Vandewalle, 2005; Witt, Daniels, Volkmann, 2012; Marceglia et al., 2011).

![Subthalamic nucleus and its connections](image)

Functional anatomical studies in both animals and humans suggest that the STN is divided into three functional areas (figure 2), with limbic, associative and motor regions respectively occupying the anterior, medial and posterior areas (Lambert et al., 2012). These subdivisions

Abbreviations: GPi: internal globus pallidus; GPe: external globus pallidus; SNr: substantia nigra pars reticulata.

functionally correspond to the five frontostriatal circuits that were presented in the section on the etiology of cognitive decline in PD earlier in this thesis. The two motor circuits originate in the primary motor, premotor and somatosensory cortical areas. The two associative circuits originate in the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex. Lastly, the limbic circuit comes from the limbic and paralimbic cortices via the striatum (Marceglia et al., 2011). As illustrated in figure 3, the STN receives both direct and indirect input from these areas (Peterson, 2016, p. 30). The close connectivity between the STN and these diverse cortical areas makes the STN central in the regulation of a wide range of functions, including motor functions, emotions, behavior and cognition (Temel et al., 2005). It has been suggested that inhibitory control is a fundamental function of the STN. Specifically, it is hypothesized that the STN plays an important role in inhibition and regulation of response thresholds during response selection under conflict or time pressure (Jahanshahi, Obeso, Baunez, Alegre & Krack, 2015).

![Figure 3 An illustration of cortico-subthalamic projections.](image)


### 1.3.3 Effects on cognitive function

Although STN DBS is becoming an increasingly popular treatment method for PD, its effect on cognitive function remains unclear (Temel et al., 2006). Most of the studies on the effect
of STN DBS so far have focused on neurological outcomes, especially motor function, and neuropsychological assessment has commonly not been included in already comprehensive treatment and research protocols. The studies that have included cognitive measures have shown variable results, and few certain conclusions have been drawn, partially due to small effect sizes (Nassery et al., 2016). Several of these studies have faced challenges with low participant numbers, short follow-up periods and difficulties acquiring suitable control groups (Xie, Meng, Xiao, Zhang & Zhang, 2016). In addition, studies have used different assessment batteries and different conceptualizations of cognitive domains, complicating the comparison of results and discovery of trends across studies. Researchers have therefore highlighted the need for further studies to increase knowledge about the exact mechanisms of cognitive deterioration (Williams et al., 2011; Xie et al., 2016).

The vast majority of research on the effect of STN DBS on cognitive function consists of self-control studies, making it harder to separate the effect of the treatment from normal PD-related cognitive decline. The only meta-analysis that exclusively included controlled trials (Xie et al., 2016) included 10 studies in their analysis, half of them following up only six months post-surgery, and no more than one study following up for longer than two years. In one study, 36% of STN DBS patients showed a profile of cognitive decline compared with a control group (Smeding, Speelman, Huizenga, Schuurman & Schmand, 2011).

**Executive functions**

The meta-analysis of Xie et al. (2016), using only controlled trials, found subtle decline on measures of executive function. This finding is generally supported among other studies (Saint-Cyr, Trépanier, Kumar, Lozano & Lang, 2000; Woods et al., 2002; Combs et al., 2015; Halpern et al., 2008). As discussed previously in this thesis, the conceptualization of executive function often differs between studies, complicating the interpretation of nuances in the research findings. Most studies base their executive function results on variations of the Stroop test. A study by Pillon et al. (2000) however, investigated the construct using three different tests; Wisconsin Card Sorting test (WCST), Color-Word Interference Test 3 (CWIT-3) and the Trail Making Test B (TMT B). They found modest, but significant decline on certain aspects of cognitive flexibility and mental capacity (TMT B), but no significant change for other aspects such as adapting to feedback (WCST), inhibition (CWIT and WCST), strategic planning (WCST) or problem solving (WCST). Saint-Cyr et al. (2000) suggest that age is an important factor when it comes to the effect of STN DBS on executive
functions, with higher age at the time of surgery being associated with more severe executive decline.

Processing speed
When it comes to the domain of processing speed, the results are inconclusive. Several studies found reduced performance (Williams et al., 2011; Pillon et al., 2000; Combs et al., 2015), though others reported no significant change (Xie et al., 2016). However, the interpretation of these results is made particularly difficult by the non-cognitive symptoms of PD. Common neuropsychological tests within the processing speed domain involve the need for rapid hand/arm movement or speech production, both of which are often impaired in PD, and influenced by STN DBS (Schapira, Chaudhuri & Jenner, 2017; Pollak et al, 2002; Halpern, Rick, Danish, Grossman & Baltuch, 2008). This problem is not unique to processing speed, but perhaps more consequential for these test results compared with other cognitive domains.

Attention/working memory
Studies assessing memory span using digit span tests have found no significant change in performance after treatment with STN DBS (Morrison et al., 2004). However, several studies have found significant declines in working memory performance (Saint-Cyr et al., 2000), typically assessed using reversed digit span. Conversely, the meta-analysis by Xie et al. (2016) found no significant change in working memory, and they receive support for this from studies outside their own analysis (e.g. Pillon et al., 2000). It is difficult to know whether the decline seen in the self-controlled studies should be attributed to STN DBS or to normal progression of the disease, especially when considering that some reduction in working memory is common in PD (Whitehead & Brown, 2009).

Word generation
A reduction in verbal fluency performance is perhaps the most consistent finding both in controlled (Cilia et al., 2007; Williams et al., 2011) and uncontrolled trials (Woods, Fields & Tröster, 2002; Saint-Cyr et al., 2000; Combs et al., 2015; Wu, Han, Sun, Hu & Wang, 2014). Phonemic fluency seems to show relatively more decline than semantic fluency, consistent with the idea of a strong executive component in phonemic word generation (Xie et al., 2016). However, a study with over 60 participants, a relatively large number for this type of clinical trial, found impairment only for semantic fluency, with no significant decline in phonemic word generation (Pillon et al., 2000).
Learning/memory

The research results on learning and memory functions following STN DBS are heterogeneous, both when it comes to verbal vs. visuospatial memory and learning vs. recall. For verbal memory, the meta-analysis by Xie et al. (2016) found reduced performances for both learning and delayed recall. Other studies support the finding of impaired long-term recall, but show no decline when it comes to learning (Saint-Cyr et al., 2000; Morrison et al., 2004; Halpern et al., 2008). A relevant question here is the duration of observed decline in verbal memory, as a review of the literature indicates that impairments seen after three months are often back within normal limits when a year has passed (Woods et al., 2002). The research on visuospatial memory after STN DBS seems to show less conflicting results. Learning, delayed recall and recognition are found to be modestly reduced in the majority of studies (Williams et al., 2011; Combs et al., 2015). However, some studies found impairments in encoding of visuospatial material and not in delayed recall (Saint-Cyr et al., 2000).

Progression of cognitive effects

A meta-analysis by Wu et al. (2014) compared cognitive effects found in studies with short (6 months to 1 year), medium (2-5 years) and long (5-9 years) follow-up periods. They found that verbal fluency progressively decreased throughout all stages. Executive function was unchanged in the intermediate stage, but declined in the early and late stages. The results were inconclusive regarding the progression of function in the areas of memory, attention, psychomotor speed and visuospatial function. As the meta-analysis included both self-controlled and controlled studies, certain conclusions cannot be drawn about the cause of the observed development of cognitive functions after DBS surgery. The meta-analysis of controlled studies by Xie et al. (2016) found decrease of global cognition, memory, verbal fluency and executive function in the follow-up from 6 months to 2 years after surgery, but no significant decline in the areas of attention, reasoning and information processing.

1.3.4 Patient selection for DBS

It is widely recognized within the medical community that appropriate selection of patients for DBS is essential for successful treatment results (Chang & Chou, 2006; Foltynie & Hariz, 2010). In order to accomplish this, several criteria for patient selection have been suggested. Firstly, it is important to review the patient’s medical history to confirm the diagnosis of
idiopathic PD. Secondly, there should be an assessment of which symptoms are negatively influencing the patient’s quality of life, as not all types of symptoms can be alleviated through DBS. The influence of dopaminergic treatments such as DBS on cognitive, psychiatric and autonomic symptoms is uncertain (Combs et al., 2015; Chaudhuri & Schapira, 2009; Castrioto, Lhommée, Moro & Krack, 2014, Wang et al., 2015). Thirdly, each case should be evaluated with respect to factors associated with unfavorable outcomes. These include behavioral problems, recent or previous psychiatric illness, poor speech articulation and a history of poor response to Levodopa (Chang & Chou, 2006). The presence of these pre-surgical factors is associated with risk of deterioration of the disease and reduced quality of life. Some degree of cognitive dysfunction is common in patients considered for DBS, however more significant cognitive dysfunction, including dementia, is considered a red flag for DBS surgery (Foltynie & Hariz, 2010).

Relevant factors when considering patients for DBS are age and duration of illness. Due to risks associated with the surgery, and uncertainty regarding possible negative consequences on an individual basis, it is customary to wait until the disease can no longer be managed satisfactorily with Levodopa (Mosley & March, 2015). The German-French EARLYSTIM trial looked at effects of DBS STN compared to treatment as usual with Levodopa in patients with a mean age of 52 and mean disease duration 7.5 years, which is a relatively young patient sample in this context. The two-year trial showed significantly higher scores on quality of life and less motor disability for the DBS-group than the Levodopa-group (EARLYSTIM Study Group, 2013). The results have been highly debated, and challenges and benefits of early DBS have been pointed out, as will be discussed later in this thesis. The many factors complicating the decision process have led to pre-surgical procedures that include thorough considerations of the risk-to-benefit ratio in each individual case (Mestre et al., 2014).

1.4 The current study

1.4.1 Research questions

The primary goal of this thesis is to investigate the effect of DBS-treatment on neuropsychological functioning at one and five years post-surgery compared to baseline level. To this end, the following research questions will be discussed.
• Change in cognitive functioning in PD patients 1 and 5 years after DBS surgery compared to pre-surgery cognitive function, giving weight to potential negative consequences of STN stimulation with respect to cognitive functions.

• Pre-operative factors predicting potential negative consequences of STN stimulation, and characteristics of those patients profiting and not profiting from DBS treatment from a cognitive point of view.

1.4.2 Hypotheses

In this study, the development of cognitive function is followed for a considerably longer period of time post-surgery than in most studies. This allows for observations of clearer negative cognitive trends, or conversely, the reversal of temporary negative effects post-surgery. After a review of the literature, the following hypotheses are made about the results of the current study:

• It is hypothesized that there will be a decline in some cognitive functions after STN DBS, however not in all of the measured constructs. Executive functions and word generation are most likely to be reduced. Within word generation, it is hypothesized that phonemic fluency will be relatively more impaired than semantic fluency. When it comes to attentional functions, working memory is likely to decline. The other functions; processing speed, verbal learning/memory and visual learning/memory, are believed to show small or non-significant changes.

