Effects of Deep Brain Stimulation of the subthalamic nucleus and the pedunculopontine nucleus on cognitive function in Parkinson's disease.

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Abstract

The general aim of this thesis was to investigate the cognitive effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the pedunclopontine nucleus (PPN) in Parkinson's disease (PD).

In Study 1, acute STN stimulation did not induce impulsivity on a probabilistic decision-making task, suggesting STN-DBS induced impulsivity may occur in tasks involving conflict, reward or time pressure. This study has clarified that the inhibitory deficits associated with STN-DBS are situation and task specific, which makes it clear why new cases of post-operative impulse control disorders are only reported in some patients.

In Study 2, the STN-DBS induced decline in verbal fluency (VF), greater for semantic than phonemic fluency, was found to be a surgical rather than an acute stimulation effect, mainly due to reduced switching but no change in cluster size. Therefore, future work in identifying the mechanisms of the STN-DBS induced VF decline should focus on surgical rather than stimulation effects.

In Study 3, patients failed to benefit from corrective feedback to enhance their learning relative to a trial-and-error version when performing visual conditional associative learning tasks (VCLT) with STN-DBS on versus off. STN-DBS seemed to influence proactive interference resolution on the VCLTs. These results have implications for the use of adjunct interventions such as speech therapy or physiotherapy following STN-DBS surgery.

In Study 4, PPN-DBS surgery did not have an impact on most aspects of cognition assessed and the only consistent decline was in switching category VF. For the two patients who developed dementia after PPN-DBS surgery, resuming low frequency stimulation improved working memory and attention.

The findings from these studies provide further evidence and clarity regarding the cognitive sequel of STN-DBS and PPN-DBS for PD and confirm that the former can be a good treatment of choice for mid to late-stage Parkinson's disease without the risk of major cognitive adverse effects.

Impact Statement

The insights that were gained from my PhD research have an impact on both the academic and clinical field of Parkinson's disease. From an academic point of view my research has contributed towards our understanding of how certain brain structures i.e. the subthalamic nucleus and pedunculopontine nucleus contribute towards motor functions and a variety of cognitive functions. This knowledge can be used in future research to understand a variety of cognitive functions and deficits not only in Parkinson's disease but also other patient and healthy populations. From a clinical perspective the findings of my research contributed to the body of evidence supporting the general safety of Deep brain stimulation procedures, and their positive effect on the motor symptoms of Parkinson's disease. However, they also indicated that in a certain Parkinson's disease population, deep brain stimulation may cause adverse cognitive events that may result in poor quality of life. This knowledge can be used in future to select possible candidates for deep brain stimulation surgery even more carefully, by fully assessing their cognitive profile. I hope my work inspires future research.

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List of conference presentations

Cognitive Neuroscience Society Meeting 2016, Poster presentation

The Subthalamic nucleus (STN) and integration of probabilistic information during decision-making: evidence from the effect of STN-DBS in PD.

Authors: Friederike Leimbach, Vladimir Litvak, Dejan Georgiev, Patricia Limousin, Tom Foltynie, Marjan Jahanshahi, Rafal Bogacz

Cognitive Neuroscience Society Meeting 2017, Poster presentation

Effects of deep brain stimulation of the subthalamic nucleus in Parkinson's disease on verbal fluency.

Authors: Friederike Leimbach, Socorro Pieters, Catherine Cheung, Leonora Wilkinson, Donna Page, Catherine Jones, Ludvic Zrinzo, Marwan Hariz, Tom Foltynie, Patricia Limousin, Marjan Jahanshahi

List of papers submitted for publication

The short-term, long-term and acute stimulation effects of subthalamic deep brain stimulation on cognitive function in Parkinson's disease – A review and meta-analysis.

Authors: Friederike Leimbach and Marjan Jahanshahi. *Under peer review*

Deep brain stimulation of the subthalamic nucleus does not affect the decrease of decision threshold during the choice process when there is no conflict, time pressure or reward.

Authors: Friederike Leimbach, Dejan Georgiev, Vladimir Litvak, Christalina Antoniades, Patricia Limousin, Marjan Jahanshahi and Rafal Bogacz, *J Cognitive Neuroscience, In* Press

The effects of deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease and Progressive Supranuclear Palsy on cognition.

Authors: Friederike Leimbach, James Gratwicke, Tom Foltynie, Marwan Hariz, Patricia Limousin, Ludvic Zrinzo and Marjan Jahanshahi. *Under peer review*

Dissociable effects of subthalamic nucleus deep brain stimulation surgery and acute stimulation on verbal fluency in Parkinson's disease.
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The effects of STN-DBS on associative learning of verbal and non-verbal information in PD.
Friederike Leimbach, Leonora Wilkinson, Soccoro Pieters, Marwan Hariz, Patricia Limousin, Marjan Jahanshahi. *Under peer review*

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Abbreviations

ACA	anterior cingulate area		HC	hippocampal cortex
APA	arcuate premotor area		Hcrt	hypocretin
AVLT	Auditory verbal learning test		HVLT-R	Hopkins verbal learning test revised
BDI	Beck depression inventory		Hz	herz
BIS	Barrat impulsiveness scale		ICD	impulse control disorder
BNT	Boston naming test		IGT	Iowa Gambling task
BTA	Brief test of attention		ITG	inferior temporal gyrus
BVMT	Brief visual memory test		JLOT	Judgement of line orientation test
CAL	conditional associative learning		LB	Lewy bodies
CANTAB	Cambridge Neuropsychological Test Automated Battery		LMT	Logical memory task
CAUD	caudate		LN	Lewy neurites
CBTT	Corsi's block tapping test		LOF	lateral orbitofrontal cortex
ChAT	choline acetyltransferase		M1	primary motor cortex
CNS	central nervous system		MC	motor cortex
CMC	cingulate motor cortex		MCI	mild cognitive impairment
CVLT	California verbal learning test		MDmc	medialis dorsalis pars magnocellularis
DA	Dopamine		MDpc	medialis dorsalis pars parvocellularis
DKEFS	Delis-Kaplan executive function scale		MMSE	mini mental state examination
DSM	diagnostic and statistical manual of mental disorders		MSA	multisystem atrophy
EC	entorhinal cortex		MSPRT	multihypothesis SPRTS
EEG	electroencephalography		NART	National adult Reading test
FEF	frontal eye fields		NMCS	Nelson modified card sorting test
fMRI	functional magnetic resonance imaging		OMOT	Odd man out test
DBS	deep brain stimulation		Orx	orexin
GNGT	Go-No-Go task		PAL	Paired associate learning
GPe	external globus pallidus		PASAT	paced auditory serial addition Task