• Pre-operative factors that are likely to predict potential negative consequences of STN DBS are age and duration of disease at the time of surgery. In addition, it is hypothesized that poorer self-reported psychological well-being and quality of life pre-surgery will be associated with stronger cognitive decline post-surgery.
2 Methods

2.1 The NORSTIM study

The current study is a part of the NORSTIM study (official title; Prognostic Factors in Parkinson's Disease Patients Treated with Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) - a Prospective Randomized Double-blind Study). NORSTIM is a prospective single-center study examining the effects of STN DBS on motor function, quality of life, psychiatric function and cognitive function in Parkinson’s disease patients treated at Oslo University Hospital (OUH) - Rikshospitalet. It is an interdisciplinary clinical trial that was formally initiated in March 2009. The study’s primary aim is identifying factors predicting good treatment outcome in order to improve patient selection. Intermediate objectives include increasing knowledge about the effects of electrode placement, studying social functioning of patients and caregivers and identifying factors predicting variations in motor function, cognitive function and quality of life. The current thesis covers a subset of the data, mainly consisting of neuropsychological test results, in addition to demographic, neurological, psychological and cognitive background information. The five-year follow-up data was collected as a part of this thesis.

2.2 Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC South East, project no. 6.2009.46), and registered in Clinical Trials in March 2009 (Clinical Trials, identifier NCT00855621). It has been conducted in accordance with the Helsinki declaration (World Medical Association, 2013), and written informed consent was collected from all participants prior to inclusion in the study.

2.3 Participants and procedure

The participants in this study were recruited through their position as patients at the Department of Neurology, OUH – Rikshospitalet. The selection procedure included confirmation of PD diagnosis, review of the medical history, assessment of the neurological aspects of the disease, brain MRI, cognitive screening using the Mattis Dementia Rating Scale
(MDRS), and evaluation of self-reported emotional functioning using the Hospital Anxiety and Depression Scale (HAD). The inclusion and exclusion criteria of the study are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Inclusion and exclusion criteria of the NORSTIM study.</th>
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</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>· Parkinson’s disease diagnosis according to the UK Brain Bank criteria</td>
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<tr>
<td>· Age 18-75 years</td>
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<tr>
<td>· Disease duration ≥ 5 years</td>
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<tr>
<td>· UPDRS motor score ≥ 20 points in the medication-off state</td>
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<tr>
<td>· 30% reduction of non-tremor motor score in medication-on state (range 0 to 108) or severe Levodopa unresponsive tremor</td>
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<tr>
<td>· Marked motor fluctuations with or without troublesome dyskinesias, and/or severe tremor, and/or intolerable side effects of dopaminergic drugs</td>
<td></td>
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<tr>
<td>· Failure of best oral medical treatment to sufficiently control symptoms</td>
<td></td>
</tr>
<tr>
<td>· Mattis Dementia Rating Scale score &gt;130 (maximum 144)</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td></td>
</tr>
<tr>
<td>· Previous surgery for Parkinson’s disease</td>
<td></td>
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<tr>
<td>· Marked axial motor symptoms unresponsive to Levodopa</td>
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<tr>
<td>· Brain MRI showing marked atrophy or white matter changes</td>
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<tr>
<td>· Increased risk of bleeding</td>
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<tr>
<td>· Comorbidities with short life expectancy</td>
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<tr>
<td>· Other surgical contra-indication</td>
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<tr>
<td>· Dementia</td>
<td></td>
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<tr>
<td>· Unstable or major psychiatric disorders (including psychosis, major depression or severe anxiety disorder)</td>
<td></td>
</tr>
<tr>
<td>· Insufficient understanding of the Norwegian language (preventing participation in the psychiatric and neuropsychological evaluations)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: UPDRS: Unified Parkinson’s Disease Rating Scale.

(Adapted with permission from Bjerknes et al., 2018)
After inclusion in the study, and 2-8 weeks prior to STN DBS surgery, baseline information was gathered regarding neurological, cognitive, neuropsychiatric and social functioning. Measures of relevance to this study are presented below. The pre-surgical evaluation also included a full psychiatric evaluation, however the majority of data from this evaluation is not included in the current study.

Neuropsychological evaluations were conducted at three time points; 2-8 weeks before, one year after and five years after STN DBS surgery. All patients were tested by experienced neuropsychologists or students trained in test administration. The same test battery was administered at all three measurement points, except tests used to estimate IQ that were administered at baseline only. The combined administration time was 1.5-2 hours, and breaks were taken where needed. All patients were tested in ‘on-phase’ regarding effect of medication.

2.4 Measures of clinical characteristics

Demographic data regarding gender, patient’s age at the time of surgery, educational level and duration of Parkinson’s disease were registered at the time of inclusion. The Hospital Anxiety and Depression Scale (HAD; Zigmond & Snaith, 1983) was used to assess self-reported emotional functioning, yielding sub-scores for anxiety and depression (Snaith, 2003). Items referring to physical aspects of anxiety (e.g. insomnia) are not included in the questionnaire, thus reducing influence from somatic comorbidity on the results (Spinhoven et al., 1997). Screening of cognitive function was performed using the Mattis Dementia Rating Scale (MDRS; Jurica, Leitten & Mattis, 2001), which results in a global measure of cognitive function based on tests within the domains of attention, initiation/perseveration, construction, conceptualization and memory. Scores range from 0 to 144, with higher scores indicating better cognitive function. MDRS has been shown to successfully differentiate between Parkinson’s disease Dementia and PD (Llebaria et al., 2008).

The Matrix Reasoning and Vocabulary subtests from Wechsler Abbreviated Scale of Intelligence (WASI) were used to estimate full scale IQ score. Matrix Reasoning is considered to measure nonverbal abstract problem-solving ability, while vocabulary is thought to measure verbal comprehension and expression (Wechsler, 1999). The measurement properties of WASI are considered sufficient for its purpose in this study;
illustrating the general intellectual level of the study sample. Further investigations of neuropsychological functioning are described below.

Information about neurological and Parkinson’s-specific variables were collected using a combination of self-report questionnaires and clinical examination by experienced neurologists. The progression of the disease was assessed using the Hoehn and Yahr scale, which divides the disease into stages on a scale from 1 to 5, with 5 being the most advanced stage (Goetz et al., 2004). The Unified Parkinson’s Disease Rating Scale (UPDRS) was used to assess self-reported motor- and non-motor aspects of daily living, the severity and impact of motor fluctuations, and motor function as assessed by a neurologist (Goetz et al., 2008). Health status, quality of life and social functioning was assessed with the Parkinson’s disease Questionnaire (PDQ-39). The PDQ-39 is a self-report measure yielding a summary index score (SI), as well as sub-scores within the areas of mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort (Jenkinson, Fitzpatrick, Peto, Greenhall & Hyman, 1997). The final neurological measure is the Levodopa equivalent daily dose (LEDD). LEDD is a standardized measure of dose intensity across different types of antiparkinsonian drugs, created for the purpose of easier comparisons of patients within and between studies (Tomlinson et al., 2010).

2.5 Neuropsychological outcome measures

The neuropsychological tests were categorized into the following domains: motor function, executive function, attention/working memory, processing speed, word generation, verbal learning/memory and visuospatial learning/memory. The choice of domains was guided by information from previous research regarding what cognitive functions are potentially sensitive to change following DBS. Relevant considerations when selecting test were sensitivity to mild cognitive impairments and suitability for repeated measurements.

Motor function

Motor function was assessed using the Grooved Pegboard Test (Model 32025, Lafayette Instruments), which measures fine motor dexterity. The scores for both dominant and non-dominant hand are included in the study.
**Executive function**

Aspects of executive functions were investigated primarily through the D-KEFS Color-Word Interference Test (CWIT; Delis, Kaplan & Kramer, 2001). There are four conditions in this test; Color Naming, Word Reading, Interference and Switching. The results of the latter two tests are included in the current domain. The Interference condition is a version of the Stroop Test, measuring inhibition of verbal responses. The Switching condition adds another layer of complexity by having the participant continually switch between the classic Stroop task and word reading. Thus, the fourth condition is considered to measure cognitive flexibility as well as inhibition (Shunk, Davis & Dean, 2010). Scores on completion time and the sum of corrected and non-corrected errors for both conditions are included in the study. The last measure of executive function in this study is the final condition of the D-KEFS Verbal Fluency Test; Category Switching (Delis et al., 2001). This test is considered to require both cognitive shifting and the ability to generate words of a semantic nature. The score included in the study represents the total number of correct responses within the time limit (60 seconds).

**Attention/working memory**

Attention and working memory were assessed using subtests from the Wechsler Adult Intelligence Scale III (WAIS-III), namely Digit Span and Number-Letter Sequencing. Digit Span forward is considered to measure memory span, whereas the backward condition and Number-Letter Sequencing rely more heavily on working memory (Wechsler, 1997).

**Processing speed**

Processing speed was measured using The Symbol Digit Modalities Test (SDMT; Smith, 1982), which is an inverse form of the Digit Symbol Test from WAIS (Wechsler, 1997). The oral version was administered in order to avoid motor dysfunction interfering with writing speed. The SDMT is commonly used as a measure of speed of information processing, visual scanning and response production (Sheridan et al., 2006). The first two conditions of the D-KEFS CWIT (Delis et al., 2001), Color Naming and Word Reading, were included as measures of information processing and response production speed.

**Word generation**

The word generation domain consists of the D-KEFS Verbal Fluency Test (Delis et al., 2001). There are three conditions in this test; Phonemic Fluency, Semantic Fluency and Category Switching. The last category is not included in the Word generation domain in this study, as it
was considered to have a strong cognitive flexibility component, making it more compatible with the tests in the executive domain. Both Phonemic and Semantic fluency are thought to involve other aspects of executive function, such as self-monitoring, initiation and organized retrieval of information (Henry & Crawford, 2004). The two tests differ in their demands on language production, as the phonemic condition is based simply on linguistic word properties while the semantic condition is based on associative thinking within categories (Delis et al., 2001).

**Verbal learning and memory**
Verbal learning and memory was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R is a list learning task consisting of three conditions; list learning (3 attempts), delayed free recall (20 min) and recognition (yes/no). The words can be divided into three categories, giving the test a semantic and organizational component (Lezak, 2012, p. 481). Scores included in the study are the total acquisition score for the three learning attempts, the score for delayed recall and the discrimination index of the recognition score. Different versions of the HVLT-R were employed at different time points in order to minimize re-test effects.

**Visuospatial learning and memory**
This domain consists of the Brief Visuospatial Memory Test-Revised (BVMT-R). The BVMT-R measures the ability to learn, copy and remember a limited number of relatively simple geometric figures (Lezak, 2012). The administration is analogous to the HVLT-R. The figures are presented simultaneously for ten seconds, and the test subjects are given three attempts at copying them. Included scores in the study are the total score from the three learning attempts, as well as the delayed recall score (25 min). Different versions of the BVMT-R were employed at different time points in order to minimize re-test effects.