PET   positron emission tomography

PD   Parkinson's disease

PD-D   Parkinson's disease dementia

Pf   parafiscular cortex

PMC   premotor cortex

PPC   posterior parietal cortex

PPNc   pedunculopontine nucleus pars compacta

PPNd   pedunculopontine nucleus pars dissipata

PUT   putamen

PVSAT   paced visual serial addition task

PWL   Paired word learning

QDQ   quick delay questionnaire

RAVLT   Rey auditory verbal learning test

RBANS   Repeatable battery of neuropsychological status

RBMT   Rivermead behavioural memory test

REM   rapid eye movements

RM   Raven's matrix

RMT   Recognition memory test

RNG   random number generation

ROCF   Rey-Osterrieth complex figure

RT   reaction time

SAS   Starkstein apathy scale

SC   somatosensory cortex

SMA   supplementary motor area

SNc   substantia nigra pars compacta

SNr   substantia nigra pars reticulate

SPRT   sequential probability ratio test

SPSRQ   sensitivity to punishment and reward questionnaire

SSRT   stop signal reaction time

STDS   Standardized test of direction sense

STG   superior temporal gyrus

STN   subthalamic nucleus

TMT   trail making test

TOH   Tower of Hanoi

UPDRS   unified Parkinson's disease rating scale

µs   microseconds

V   Voltage

VAmc   ventralis anterior pars magnocellularis

VApc   ventralis anterior pars Parvocellularis

VCLT   visual conditional associative learning task

VF   verbal fluency

VFDT   Visual form discrimination test

VLm   ventralis lateralis pars medialis

VLo   ventralis lateralis pars oralis

VP   ventral pallidum

VS   ventral striatum

VL   ventral lateral nucleus

WAIS   Wechsler adult intelligence scale

WASI   Wechsler abbreviated scale of intelligence

WCST   Wisconsin card sorting test

WMS   Wechsler memory scale

WPT   weather prediction task

ZI   zona incerta

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Für Mama

Chapter 1. Introduction

1.1 The basal ganglia, the subthalamic nucleus and the pedunculopontine nucleus
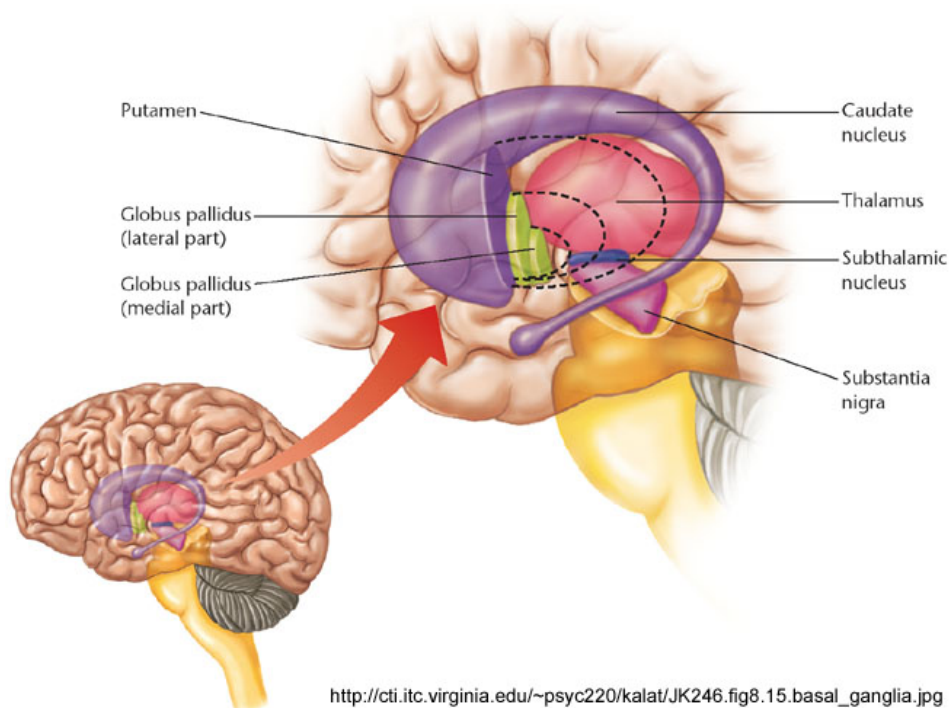
Figure 1.2 The nuclei of the basal ganglia and their location in the human brain.

The basal ganglia are a collection of brain areas that are considered to be involved in response selection (Redgrave, Prescott & Gurney, 1999). The nuclei of the basal ganglia include the subthalamic nucleus (STN) and the striatum as the input areas of the basal ganglia, the globus pallidus (GP) and the substantia nigra (SN). The striatum consists of the caudate and putamen and the GP has an internal and external segment (GPi) and (GPe) respectively. Furthermore, the SN consists of the SN pars compacta (SNc) and the SN pars reticulata (SNr). The GPi and the SNr are the main output pathways of the basal ganglia. Figure 1.1 is a schematic representation of the basal ganglia in a human brain. The connections between the basal ganglia and the cortex are called cortico-striatal circuits. Alexander, DeLong and Strick (1986) described five such circuits (Figure 1.2). These were the motor circuit between the supplementary motor area and the motor cortex and the putamen, the associative circuit between the dorsolateral prefrontal cortex and the dorsal caudate, the limbic circuit between the anterior cingulate cortex and the ventral striatum, the orbitofrontal circuit between this area of the frontal cortex and the caudate, and the circuit between the frontal eye fields and the caudate. Originally