### 2.6 Data analysis

Data analyses were completed using the Statistical Package for Social Sciences (IBM SPSS statistics, version 25). All neuropsychological test scores were converted to T-scores in order to describe neuropsychological function in relation to normative means, and to calculate composite scores within cognitive domains. Variables were created for the difference of mean scores between measurement time points, e.g. the difference between mean scores at baseline
and five years post-surgery. In addition, a Global cognitive index score was created by averaging all cognitive domain scores from the pre-operative assessment. The choice of statistical tests was guided by research questions and assessments of variables in regard to violations of assumptions and statistical requirements. The normality of the distributions of scores was assessed using the Kolmogorov-Smirnov test, applying a significance level of \( p = .05 \). The Kolmogorov-Smirnov test has its limitations, mainly that it tends to overestimate normality in small samples and underestimate normality in large samples (Howell, 2013, p. 78). Therefore, other methods of evaluating normality were also used, including assessment of histograms, P-P plots and values of skewedness and kurtosis (Field, 2013, p. 182).

2.6.1 Descriptive statistics

Descriptive statistics were used to report demographic, cognitive, neuropsychiatric and neurological characteristics of the study sample. As the distribution of results on a few measures were not normally distributed, median values with 1\(^{st}\) and 3\(^{rd}\) quartiles are reported as measures of central tendency in addition to means and standard deviations. In the text, variables are described either using means and standard deviations or medians and quartiles, depending on the evaluation of normality of the distributions.

2.6.2 Comparisons with normative mean

One sample \( t \)-tests were used to investigate whether the neuropsychological function of the study group significantly differed from the normative mean at baseline, 1 year and 5 years after STN DBS surgery. The analyses were performed using the cognitive domain scores.

2.6.3 Repeated measures

Analysis of variance (ANOVA) for repeated measures was used to investigate the differences between scores at the three measurement points. Repeated measures ANOVA calculates an \( F \)-ratio, which is the ratio of systematic to unsystematic variation. Thus, it gives information about what proportion of the variance represents a significant change (Howell, 2013, p. 461).

The statistical assumptions for the use of repeated measures ANOVA include dependent variables on a continuous level, independent variables consisting of at least two related groups, no significant outliers and approximately normally distributed residuals (Field, 2013,
p. 555), all of which are true for this data set. The final assumption of repeated measures
ANOVA is that of sphericity, which is the assumption that the variances of the differences
between conditions are approximately equal (Field, 2013, p. 545). Sphericity was assessed
using Mauchly’s Test. The majority of variables did not violate sphericity, and therefore the
significance values of the $F$-ratio for assumed sphericity were used when reporting the results
for these variables. As all epsilon values were higher than .75, the Huynh-Feldt correction
was used when reporting the significance of the $F$-ratio for the variables that violated
sphericity. This is recommended practice, as the alternative correction, the Greenhouse-
Geisser correction, is too conservative for epsilon values higher than .75 (Field, 2013, p. 548).
The significance of the $F$-ratios was evaluated using a significance level of $p = 0.05$.

2.6.4 Pairwise comparisons

Post-hoc pairwise comparisons were made between all combinations of the three time points.
The analysis was performed using the paired-samples $t$-test, which investigates whether the
difference between two means represents a significant change or random variation (Howell,
2013, p. 198).

The paired-samples $t$-test is a parametric test, which implies an assumption of normally
distributed data. However, the assumption of normality does not refer to the distribution of
scores in the two variables, but the sampling distribution of the differences between scores.
The latter approaches normality with increasing sample sizes even when the original variables
are not normally distributed, according to the central limit theorem (Howell, 2013, p. 178).
Howell recommends sample sizes of at least $n = 30$ when using variables that are not
themselves normally distributed (2013, p. 179). The sample size in the current study is $n = 55$,
with some variation between variables due to missing scores. Thus, the $t$-test could be used
for all variables, even though a few were not normally distributed. However, non-normally
distributed scores are considered to have a somewhat lower probability of generating
normally distributed sampling distributions than normally distributed scores (Field, 2013, p.
169). As a safety measure, the Wilcoxon signed-rank test, which is recognized as the non-
parametric equivalent of the paired-samples $t$-test (Field, 2013, p. 228), was used to confirm
significant effects for the comparisons involving non-normally distributed variables.
2.6.5 Gender differences

Potential gender differences were investigated using a $t$-test for independent samples. Dependent variables were the cognitive domain difference scores between baseline and 1 year post-operatively, between baseline and 5 years, and between 1 and 5 years. The independent grouping variable was gender, with $n = 14$ women and $n = 41$ men. All $t$-tests were evaluated using a significance level of $p = 0.05$. Results are presented descriptively, using bootstrap estimates of confidence intervals.

2.6.6 Regression analysis

Linear simple regression analysis was chosen to investigate the second research question of this study; whether pre-operative factors predicted cognitive outcome. Linear simple regression was considered a suitable method for this type of analysis, as it describes the relationship between a predictor and an outcome variable (Field, 2013, p. 294). Because the sample size in this study is sufficiently larger than $n = 30$, it could be assumed that the sampling distributions are normally distributed because of the central limit theorem (Howell, p. 178). As a safety measure, the bootstrap confidence intervals, which do not rely on assumptions of normality (Field, 2013, p. 320), are reported in the results. When investigating one predictor at a time, Field (2013, p. 313) recommends sample sizes of $n = 55$ and $n = 25$ in order to obtain reliable regression models with medium ($R^2 = .13$) and large ($R^2 = .26$) effect sizes, respectively. Thus, the sample sizes in this study should result in sufficient statistical power for the regression analyses.

Correlation analysis was performed as a part of the planning stage of the regression analysis, giving information about potentially relevant combinations of variables. Pre-operative measures of demographic and clinical characteristics were compared with cognitive domain difference scores, specifically the difference scores between baseline (pre-operative) and one year post-surgery (T2-T1), and between baseline and five years post-surgery (T3-T1). The correlation analyses were performed using Spearman’s correlation, a non-parametric test, as investigations of normality showed skewness or kurtosis of the distributions of a few of the included variables. By ranking the data before applying Pearson’s equation, Spearman’s test minimizes the influence of non-normality, thus comparing variables with differing distribution patterns on more equal grounds (Field, 2013, p. 276). Statistical criteria were used to select relevant combinations of variables for the regression. The criteria were defined
widely in order to avoid missing potentially meaningful combinations for regression analysis. Correlation coefficients of 0.10 are considered as small, 0.30 as medium and 0.50 as large (Cohen, 1988). The chosen criteria were correlation coefficients within or approximating the medium and large ranges with two-tailed significance levels of at least 0.08.

Based on the correlational results with the cognitive domain difference scores T2-T1, the pre-operative clinical characteristics a) age, b) duration of Parkinson’s disease, c) scores on the Hospital Anxiety and Depression Scale (total score and anxiety subscale), d) Hoehn and Yahr scale (off) and e) part IV of the Unified Parkinson’s Disease Rating Scale were chosen as dependent variables for the regression analysis. For the cognitive domain difference scores T3-T1, the included characteristics were a) age, b) duration of Parkinson’s disease c) Global cognitive index and d) scores on the Hospital Anxiety and Depression Scale (total score and anxiety subscale). Linear simple regression was performed for each of the dependent variables, with correlating cognitive domain difference scores as independent variables. The difference scores between baseline and 1 year post-operatively and between baseline and 5 years were used in the analysis.
3 Results

3.1 Characteristics of the study sample

Demographic and clinical characteristics of the study sample are presented in table 2. The total sample consisted of $n = 55$ participants, of which $n = 14$ were women and $n = 41$ men. Mean age at the time of surgery was 60 years ($SD = 6.93$), with pre-operative disease duration averaging 11.6 years ($SD = 4.48$). The median length of education was 15 years ($Q1 = 12$, $Q3 = 15$), reflecting a relatively high educational level. The mean WASI full scale IQ score of 107.3 ($SD = 14.44$) supports this impression.

The median score on the Mattis Dementia Rating Scale (MDRS) was 142 ($Q1 = 139$, $Q2 = 143$) on a scale from 0 to 144, with higher scores reflecting better cognitive functioning. The median score on the Hospital Anxiety and Depression Scale (HAD) was 6 ($Q1 = 3$, $Q2 = 12$), yielding comparable scores for anxiety ($Md = 3$, $Q1 = 1.3$, $Q3 = 6$) and depression ($Md = 3$, $Q1 = 1$, $Q3 = 6$). The mean scores for both anxiety and depression are in the normal range (0-7; Snaith, 2003), however the distribution measures show that some participants score higher than this threshold.

Levodopa equivalent daily doses (LEDD) are commonly classified as low at < 400 mg and high at > 1200 mg (Nyholm, Karlsson, Lundberg & Askmark, 2009). The study sample had a mean pre-operative LEDD of 1305 ($SD = 442.78$). The evaluation of disease progression with the Hoehn and Yahn scale showed that the median score was 2 ($Q1 = 2$, $Q3 = 2.5$) when measured on medication, and 2.5 ($Q1 = 2$, $Q3 = 3$) off medication. A score of 2 reflects bilateral neurological involvement without impairment of balance, while an increase to 3 would involve mild to moderate disability (Goetz et al., 2004). Martínez-Martín et al. (2015) have proposed cutoff scores on the Unified Parkinson’s Disease Rating Scale. Based on their classification, the average scores of the study sample were in the moderate range for mentation, behavior and mood (part I), activities of daily living (part II), motor function while off medication (part III off) and complications of therapy (part IV). Motor examination while on medication (part III on) yielded scores in the mild range. The Parkinson’s disease Questionnaire yields scores from 0 to 100 on all scales, with 0 reflecting no problems and 100 reflecting a high level of problems (Hagell & Nygren, 2007). The summary index, considered to represent different aspects of quality of life, showed a mean score of 26.9 ($SD = 12.00$) in the study group. The highest scores were seen for physical aspects such as bodily discomfort.
(Mdn=45.8, Q1=25, Q3=66.7), activities of daily living (Mdn=37.5, Q1=16.7, Q3=54.2) and mobility (Mdn=31.3, Q1=15, Q3=53.1).

Table 2  
Demographic and clinical characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median [Q1, Q3]</th>
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<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td>60.0 (6.93)</td>
<td>61 [56, 64]</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.6 (2.95)</td>
<td>15 [12, 15]</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>11.6 (4.48)</td>
<td>11 [8, 14]</td>
</tr>
<tr>
<td>Age at debut of disease</td>
<td>48.4 (6.39)</td>
<td>49.5 [43, 53.3]</td>
</tr>
</tbody>
</table>

| Cognitive and neuropsychiatric characteristics |           |                 |
| WASI full scale IQ       | 107.3 (14.44) | 105.4 [99, 118]|
| Mattis Dementia Rating Scale (MDRS) | 140.5 (3.30) | 142 [139, 143] |
| Hospital Anxiety and Depression Scale (HAD) | 7.9 (5.41) | 6 [3, 12]      |
| HAD anxiety              | 4.1 (3.25) | 3 [1.3, 6]     |
| HAD depression           | 3.9 (3.49) | 3 [1, 6]       |

| Neurological and Parkinson-specific characteristics |           |                 |
| Levodopa equivalent daily dose (LEDD) | 1305 (442.78) | 1292 [991, 1492] |
| Hoehn and Yahn            |           |                 |
| On medication             | 2.1 (0.39) | 2 [2, 2.5]      |
| Off medication            | 2.8 (0.83) | 2.5 [2, 3]      |
| Unified Parkinson’s Disease Rating Scale (UPDRS) |           |                 |
| I. Mentation, Behavior and Mood | 11.4 (6.15) | 10.5 [6.8, 16] |
| II. Activities of Daily Living | 17.4 (7.25) | 16.4 [13.8, 22.3] |
| III. Motor Examination    |           |                 |
| On medication             | 15.0 (9.42) | 14 [7, 19]      |
| Off medication            | 49.1 (13.30) | 48.5 [40, 58.5] |
| IV. Complications of Therapy | 9.6 (3.57) | 10 [8, 12]      |
| Parkinson’s Disease Questionnaire (PDQ-39) |           |                 |
| Summary Index             | 26.9 (12.00) | 26.8 [17.5, 36.7] |
| Mobility                  | 34.6 (21.89) | 31.3 [15, 53.1] |
| Activities of daily living | 37.0 (21.79) | 37.5 [16.7, 54.2] |
| Emotional well-being      | 17.3 (15.77) | 12.5 [4.2, 25]  |
| Stigma                    | 25.3 (21.87) | 25 [4.7, 43.8]  |
| Social support            | 11.6 (16.78) | 0 [0, 16.7]     |
| Cognition                 | 24.8 (17.34) | 18.8 [12.5, 32.8] |
| Communication             | 19.3 (16.42) | 16.7 [8.3, 33.3] |
| Bodily discomfort          | 45.2 (22.64) | 45.8 [25, 66.7] |

**Bold font indicates the measure of central tendency considered the most informative for each distribution.**
3.2 Neuropsychological functioning

Neuropsychological test results from the three measurement points, with mean scores and standard deviations, are presented in table 3.

3.2.1 Pre-operative function - comparisons with normative mean

At baseline, all mean domain scores significantly differ from the normative average ($T=50$) according to a one sample $t$-test. With two exceptions, the $t$-values range from -5.00 to -2.62, with significance levels from $p = .011$ to $p = .000$. The first exception is motor function, with substantially lower mean baseline scores ($T=35.20$) than the other domains, resulting in a $t$-score of -13.64, $p = .000$. The other exception is word generation, the only mean domain score with a higher value ($T=55.10$) than the normative average, $t = 3.45$, $p = 0.011$.

The domains that show the greatest reduction compared with the normative mean from baseline to the 1-year follow-up are processing speed (from $t = -4.23$, $p = .000$, to $t = -7.12$, $p = .000$), executive function (from $t = -3.50$, $p = .001$, to $t = -5.60$, $p = .000$) and word generation (from $t = 3.45$, $p = .001$, to $t = -1.08$, $p = .288$). Word generation is no longer significantly different from the normative mean at the one-year-follow-up, however this still represents a substantial change, as the results of the study group were significantly better than the normative mean at baseline. The performances in domains of motor function, attention/working memory and verbal learning/memory remain relatively unchanged, while visuospatial learning/memory is no longer significantly different than the normative mean after one year, $t = -1.99$, $p = .053$.

Five years post-surgery, the study sample differs more from the normative mean than at baseline and the one-year-follow-up. The domains of processing speed, attention/working memory, executive function, verbal learning/memory and visual learning/memory now all show $t$-scores in the range from -11.38 to -4.50, with significance levels of $p = .000$. Word generation, which started out above average, is now almost at the level of the other functions, $t = -4.42$, $p = .000$. Motor function shows approximately the same difference from the normative mean as it did at baseline and after one year, $t = -13.33$, $p = .000$. 
3.2.2 Repeated measures ANOVA

F-ratios and their significance levels (p) from the repeated measures ANOVA are presented in table 3. The results show that neuropsychological test results significantly differ from each other over the three measurement points within the domains of motor function, \( F(2, 68) = 17.42, p = .000 \), processing speed, \( F(1.68, 67.34) = 64.64, p = .000 \), attention/working memory, \( F(1.75, 78.66) = 17.92, p = .000 \), executive functions, \( F(2, 68) = 21.34, p = .000 \), word generation, \( F(1.63, 65.21) = 39.46, p = .000 \), and visual learning/memory, \( F(2, 86) = 13.11, p = .000 \). The only domain score with a non-significant F-ratio is verbal learning/memory, \( F(2, 90) = 1.90, p = .156 \).

Within the domains of motor function, processing speed, attention/working memory, word generation and visual learning/memory, domain scores and subtests show F-ratios and significance levels in more or less the same range, whereas the domains of executive functions and verbal learning/memory show more uneven results. For executive functions, the largest discrepancy is seen between the time needed to complete CWIT 3, \( F(1.80, 72.09) = 33.43, p = .000 \), and the number of errors that were made, \( F(2, 78) = 3.78, p = .028 \). The same trend is seen for CWIT 4, with a larger F-ratio on the time measure, \( F(2, 74) = 18.46, p = .000 \), than the error measure \( F(2, 68) = 8.04, p = .001 \). Nevertheless, all measures of executive functions show significant change over the three time points, according to the chosen alpha level of .05. As previously stated, the change in the verbal learning/memory domain score is not significant, \( F(2, 90) = 1.90, p = .156 \). However, the only non-significant F-ratio on the HVLT-R is the total acquisition score for the three learning attempts, \( F(2, 92) = 1.29, p = .281 \). Both delayed recall, \( F(2, 90) = 4.83, p = .010 \), and recognition, \( F(2, 90) = 4.27, p = .017 \), show significant change between the three measurement points.
Table 3  Neuropsychological outcome

<table>
<thead>
<tr>
<th>Domains/tests</th>
<th>Baseline (T1) M (SD)</th>
<th>1 år (T2) M (SD)</th>
<th>5 år (T3) M (SD)</th>
<th>F</th>
<th>p</th>
<th>Pairwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grooved Pegboard dom. hand</td>
<td>35.2 (8.00)</td>
<td>36.2 (7.92)</td>
<td>30.6 (8.86)</td>
<td>17.42</td>
<td>.000</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
<tr>
<td>Grooved Pegboard non-dom. hand</td>
<td>35.2 (9.58)</td>
<td>35.3 (7.84)</td>
<td>30.8 (8.38)</td>
<td>12.19</td>
<td>.000</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol-Digit Modalities Test – Oral (SDMT)</td>
<td>45.1 (8.36)</td>
<td>41.9 (8.03)</td>
<td>32.8 (9.89)</td>
<td>64.64</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Color-Word Color Naming (1)</td>
<td>44.4 (10.10)</td>
<td>40.9 (11.04)</td>
<td>31.1 (11.53)</td>
<td>57.55</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Color-Word Word Reading (2)</td>
<td>47.8 (10.33)</td>
<td>46.3 (8.93)</td>
<td>35.8 (12.01)</td>
<td>42.39</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td><strong>Attention/working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-III Digit Span</td>
<td>46.9 (7.40)</td>
<td>46.1 (8.32)</td>
<td>42.8 (8.27)</td>
<td>17.92</td>
<td>.000</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
<tr>
<td>WAIS-III Letter-Number Sequencing</td>
<td>47.0 (9.90)</td>
<td>45.3 (10.21)</td>
<td>42.0 (11.72)</td>
<td>9.54</td>
<td>.001</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color-Word Interference (3, time)</td>
<td>46.7 (10.29)</td>
<td>42.1 (12.54)</td>
<td>32.9 (14.39)</td>
<td>33.43</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Color-Word Interference (3, errors)</td>
<td>46.6 (12.33)</td>
<td>46.4 (11.46)</td>
<td>41.0 (13.93)</td>
<td>3.76</td>
<td>.028</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
<tr>
<td>Color-Word Switching (4, time)</td>
<td>43.3 (11.73)</td>
<td>39.9 (13.37)</td>
<td>33.7 (12.88)</td>
<td>18.46</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Color-Word Switching (4, errors)</td>
<td>49.0 (10.43)</td>
<td>42.8 (13.98)</td>
<td>41.0 (14.20)</td>
<td>8.04</td>
<td>.001</td>
<td>T1 &gt; T3, T1 &gt; T2</td>
</tr>
<tr>
<td>Verbal Fluency Category Switching (3)</td>
<td>47.2 (11.20)</td>
<td>43.0 (11.08)</td>
<td>38.7 (11.48)</td>
<td>8.75</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td><strong>Word generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency Phonemic (1)</td>
<td>52.4 (14.01)</td>
<td>45.8 (13.60)</td>
<td>41.2 (12.30)</td>
<td>22.29</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Verbal Fluency Semantic (2)</td>
<td>57.8 (10.33)</td>
<td>51.0 (11.46)</td>
<td>42.4 (14.59)</td>
<td>37.71</td>
<td>.000</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td><strong>Verbal learning/memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test-R (total)</td>
<td>43.3 (9.96)</td>
<td>40.9 (10.65)</td>
<td>40.0 (10.16)</td>
<td>1.90</td>
<td>.156</td>
<td>T1 &gt; T3, T1 &gt; T2, T2 &gt; T3</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test-R (delayed)</td>
<td>41.9 (12.45)</td>
<td>39.2 (12.78)</td>
<td>41.5 (12.23)</td>
<td>1.29</td>
<td>.281</td>
<td></td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test-R (recognition)</td>
<td>42.1 (13.61)</td>
<td>36.9 (11.84)</td>
<td>37.4 (11.07)</td>
<td>4.83</td>
<td>.010</td>
<td>T1 &gt; T3, T1 &gt; T2</td>
</tr>
<tr>
<td><strong>Visual learning/memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test-R (learning)</td>
<td>46.4 (10.15)</td>
<td>46.9 (11.15)</td>
<td>41.3 (13.04)</td>
<td>13.11</td>
<td>.000</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test-R (delayed)</td>
<td>45.4 (10.25)</td>
<td>46.2 (11.94)</td>
<td>40.3 (13.23)</td>
<td>12.15</td>
<td>.000</td>
<td>T1 &gt; T3, T2 &gt; T3</td>
</tr>
</tbody>
</table>

Note: M (SD) = Mean (Standard Deviation)
### 3.2.3 Pairwise comparisons

Table 3 shows which pairs of mean neuropsychological test scores significantly differ from each other according to pairwise comparisons with the paired-samples $t$-test and the Wilcoxon signed-rank test. $t$-scores and significance levels of paired domain scores are presented below.