it was thought that the basal ganglia control movement via the direct and indirect pathway (Albin, Young, & Penney, 1989; DeLong, 1990) (see Figure 1.3). According to this model all inputs from the cerebral cortex enter the basal ganglia via the striatum and get passed on to the direct – from striatum to GPi/SNr - (movement initiation) or the indirect – from striatum to GPe to STN to GPi/SNr - (movement inhibition) pathway. Normal motor functioning is achieved through balanced activity across the two pathways. Therefore, an imbalance in activity between the direct and indirect pathway leads to hypokinetic (e.g. Parkinson's disease) or hyperkinetic (e.g. Huntington's disease) disorders (Albin et al., 1989, De Long, 1990).
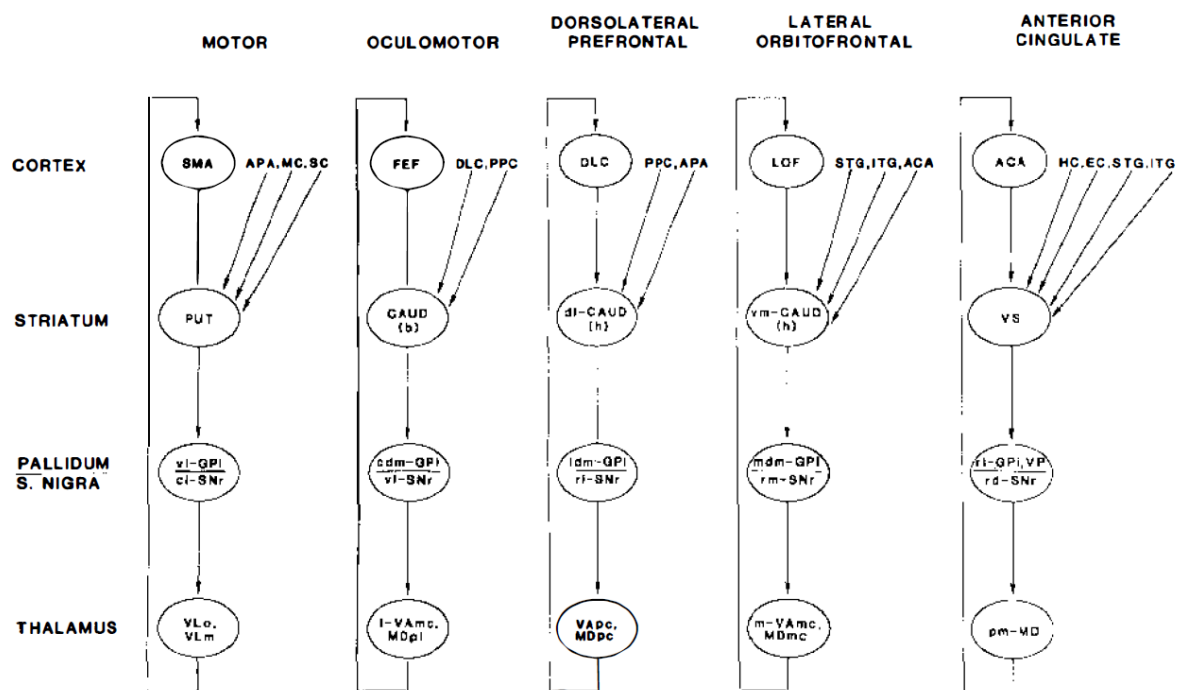
Figure 1.2 Basal ganglia-thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra and thalamus. From Alexander, et al.(1986). Annu Rev Neurosci, 9, 357-381.
ACA= anterior cingulate area; APA= arcuate premotor area; CAUD= caudate, (b) body, (h) head; DLC= dorsolateral prefrontal cortex; EC= entorhinal cortex; FEF= frontal eye fields; GPi= internal segment of the globus pallidus; HC= hippocampal cortex; ITG= inferior temporal gyrus; LOF= lateral orbitofrontal cortex; MC= motor cortex; MDmc= medialis dorsalis pars magnocellularis; MDpc= medialis dorsalis pars parvocellularis; PPC= posterior parietal cortex; PUT= putamen; SC= somatosensory cortex; SMA= supplementary motor area; SNr= substantia nigra pars reticulate; STG= superior temporal gyrus; VAmc= ventralis anterior pars magnocellularis; Vapc= ventralis anterior pars parvocellularis; VLm= ventralis lateralis pars medialis; VLo= ventralis lateralis pars oralis; VP= ventral pallidum; VS= ventral striatum; cl-= caudolateral; cdm-= caudal dorsomedial; dl-=dorsolateral;l-= lateral; ldm-= lateral dorsomedial; m-= medial; mdm-= medial dorsomedial; pm= posteromedial; rd-= rostrodorsal; rm-=rostromedial; vm-= ventromedial; vl-= ventrolateral.