**Motor function**

In the time from before surgery (T1) to one year after (T2), there is no significant change in mean domain scores; $-0.72, 95\% \text{ CI } [-2.88, 1.44]$, $t(49) = -0.669, p = .507$. In the four years that follow, from one (T2) to five (T3) years post-operatively, performance decreases significantly; $7.43, 95\% \text{ CI } [4.79, 10.07]$, $t(34) = 5.72, p = .000$, resulting in an overall significant decline from T1 to T3; $6.26, 95\% \text{ CI } [3.34, 9.19]$, $t(35) = 4.34, p = .000$.

**Processing speed**

All combinations of the three mean domain scores are significantly different from each other, showing reductions in performance from T1 to T2; $3.79, 95\% \text{ CI } [1.85, 5.74]$, $t(49) = 3.92, p = .000$, from T2 to T3; $9.31, 95\% \text{ CI } [6.97, 11.65]$, $t(40) = 8.05, p = .000$, and from T1 to T3; $13.00, 95\% \text{ CI } [10.23, 15.77]$, $t(42) = 9.47, p = .000$. 

![Figure 4 Development of mean motor function domain scores over measurement points, with standard deviations.](image1)

**Figure 4 Development of mean motor function domain scores over measurement points, with standard deviations.**

![Figure 5 Development of mean processing speed domain scores over measurement points, with standard deviations.](image2)

**Figure 5 Development of mean processing speed domain scores over measurement points, with standard deviations.**
**Attention/working memory**

The mean scores of the attention/working memory domain decline significantly between T1 and T3; 4.78, 95% CI [2.93, 6.64], t(46) = 5.19, p = .000, as well as between T2 and T3; 4.09, 95% CI [2.10, 6.09], t(45) = 4.13, p = .000. However, there is no significant change between T1 and T2; 1.04, 95% CI [-0.26, 2.34], t(50) = 1.60, p = .115.

**Executive functions**

All combinations of the three mean domain scores are significantly different from each other, showing reductions in performance from T1 to T2; 4.41, 95% CI [2.29, 6.52], t(47) = 4.18, p = .000, from T2 to T3; 4.88, 95% CI [2.24, 7.52], t(34) = 3.75, p = .001, and from T1 to T3; 8.76, 95% CI [6.07, 11.45], t(37) = 6.59, p = .000.

**Word generation**

The largest decline of mean domain score in this study is seen for word generation from T1 to T3; 13.37, 95% CI [9.75, 16.98], t(42) = 7.47, p = .000. The decline is steady across measurement points, yielding significant results of comparisons between T1 and T2; 6.86, 95% CI [4.63, 9.09], t(50) = 6.18, p = .000, as well as between T2 and T3; 7.80, 95% CI [5.01, 10.58], t(40) = 5.66, p = .000.
**Verbal learning/memory**

As expected considering the non-significant repeated measures ANOVA, no significant differences are found between measurement points for the domain score of verbal learning/memory. However, the decline of mean scores for delayed recall is significant from T1 to T2; 5.22, 95% CI [1.35, 9.09], \(t(50) = 2.70, p = .009\), and from T1 to T3; 4.81, 95% CI [0.90, 8.73], \(t(47) = 2.47, p = .017\). In addition, mean recognition performance shows significant decline between T2 and T3; 5.35, 95% CI [1.84, 8.86], \(t(45) = 3.07, p = .004\), and between T1 and T3; 4.27, 95% CI [0.17, 8.37], \(t(47) = 2.10, p = .042\).

**Visual learning/memory**

Within the domain of visual learning/memory, there is no significant change in mean domain score between T1 and T2; -0.30, 95% CI [-2.89, 2.29], \(t(50) = -0.24, p = .815\). From T2 to T3 results show significant decline; 7.10, 95% CI [4.40, 9.80], \(t(43) = 5.30, p = .000\), resulting in an overall significant change between T1 and T3; 6.08, 95% CI [2.83, 9.33], \(t(45) = 3.77, p = .000\).

### 3.2.4 Gender differences

A comparison of men’s and women’s domain difference scores, using an independent samples t-test, showed no significant gender differences in development of scores between baseline and five years post-operatively (T3-T1) or from one to five years post-operatively (T3-T2). From baseline to one year post-surgery (T2-T1), the only domain difference score with a significant gender difference was processing speed. Men showed a mean reduction in T-scores of \(M = -5.40, SE = 1.08\), while women’s scores did not decline, \(M = 0.33, SE = 1.70\). The mean difference between men and women was 5.72, 95% CI [2.15, 9.87], \(t(48) = 2.84, p = 0.008\).
3.3 Predictors of neuropsychological outcome

3.3.1 Exploratory correlational analysis

Spearman’s correlation analysis was used to compare pre-operative demographic and clinical characteristics of the study sample with cognitive domain difference scores from baseline to one (T2-T1) and five (T3-T1) years post-surgery.

**Correlations with cognitive domain difference scores T2-T1**

Higher age and longer duration of disease were associated with more decline in motor function, attention/working memory, executive function and visual learning/memory. When it comes to age, the strongest relationship was seen with visuospatial memory, $r_s = -0.403$, $p = 0.003$, followed by executive function, $r_s = -0.350$, $p = 0.015$, motor function, $r_s = -0.296$, $p = 0.037$, and attention/working memory, $r_s = -0.289$, $p = 0.040$. Duration of disease was most strongly associated with change in executive functions, $r_s = -0.401$, $p = 0.005$, followed by attention/working memory, $r_s = -0.357$, $p = 0.010$, visual learning/memory, $r_s = -0.334$, $p = 0.017$, and motor function, $r_s = -0.306$, $p = 0.031$. Motor function also correlated with the HAD total score, $r_s = 0.363$, $p = 0.011$, and the HAD anxiety subscale, $r_s = 0.310$, $p = 0.032$. Higher pre-operative symptom severity as measured by The Hoehn and Yahr scale did not show a significant association with change in executive function, $r_s = 0.284$, $p = 0.051$, however it met the criteria for inclusion in the regression analysis ($p \leq 0.08$). Higher (worse) scores on Part IV of the Unified Parkinson’s Disease Rating Scale (UPDRS IV), which measures complications of treatment and stability of treatment effects, was associated with less decline in verbal learning/memory $r_s = 0.387$, $p = 0.005$. There was no significant relationship between any of the cognitive domain difference scores and education, the Global cognitive index, Levodopa equivalent daily dose, Hoehn and Yahr scale (on), the HAD depression subscale, the summary index of the Parkinson’s Disease Questionnaire, or parts I, II and III of the Unified Parkinson’s Disease Rating scale.

**Correlations with cognitive domain difference scores T3-T1**

The pre-operative characteristic that correlated with the highest number of cognitive domain difference scores was age. Higher age at time of surgery was associated with more decline in attention/working memory, $r_s = -0.287$, $p = 0.051$, executive functions, $r_s = -0.310$, $p = 0.059$, word generation, $r_s = -0.417$, $p = 0.005$, and visual learning/memory, $r_s = -0.325$, $p = 0.028$. Longer duration of Parkinson’s disease was related to more decline in executive functions, $r_s$
Higher Global cognitive index scores were associated with less decline in executive functions, \( r_s = .358, p = .027 \). Finally, higher (worse) scores on the Hospital Anxiety and Depression Scale (HAD) were related to less decline in motor function, both for the total score, \( r_s = .410, p = .016 \), and the anxiety subscale, \( r_s = .368, p = .032 \). There was no significant relationship between any of the cognitive domain difference scores and education, Levodopa equivalent daily dose, Hoehn and Yahr scale, the Unified Parkinson’s Disease Rating scale, the HAD depression subscale or the summary index of the Parkinson’s Disease Questionnaire.

### 3.3.2 Regression analysis

Results of the simple linear regression analyses are presented in table 4 for predictions of change in neuropsychological performance from T1 to T2 and table 5 for T1 to T3. As previously stated, correlation coefficients showing two-tailed significance levels of at least \( p = 0.08 \) defined which variables were included in the regression analyses.

**Predictors of change from baseline to one year post-surgery**

From T1 to T2, the predictor variable that influenced the highest number of cognitive domain difference scores was age, which predicted 8\% \( (p = .030) \) of the change in motor function, 10\% \( (p = .019) \) of the change in attention/working memory performance, and 14\% \( (p = .007) \) of the change in visual learning/memory. Duration of disease explained 9\% \( (p = .032) \) of the change in attention/working memory performance and 8\% \( (p = .050) \) of the change in executive functions. UPDRS IV predicted 12\% \( (p = .003) \) of change in verbal learning/memory performance. Lastly, Hoehn and Yahr scale (off) predicted 12\% of the change in executive functions.

**Predictors of change from baseline to five years post-surgery**

From T1 to T3, the strongest relationship was seen between duration of disease and subsequent development of executive functions, with disease duration predicting 20\% \( (p = .010) \) of the change in executive function performance. Disease duration also predicted 11\% \( (p = .043) \) of the change in visual learning/memory. The predictor that influenced the highest number of cognitive domains was age, predicting 10\% \( (p = .009) \) of change in attention/working memory, 12\% \( (p = .038) \) in executive functions, 16\% in word generation \( (p = .011) \) and 12\% \( (p = .016) \) in visual learning/memory. Scores on the Global cognitive index predicted 13\% \( (p = 0.37) \) of the change in executive function performance.
**Table 4  Linear model of predictors of change in cognitive functions from baseline (T1) to 1 year post-surgery (T2)**

Confidence intervals (95% bias corrected and accelerated) and standard errors based on 1000 bootstrap samples.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cognitive domain (T2-T1)</th>
<th>b</th>
<th>(95% BCa CI)</th>
<th>SE B</th>
<th>β</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>60.41</td>
<td>(58.55, 62.26)</td>
<td>0.93</td>
<td>.001</td>
<td>.08</td>
<td></td>
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</tr>
<tr>
<td>Motor function</td>
<td>-0.26</td>
<td>(-0.49, -0.03)</td>
<td>0.12</td>
<td>-.28</td>
<td>.030</td>
<td></td>
<td></td>
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<tr>
<td>Constant</td>
<td>11.79</td>
<td>(1.80, 20.52)</td>
<td>4.89</td>
<td>.020</td>
<td>.10</td>
<td></td>
<td></td>
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<tr>
<td>Attention/working memory</td>
<td>-0.21</td>
<td>(-0.36, -0.05)</td>
<td>0.19</td>
<td>-.32</td>
<td>.019</td>
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<td>Constant</td>
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<td>9.85</td>
<td>.124</td>
<td>.11</td>
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<td>Executive functions</td>
<td>-0.34</td>
<td>(-0.70, -0.02)</td>
<td>0.17</td>
<td>-.34</td>
<td>.057</td>
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<tr>
<td>Constant</td>
<td>29.55</td>
<td>(10.37, 51.06)</td>
<td>10.08</td>
<td>.007</td>
<td>.14</td>
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<tr>
<td>Visual learning/memory</td>
<td>-0.49</td>
<td>(-0.84, -0.18)</td>
<td>0.17</td>
<td>-.37</td>
<td>.007</td>
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<td></td>
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<td><strong>Duration of disease</strong></td>
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<td></td>
</tr>
<tr>
<td>Constant</td>
<td>11.67</td>
<td>(10.42, 12.97)</td>
<td>0.64</td>
<td>.001</td>
<td>.06</td>
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<td>-0.15</td>
<td>(-0.31, 0.01)</td>
<td>0.08</td>
<td>-.25</td>
<td>.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>11.31</td>
<td>(10.16, 12.62)</td>
<td>0.63</td>
<td>.001</td>
<td>.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>-0.29</td>
<td>(-0.56, -0.02)</td>
<td>0.13</td>
<td>-.29</td>
<td>.032</td>
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<tr>
<td>Constant</td>
<td>0.89</td>
<td>(-5.46, 7.23)</td>
<td>3.22</td>
<td>.794</td>
<td>.08</td>
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<td></td>
</tr>
<tr>
<td>Executive functions</td>
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<td>(-1.00, -0.05)</td>
<td>0.24</td>
<td>-.29</td>
<td>.050</td>
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<td></td>
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<tr>
<td>Constant</td>
<td>5.79</td>
<td>(-0.14, 12.83)</td>
<td>3.36</td>
<td>.082</td>
<td>.06</td>
<td></td>
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<tr>
<td>Visual learning/memory</td>
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<td>(-1.13, 0.02)</td>
<td>0.30</td>
<td>-.24</td>
<td>.111</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAD total score</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-2.80</td>
<td>(-6.83, 1.44)</td>
<td>2.11</td>
<td>.202</td>
<td>.09</td>
<td></td>
<td></td>
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<tr>
<td>Motor function</td>
<td>0.42</td>
<td>(-0.21, 0.84)</td>
<td>0.22</td>
<td>.30</td>
<td>.059</td>
<td></td>
<td></td>
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<tr>
<td><strong>HAD anxiety subscale</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
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<td>(-5.76, -1.16)</td>
<td>1.75</td>
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<td>.08</td>
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<td>Motor function</td>
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<td>(0.01, 1.30)</td>
<td>0.34</td>
<td>.29</td>
<td>.052</td>
<td></td>
<td></td>
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<tr>
<td><strong>UPDRS IV</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>9.76</td>
<td>(8.80, 10.67)</td>
<td>0.48</td>
<td>.001</td>
<td>.12</td>
<td></td>
<td></td>
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<tr>
<td>Verbal learning/memory</td>
<td>0.13</td>
<td>(0.04, 0.22)</td>
<td>0.05</td>
<td>.34</td>
<td>.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hoehn and Yahr scale (off)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>2.91</td>
<td>(2.62, 3.19)</td>
<td>0.15</td>
<td>.001</td>
<td>.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td>0.04</td>
<td>(0.01, 0.07)</td>
<td>0.02</td>
<td>.35</td>
<td>.030</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: HAD: Hospital Anxiety and Depression Scale, UPDRS: Unified Parkinson’s Disease Rating Scale.
Table 5  
Linear model of predictors of change in cognitive functions from baseline (T1) to 5 years post-surgery (T3)
Confidence intervals (95% bias corrected and accelerated) and standard errors based on 1000 bootstrap samples.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cognitive domain (T3-T1)</th>
<th>b</th>
<th>(95% BCa CI)</th>
<th>SE B</th>
<th>β</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Constant</td>
<td>11.93</td>
<td></td>
<td>(-0.58, 23.98)</td>
<td>6.27</td>
<td>.057</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>-0.28</td>
<td></td>
<td>(-0.48, -0.08)</td>
<td>0.10</td>
<td>-.32</td>
<td><strong>.009</strong></td>
<td></td>
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<tr>
<td>Constant</td>
<td>14.72</td>
<td></td>
<td>(-8.37, 36.14)</td>
<td>11.15</td>
<td>.195</td>
<td></td>
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<tr>
<td>Executive functions</td>
<td>-0.40</td>
<td></td>
<td>(-0.78, -0.04)</td>
<td>0.19</td>
<td>-.35</td>
<td><strong>.038</strong></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>25.91</td>
<td></td>
<td>(-3.75, 52.90)</td>
<td>14.16</td>
<td>.067</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Word generation</td>
<td>-0.66</td>
<td></td>
<td>(-1.13, -0.20)</td>
<td>0.24</td>
<td>-.40</td>
<td><strong>.011</strong></td>
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<tr>
<td>Constant</td>
<td>26.11</td>
<td></td>
<td>(-2.26, 48.38)</td>
<td>12.63</td>
<td>.045</td>
<td></td>
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</tr>
<tr>
<td>Visual learning/memory</td>
<td>-0.54</td>
<td></td>
<td>(-0.92, -0.10)</td>
<td>0.21</td>
<td>-.35</td>
<td><strong>.016</strong></td>
<td></td>
</tr>
</tbody>
</table>

| **Duration of disease**       |                          |       |              |      |       |        |      |
| Constant                      | 0.05                     |       | (-6.75, 6.96) | 3.53 | .998  | .20    |
| Executive functions           | -0.75                    |       | (-1.34, -0.24) | 0.29 | -.45  | **.010**|
| Constant                      | 2.86                     |       | (-4.85, 11.70) | 4.23 | .509  | .11    |
| Visual learning/memory        | -0.77                    |       | (-1.58, -0.09) | 0.38 | -.33  | **.043**|

| **Global cognitive index**    |                          |       |              |      |       |        |      |
| Constant                      | 47.40                    |       | (45.00, 49.85) | 1.24 | .001  | .13    |
| Executive function            | 0.22                     |       | (0.01, 0.40)  | 0.10 | .36   | **.037**|

| **HAD total score**           |                          |       |              |      |       |        |      |
| Constant                      | -10.10                   |       | (-14.97, -4.49) | 2.64 | .001  | .09    |
| Motor function                | 0.524                    |       | (-0.23, 1.20)  | 0.37 | .30   | .189   |

| **HAD anxiety subscale**      |                          |       |              |      |       |        |      |
| Constant                      | -9.60                    |       | (-14.10, -5.62) | 2.12 | .001  | .10    |
| Motor function                | 0.95                     |       | (-0.05, 2.26)  | 0.58 | .31   | .111   |

Abbreviations: HAD: Hospital Anxiety and Depression Scale.
4 Discussion

This thesis aimed to investigate change in cognitive functioning in PD patients 1 and 5 years after DBS surgery, in addition to pre-operative factors predicting potential negative consequences of STN stimulation, and characteristics of those patients profiting and not profiting from DBS treatment from a cognitive point of view. Main findings of relevance to these research questions are discussed below.

4.1 Change in cognitive functioning after DBS STN

Compared with normal aging

Results from baseline neuropsychological assessments showed that the study sample’s performance already differed significantly from the normative average before DBS-surgery. All cognitive domain scores except word generation were below average. Nevertheless, all domain scores were within one standard deviation from $T = 50$, with the exception of motor function, which stood out as the poorest baseline function with a mean $T$-score of 35.2. This is to be expected considering the neurological clinical features of PD.

Another domain score that stood out was word generation, with a mean $T$-score of 55.1, which is almost a standard deviation higher than the second highest domain score (attention, $T = 46.9$). This could be related to the study sample’s high general ability level, as WASI FSIQ and the baseline word generation domain scores correlated significantly $r = .470 \ (p = .000)$. However, WASI FSIQ also correlated with functions that were below the normative average at baseline, like executive functions $r = .448 \ (p = .001)$. This pattern of correlations, although with somewhat smaller coefficients, is consistent with that found by Lee et al. (2012), using a large study sample ($n = 472$) of a similar age range as the current study (65-88). Thus, it seems correlations with general cognitive ability alone does not fully explain the discrepancy between word generation and other functions. Factor analyses have shown that verbal fluency has a strong language component (Unsworth, Spillers & Brewer, 2011; Whiteside et al. 2016), perhaps contributing to the strong word generation performance of this highly educated study sample. As previously mentioned, verbal functions other than fluency are among the least affected cognitive functions in PD (Lezak, 2012).
Limitations of the normative data could be a contributing factor to the observed discrepancy between verbal fluency and other cognitive domains. Performance on measures of verbal fluency has been shown to be influenced by educational level (Obeso, Casabona, Bringas, Álvarez & Jahanshahi, 2011; Kawano et al., 2010). The normative data that was used in the current study is not education-specific. Thus, it is possible that the observed results would have been closer to average if compared with a more representative normative population. However, the same could be said for several of the test in this study, and no other results were above the normative mean. Linguistic differences between English and Norwegian is another potential influence, as the normative data is based on the performance of English-speakers. However, a Norwegian normative study found no significant differences in performance between the Norwegian normative sample and comparable normative data from English-speakers (Egeland, Landrø, Tjemsland & Walbækken, 2006).

Overall, the study sample performed below the normative average pre-surgery, consistent with findings of cognitive decline even in the early stages of PD (Aarsland, Brønnick & Fladby, 2011; Elgh et al., 2009). However, motor function was the only function that could be classified as impaired based on the Movement Disorder Society Task Force’s guidelines of a range of one to two standard deviations below average (Litvan et al., 2012). Nevertheless, as this is a highly educated group with a general cognitive ability level above average, it is likely that the ipsative change from premorbid functioning is greater than that which is reflected by normative comparisons.

From baseline to one year post-operatively, performance declines compared to the normative sample within the central domains of processing speed, executive function and word generation. Between one and five years post-surgery, more extensive decline compared to the normative sample is seen for all domains except motor function. Thus, it appears that the study sample’s cognitive performances decline at a faster pace than those of the normal population. In the following, the question of whether these changes should be attributed to DBS STN or normal progression of PD will be discussed.

**Compared with normal progression of Parkinson’s disease**

A question of relevance to the following discussion is in what way the timing of cognitive changes influences the interpretation and attribution of results to STN DBS or normal progression of PD. This is a challenging question to answer, as the vast majority of studies on
cognitive consequences of STN DBS have follow-up periods that only last between 6 months and 2 years. As previously mentioned, the meta-analysis by Wu et al. (2014) indicated that executive function declined in the first year following surgery, remained stable between 2 and 5 years, and then continued to decline between 5 and 9 years post-operatively. A possible interpretation is that the observed change in the first stage represents the effect of the STN DBS intervention, that this effect stabilizes after the first year, and that the decline in later stages represents normal progression of PD. However, as the meta-analysis included self-control studies, conclusions about causality cannot be drawn. A controlled study with a follow-up period of 6 years found largely comparable decline of cognitive function in the STN DBS and control group, however they did not measure function between baseline and 6 years post-surgery (Merola et al., 2014). A systematic review of 1400 patients receiving STN DBS, with a mean follow-up period of 13 months (95% CI = 4-21) showed reduced function in several cognitive domains (Temel et al., 2006), consistent with results of controlled studies with similar follow-up periods (Zahodne et al., 2009; Smeding et al., 2006). In addition, Aybek et al. (2007) found significantly higher incidence rates of dementia in the year following STN DBS surgery than the highest rates that have been reported for medicated PD patients. Taken together, these studies indicate that STN DBS has an effect on cognitive function in the year following surgery, and that this effect lessens over time, with cognitive function several years after surgery more likely representing normal progression of PD. Nevertheless, due to the lack of controlled studies with long follow-up periods, the possibility of long-term effects of STN DBS cannot be ruled out.