Revision of this classic model of basal ganglia led to the addition of a third 'hyperdirect' pathway (Monakow, Akert, & Kunzle, 1978; Nambu, Takada, Inase, & Tokuno, 1996) (see

Figure 1.3). Inputs from the cortex do not only enter the basal ganglia through the striatum but the STN also receives direct cortical inputs, which are forwarded to the output nuclei and cause tonic inhibition. Cortical connections with the basal ganglia are divided into three functionally differentiated loops, namely the sensorimotor, associative and limbic loops. Within the striatum cortical afferents from sensorimotor regions enter through the post-commissural dorsal putamen; those from associative areas are connected with the pre-commissural putamen and caudate; and limbic projections are made to the nucleus accumbens, the ventral caudate and ventral putamen (Parent & Hazrati, 1995).
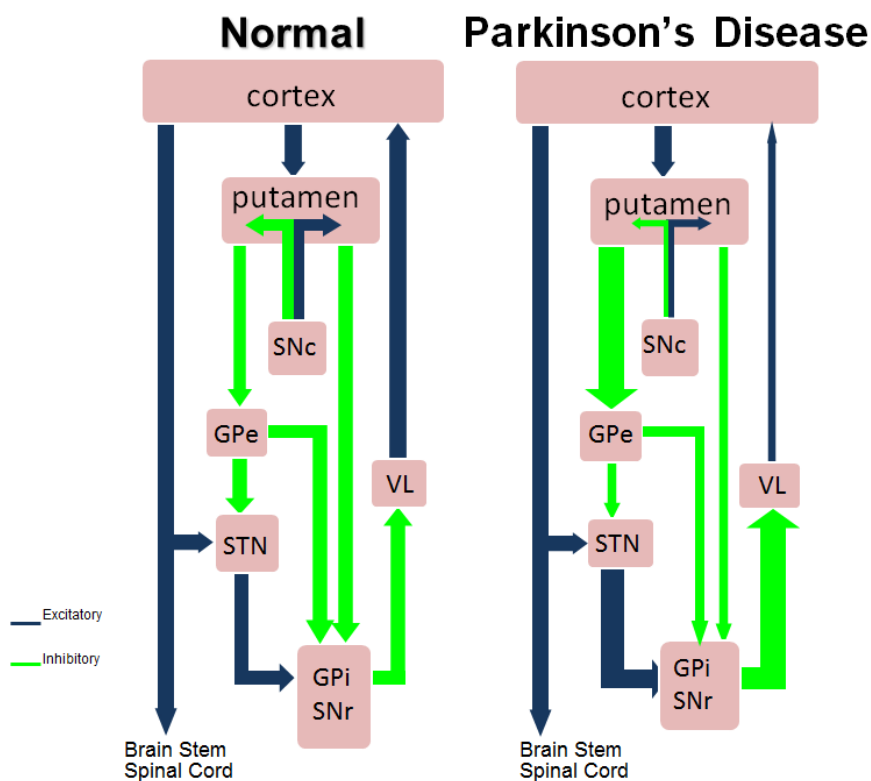
Figure 1.3 Schematic representation of the direct, indirect and hyperdirect pathways in the healthy brain and in the Parkinson's disease (PD) brain.
SNc= Substantia nigra pars compacta; GPe= External segment of the globus pallidus; STN= Subthalamic nucleus; GPi= internal segment of the globus pallidus, SNr= Substantia nigra pars reticulate; VL= Ventral lateral nucleus.