Processing speed
While a meta-analysis of controlled studies on the effect of STN DBS showed no significant change in processing speed (Xie et al., 2016), the current study paints a different picture, thus supporting other meta-analyses and individual studies that found significant decline of processing speed, though without control groups (Williams et al., 2011; Combs et al., 2015). As previously mentioned, the assessment of processing speed in PD is complicated by impairments in motor function and speech production (Schapira, Chaudhuri & Jenner, 2017). Muslimovic, Post, Speelman & Schmand (2005) investigated cognitive function in a group of newly diagnosed PD patients who displayed motor symptoms well within the mild range on the UPDRS scale (mean = 16.8). Regardless of short disease duration and low level of neurological symptoms, they found significantly worse processing speed performance in the
PD group than in healthy controls, using similar measures of processing speed as the current study (WAIS Digit Symbol test and D-KEFS Color-Word Color Naming and Word Reading).

Thus, it is likely that some of the observed decline in the current study should be attributed to normal progression of cognitive decline in PD. This hypothesis is supported by the fact that the reduction in function is also substantial in the later stages of the study, when normal progression is likely to have more influence than STN DBS. When looking at the development in this first year, there is a greater reduction of performance on the SDMT than the less complex D-KEFS CWIT subtests Color Naming and Word Reading. The SDMT is a sensitive test that involves higher order cognitive functions such as working memory, complex scanning and selective attention (Lezak, 2012, p. 421). Thus, it is possible that the observed decline of processing speed in the first year represents indirect consequences of decline in executive function or working memory. After the first year, the less complex measures of processing speed (CWIT 1+2) comprise the majority of processing speed reduction, more likely reflecting normal progression of PD.

Executive functions and attention/working memory
Executive impairments are among the most established findings in normally developing PD (Kehagia, Barker & Robbins, 2013; Zgaljardic et al., 2003), even in early stages (Muslimovic et al., 2005). It has been proposed that main features of the executive impairments in PD are dysfunction of higher order attentional functions and disruption of balance between inhibition and facilitation, leading to challenges with shifting, suppression of irrelevant stimuli and initiation/internally cued behavior (Emre, 2003; Kudlicka, Clare & Hindle, 2013). The current study found moderate decline of overall executive function performance across measurement points. Considering the amount of change between the 1- and 5-year-follow-up, the decline in the first year is higher than would be expected, indicating that in the short term, STN DBS has an influence on executive function. This finding is consistent with previous research on the effect of STN DBS (Xie et al., 2016, Combs et al., 2015, Halpern et al., 2008).

Performances on switching (D-KEFS CWIT 4 and Verbal Fluency 3) and inhibition (CWIT 3) are comparable at baseline, but inhibition shows somewhat more decline after five years. When looking at the difference between time points, it seems that this development takes place between one and five years post-surgery, perhaps reflecting normal progression of PD rather than effects of DBS treatment. Conversely, between baseline and one year, switching is somewhat more affected than inhibition when considering the numbers of errors that are
made. This is consistent with the findings of Pillon et al. (2000), who investigated change in several aspects of executive function after STN DBS, but inconsistent with other studies showing stronger decrease of inhibition than switching (Wu et al., 2014).

A comparison of time and error measures independently of inhibition/switching condition shows noteworthy differences, with time measures showing more significant decline than error measures. This is an interesting finding considering the observed marked reduction in processing speed in the current study in combination with other research showing relationships between processing speed and performance on time sensitive measures of executive function (Albinet, Boucard, Bouquet & Audiffren, 2012; Nelson, Yoash-Gantz, Pickett & Campbell, 2009). However, as previously discussed, features of executive function also play a part in processing speed, especially as task complexity increases, making this a complicated two-way relationship (Cepeda, Blackwell & Munakata, 2013, Lezak, 2012).

Another function with close ties to executive function is working memory, consisting of functions like storage, processing, supervision and coordination (Oberauer, Heinz-Martin, Wilhelm & Wittman, 2004). The current study found significant reductions in working memory performance between the 1- and 5-year follow-up, but not in the first year after surgery, suggesting that the observed modest decline in working memory is not an immediate consequence of STN DBS.

**Word generation**

A reduction of verbal fluency performance is among the most established findings after STN DBS (Wu et al., 2014, Xie et al., 2016), and the results of the current study support this finding. Between baseline and the one-year follow-up, word generation represents the largest decline of all the cognitive domains, with phonemic and semantic fluency declining at the same rate. Even though reductions in verbal fluency are common in the normal PD population (Lezak, 2012), such a substantial decline over the course of only one year likely represents an effect of the DBS intervention.

From one to five years post-operatively, a different pattern emerges, with semantic fluency performance declining more than phonemic fluency. This is consistent with findings of stronger impairments in semantic than phonemic fluency in the general PD population (Henry & Crawford, 2004), but inconsistent with findings of relatively more decline in phonemic than semantic fluency following STN DBS (Xie et al., 2016). Taken together, these results
could indicate that the observed decline in semantic fluency in the latter years of the study are a result of normal progression of cognitive changes in PD, rather than the stimulation treatment itself. In fact, Pillot et al. (2000) found significant decline in semantic fluency performance, but not in phonemic fluency, regardless of DBS stimulation being “on” or “off” at the time of assessment. However, their results were based on a follow-up period of only one year.

Verbal fluency is a complex cognitive function, relying on both executive and verbal processes. It has been suggested that verbal fluency could be broken down into clustering and switching components, and that these two components in turn are affected by other cognitive abilities. In this context, switching entails the ability to continually update and generate categories or single items, and is considered to rely on executive functions. Clustering, on the other hand, reflects the number of words one is able to fill into the generated categories, and is thought to rely more on linguistic knowledge base (Unsworth, Spillers & Brewer, 2011). Other cognitive functions that could influence verbal fluency performance are inhibition of earlier or incorrect responses and efficient verbal retrieval and recall (Henry & Crawford, 2004). The latter is sometimes referred to as lexical access speed, and could be influenced by both cognitive speed and aspects of semantic memory (Shao, Janse, Visser & Meyer, 2014). In fact, processing speed is becoming increasingly acknowledged as an important contributor to verbal fluency along with verbal and executive functions (McDowd et al., 2011; Elgamal, Roy & Sharratt, 2011).

From baseline to one year post-operatively, phonemic and semantic fluency decreases at the same rate, with cooccurring declines in executive function, processing speed and verbal recall/semantic retrieval. Thus, considering the aforementioned research on cognitive functions influencing verbal fluency, it is possible that the observed decline in verbal fluency after DBS surgery is an indirect consequence of DBS’s effects on other cognitive functions. Some argue that the same underlying cognitive functions affect phonemic and semantic fluency equally (Unsworth, Spillers & Brewer, 2011), however studies using clinical groups like PD and Alzheimer patients indicate differential influence of cognitive deficits on phonemic and semantic aspects of verbal fluency (e.g. Henry & Crawford, 2004). The current study supports the latter position, as the notable decline in semantic relative to phonemic fluency points to different processes taking place in the two conditions. From one to five years post-surgery, semantic fluency decreases more than phonemic fluency, while executive
functions show about the same reduction as between the first two measurement points. The disproportionate reduction in semantic fluency does not seem to be caused by semantic retrieval, which remains stable from one to five years post-surgery. However, the reduction in semantic fluency is accompanied by a noteworthy decline in processing speed. A possible explanation is that the reduction in processing speed affected the speed of retrieval from semantic memory to a larger degree than the speed of the executive processes that are considered to underlie phonemic fluency.

Memory and learning
Both verbal and visuospatial memory are among the cognitive functions showing the least amount of change in the years following DBS surgery. The only measure to significantly differ between surgery and the 1-year-follow-up is delayed verbal recall. This finding is consistent with the hypothesis of specific problems with the retrieval process in PD. Proponents of this hypothesis suggest that the problems with free recall are caused by deficits in executive functions, specifically an inability to generate retrieval strategies or initiate retrieval processes (Whitehead & Brown, 2009; Dubois & Pillon, 1997). Other studies have identified this trend after STN DBS (Saint-Cyr et al., 2000; Morrison et al., 2004; Halpern et al., 2008), however it is also seen in normally developing PD (Costa et al., 2014; Whitehead & Brown, 2009). Factors supporting the possibility of the observed decline being caused by the DBS intervention are that it took place within the first year after DBS, that it did not decline significantly in the years that followed, and that it cooccurred with the decline of other functions that have been identified as contributors to the free recall process, namely executive function and processing speed (Higginson et al., 2003; Beudouin, Clarys, Vanneste & Isingrini, 2009). Thus, it is possible that the reduction in delayed verbal recall is directly or indirectly caused by STN DBS surgery.

Overall, visuospatial memory function shows greater reductions than verbal memory function, though this reduction takes place between 1 and 5 years post-surgery, with no significant change in the first year. Thus, the results of this study are inconsistent with those of other studies that have found modest reductions of both encoding (Saint-Cyr et al., 2000), recall and recognition (Williams et al., 2011; Combs et al., 2015) of visuospatial material in the first couple of years after STN DBS. The observed decline between 1 and 5 years likely represents normal development of PD, as visuospatial impairments are an established finding in the PD population, especially in late stages of the disease (Seichepine et al., 2015; Mills et al., 2016).
4.2 Predictors of change in cognitive function

Research on the effects of STN DBS on outcome measures like disease deterioration and quality of life have identified pre-operative factors that are contraindicative to DBS, such as behavioral problems, recent or previous psychiatric illness, a history of poor response to Levodopa and significant cognitive dysfunction (Chang & Chou, 2006; Foltynie & Hariz, 2010). Less research has been conducted on what factors predict cognitive change after STN DBS. In the current study, the pre-operative characteristics that were identified as predictors of change in cognitive function are age, duration of disease, baseline cognitive function (global cognitive index) and severity of PD-related neurological symptoms as measured by the UPDRS IV and Hoehn and Yahr scale (off). In the following section, their contributions to cognitive outcome is discussed in light of relevant research and potential mechanisms of influence.

**Age and duration of disease**

Age and duration of disease at the time of surgery are closely related concepts. Nevertheless, linear regression analysis showed that they influenced the development of cognitive function in somewhat different ways. In the first year, age predicted change in motor function (8%), attention/working memory (10%) and visual learning/memory (14%), while duration of disease explained development of results in attention/working memory (9%) and executive functions (8%). The predictions are modest, but significant, and the influence of age on change in visual learning/memory is above the commonly used threshold for medium effect sizes ($R^2 \geq 13$; Field, 2013, p. 313).

These results are of relevance to the ongoing discussion about the timing of DBS treatment. A central study in this discussion is the German-French EARLYSTIM trial, which found better treatment results for relatively young patients (mean age 52) receiving STN DBS than those receiving standard Levodopa treatment (EARLYSTIM Study Group, 2013). They investigated outcome measures like quality of life and motor function. The results of the current study indicate that the same trend is seen for certain aspects of cognitive function, with higher age and longer disease duration predicting more cognitive decline in the first year after surgery, consistent with previous research with and without control groups (Smeding et al., 2011; Odekerken et al., 2015).
The possibility of beginning DBS treatment earlier brings with it challenges like the risk of a ceiling effect for benefits of treatment and high costs associated with highly qualified long-term follow-up (Schüpbach et al., 2014). In addition, the different subtypes and trajectories of disease progression in PD are not fully understood, and known subtypes can be difficult to differentiate without observing disease progression over several years (Marras & Lang, 2013). Therefore, early DBS could increase the risk of including patients who go on to exhibit neurological, psychological and cognitive features that are related to poor outcome of DBS. On the other hand, early DBS could prevent or postpone the development of complications of PD, such as side effects from high doses of medication like motor fluctuations, dyskinesias, confusion, delirium and psychotic symptoms (Foltynie & Hariz, 2010; Olanow & Stocchi, 2017; Combs & Cox, 2017). In addition, severe psychosocial consequences of PD and deterioration of quality of life can be difficult to reverse.

The results of predictions of cognitive change from baseline to five years post-surgery are likely influenced by normal development of cognitive decline in PD. Nevertheless, it cannot be ruled out that some proportion of the relationships between predictors and outcome reflect long-term effects of chronic STN stimulation. After five years, age still predicts change in attention/working memory (10%) and visual learning/memory (12%), and duration of disease still explains a proportion of the change in executive function performance (20%). Thus, age is no longer a significant predictor of change in motor function, and disease duration no longer predicts change in attention/working memory performance. The transient quality of these relationships could indicate that they were temporary effects of the DBS intervention, or that other unidentified factors became more influential as time passed.

Between 1 and 5 years post-surgery, age predicted change in performance within executive functions (12%) and word generation (16%), while duration of disease predicted change in visual learning/memory (11%). Executive function and word generation are known to progressively decline in normally developing PD (Henry & Crawford, 2004; Kudlicka, Clare & Hindle, 2011), and visuospatial functions become more prominent in later stages of the disease, especially in those patients whose cognitive impairments develop into Parkinson’s disease dementia (Emre, 2003). Thus, it seems likely that these results reflect normal progression of PD. The fact that age predicted change in verbal fluency after five years, and not after one year, indicates that the observed decline in verbal fluency in the first year following STN DBS is not mediated by participants’ age at the time of surgery.
Baseline cognitive function

Serious cognitive dysfunction and dementia are recognized as important exclusion factors for STN DBS (Foltynie & Hariz, 2010). Less is known about the impact of mild cognitive impairments (MCI) and normal variation of cognitive function in PD, as most studies on outcome of DBS STN have focused on non-cognitive predictors and outcome measures such as neurological functioning or quality of life (Lang et al., 2006). One exception is a study by Kim et al. (2014), who found pre-operative MCI to be a risk factor for global cognitive decline one year after STN DBS. Looking at predictive properties of specific cognitive domains, Smeding et al. (2011) found cognitive outcome to be predicted by baseline attention performance, but not by processing speed or verbal fluency.

In the current study, baseline Global cognitive index score significantly predicted 13% of the variation of decline in executive function performance after five years, but showed no predictive ability of change in performance in any cognitive domains after one year. Thus, baseline cognitive function did not appear to be a predictor of short-term cognitive outcome following STN DBS, inconsistent with the trend observed by Kim et al. (2014), and more in line with those of Smeding et al. (2011). However, the selection procedure of the current study did not allow for inclusion of patients with notable cognitive impairments, perhaps limiting the range of Global cognitive index scores in the lower end of the scale. Therefore, an alternative explanation is that the cognitive inclusion criteria, defined as Mattis score >130, succeeded in excluding candidates with high risk of post-operative deterioration due to severe pre-operative cognitive impairments.

Severity of PD-related neurological symptoms

Higher (worse) scores on the UPDRS-IV and Hoehn and Yahr scale (off) predicted less decline in verbal learning/memory (12%) and executive function (12%), respectively. They predicted change between baseline and the one-year follow-up, and not between baseline and five years. As such, it is possible that the predictions are connected to effects of the STN DBS intervention. As previously stated, the UPDRS-IV measures motor complications and stability of treatment effects. Thus, the results of the current study indicate that more unstable treatment effects pre-surgery predicts less decline in verbal learning/memory post-surgery. This is inconsistent with results from Smeding et al. (2011), who found that low response to medication at baseline predicted cognitive decline post-surgery.
The Hoehn and Yahr scale estimates disease progression by measuring the severity of neurological symptoms. In the current study, Hoehn and Yahr scores as measured while patients were off medication, and not whilst on medication, were related to less decline in executive function. That is, more severe non-medicated pre-operative motor symptoms predicted less decline in executive function one year post-surgery. The fact that the same relationship was not observed between executive function and Hoehn and Yahr “on” scores indicates that the rank order of participants’ scores in the two group were different. In that case, the patients with the worst “off”-scores were not the same as the ones with worst “on”-scores. This would mean that the ones with worse “off”-scores had relatively better effects of medication compared with the overall study sample. If so, these results indicate that higher responsiveness to Levodopa is related to less decline in executive function post-operatively. This would be in line with results from Smeding et al. (2011).

There is general consensus that high responsiveness to Levodopa predicts favorable neurological outcome of STN DBS (e.g. Bronstein et al., 2011). In the current study, predictions with Hoehn and Yahr “off” indicated that the same trend is seen for cognitive outcome, while predictions with UPDRS-IV did not. The latter predicted change in verbal learning/memory outcome, which was one of the cognitive domains showing the least amount of change following STN DBS. Hoehn and Yahr “off” predicted change in executive functions, which is commonly found to be reduced following STN DBS. Therefore, the results from Hoehn and Yahr, indicating that higher pre-operative responsiveness to Levodopa predicts favorable executive outcome, are perhaps the most clinically relevant.

4.3 Strengths and limitations of the study

One of the strengths of this study is that is has a longer follow-up-period than most comparable studies, thus allowing for observations of clearer trends or reversal of transient negative effects of DBS surgery. In addition, the study uses standardized measures of pre-operative characteristics and neuropsychological function. The measures of neuropsychological function cover a range of domains of relevance to the research questions, and considerations were made with regard to suitability for repeated measurements. Even though measures were taken to avoid them, the possibility of learning effects cannot be ruled out. However, considering the design of the current study, learning effects would not create false positive results, but rather limit the size of observed trends.
As previously discussed, the normative data was not education-specific, complicating the interpretation of results in a study with highly educated participants. In addition, the analysis of neuropsychological changes would have been more complete if it included a measure of visuospatial function. A larger number of participants would be ideal with regard to statistical strength. There is a clear majority of men \( (n = 41) \) versus women \( (n = 14) \) in the study. However, as research has shown 91\% higher incidence rates for men (19.0 per 100 000) than women (9.9 per 100 000) (Van Den Eeden et al., 2003), the uneven gender distribution of the study sample should not adversely affect generalizability of results.

The most considerable limitation of the study is its lack of a clinical control group, substantially affecting the degree to which conclusions can be drawn about causality. Acquiring suitable control groups for this type of research is difficult. STN DBS is a relatively new treatment method, and patients are normally not offered this treatment until medication (Levodopa) ceases to have sufficient treatment effects (Mosley & March, 2015). At the same time, the suitable control group for an STN DBS treatment group would be patients still having an effect from Levodopa (Xie et al., 2016). Different disease mechanisms could be in place in the two patient groups, and the comparison between them is therefore flawed. However, much is known about the normal development of cognitive functioning in PD, creating some grounds of comparison for self-control studies.

The analyses in the current study are based largely on comparisons of means, as this is useful when investigating trends and systematic differences. However, it is important to keep in mind that potentially important information about the trajectories of subgroups are hidden in this type of study design. Lastly, it would have been of interest to include more measures of pre-operative clinical characteristics in order to identify more factors of relevance to selection procedures for STN DBS. Relevant additional information would have been more detailed measures of psychological functioning and quality of life, self-reported executive function and information from relatives/spouses.

### 4.4 Implications and further research

The current study has contributed to increased knowledge about an important aspect of treatment with STN DBS. Firstly, it has presented information about the cognitive consequences of this procedure, both short- and long-term. This information enables patients, relatives/spouses and health professionals to make more informed treatment choices with
regard to individual patient’s priorities and needs. Secondly, the current study has given information about predictors of cognitive function following STN DBS, thus contributing to the ongoing process of selecting optimal inclusion and exclusion criteria for this treatment method. Future research should aim to resolve the current conflicting and inconclusive nature of research findings on cognitive effects of STN DBS. To this end, there is a need for more controlled studies that include longer follow-up periods. Another important area of future research is further investigation of risks and benefits associated with earlier initiation of STN DBS treatment.

4.5 Conclusions

The primary aim of this thesis was to investigate the effect of STN DBS-treatment on neuropsychological functioning. A central part of this investigation was describing the study group’s changes in cognitive functioning one and five years after DBS surgery compared with baseline levels. Already at baseline, it was apparent that the study group performed somewhat lower than the normative average, despite their high educational level. Overall, the decline of function in the years following DBS surgery was more rapid than that of the normative population.

A more challenging question to answer was the degree to which the observed decline differed from the cognitive changes in normally developing PD. When looking at the timing of the observed changes, in combination with knowledge from other research about normal development of PD and effects of STN DBS on cognition, the results of the current study indicate that processing speed, executive functions (inhibition and switching), word generation and delayed verbal recall were affected by STN DBS. As discussed, the relationships between these functions are dynamic and complex, raising the question of which functions are directly affected by STN DBS, and which are indirectly influenced by the decline of other functions. The pattern of results in the current study indicates that decline in executive function plays a central role in these interactions, consistent with theories of underlying mechanisms of change of cognition in PD. In addition, the current study supports the recurring finding of reduced verbal fluency following STN DBS. Working memory and verbal/visuospatial memory functions other than delayed verbal recall appeared to be relatively well-preserved following DBS surgery.
The other central question of this thesis was to identify pre-operative characteristics predicting cognitive outcome of STN DBS treatment. The results showed that age and duration of disease were the strongest predictors of cognitive outcome, including changes in motor function, attention/working memory, visual learning/memory and executive function in the year following STN DBS. In addition, measures of pre-operative neurological symptom severity and stability of treatment effects predicted outcome of executive function and verbal learning/memory, respectively. Between one and five years post-operatively, when normal progression of PD is more likely to influence results, age and duration of disease were still important predictors, together with baseline global cognitive function.

In conclusion, the results of the current study indicate that STN DBS treatment adversely affects some, but not all, domains of cognitive function. The results further indicate that age and duration of disease are the most important pre-operative characteristics to take into account when considering patients for STN DBS treatment, from a cognitive point of view. However, further research is needed to separate the effects of STN DBS on cognitive function from normal progression of PD.
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