1.1.2 The subthalamic nucleus

The subthalamic nucleus is lens-shaped and has the approximate dimensions of 3 x 5 x 12 mm in humans. Despite its relatively small size, the STN is considered to be involved in modulating the activity of the output nuclei of the basal ganglia. Similar to the other input region of the basal ganglia, the striatum, the STN can be topographically divided into motor, associative and limbic regions (Figure 1.4). Afferents from the primary motor cortex (M1) have connections with the dorsolateral STN, whereas other motor areas including the supplementary motor area (SMA), the premotor cortex (PMC) and cingulate motor cortex (CMC) innervate with the dorsomedial STN (Nambu et al., 1996; Nambu, Tokuno, Inase, & Takada, 1997; Takada et al., 2001). The ventrolateral STN receives mainly associative inputs from pallidum and the ventromedial part of the STN innervates with limbic pallidal areas (Karachi et al., 2005; Shink, Bevan, Bolam, & Smith, 1996).
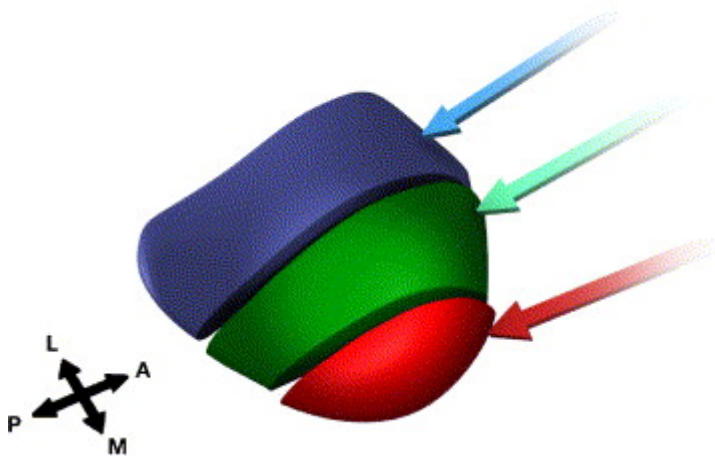
Figure 1.4 Functional subdivisions of the primate subthalamic nucleus (STN). The somatomotor part is located dorsolaterally (blue), the associative part is ventromedially located (green) and the limbic part is the medial end (red). From Temel et al. (2005). Prog Neurobiol, 76(6), 393-413.
P= Posterior; A= Anterior; L= Lateral; M= Medial (Temel, Blokland, Steinbusch & Visser-Vandewalle, 2005).

Cortical inputs to the STN are glutamatergic (Moriizumi, Nakamura, Kitao & Kudo, 1987; Romansky, Usunoff, Ivanov & Galabov, 1979), whereas inputs originating from the pallidum are GABAergic in nature and provide the main inhibitory input to the STN (Fonnum, Gottesfeld & Grofova, 1978; Oertel and Mugnaini, 1984; Smith et al., 1987, 1990a; Smith and Parent, 1988). The STN also receives glutamatergic inputs from the thalamus (Mouroux and Feger, 1993; Nieoullon, Scarfone, Kerkerian, Errami & Dusticier, 1985; Scatton and Lehmann, 1982), more specifically from the parafascicular and

centromedian nuclei (Feger et al., 1994, 1997; Sadikot et al., 1992; Sugimoto and Hattori, 1983; Sugimoto et al., 1983). In primates, projections from the parafascicular nucleus target the medial rostral portion of the STN and the centromedian nucleus projects to the dorsolateral motor region of the STN (Sadikot et al., 1992). Furthermore, the STN receives projections from several brain stem areas, such as dopaminergic projections from the SNc (Brown et al., 1979; François et al., 2000; Lavoie et al., 1989), cholinergic (Gerfen et al., 1982; Jackson & Crossman, 1983; Lavoie & Parent, 1994b; Lee et al., 1988) and non-cholinergic projections (Mesulam et al., 1992; Rye et al., 1987) from the pedunculopontine nucleus (PPN) and serotoninergic projections from the raphe nucleus (Canteras et al., 1990; Woolf & Butcher, 1986).

In primates and rodents, the majority of the efferent projections from the STN target both segments of the GP (Feger et al., 1997; Parent & Hazrati, 1995; Smith et al., 1990b) and are glutamatergic in nature (Carpenter 1981a, b; Smith et al., 1990b). The STN also projects to the SN (Parent & Hazrati et al., 1995; Smith et al., 1990b), mainly targeting the SNr. Projections to the SNc contribute to the regulation of dopamine release (Groenewegen & Berendse, 1990; Parent & Hazrati, 1995; Smith et al., 1990b). In rodents and felines projections from the STN to the SN are mainly glutamatergic (Chang et al., 1984; Kita & Kitai, 1987; Rinvik & Ottersen, 1993). The STN also sends excitatory projections to the striatum (Kita & Kitai, 1987; Smith et al., 1990b).

The findings of animal studies using virus-tracking procedures (Haynes & Haber, 2013), and functional imaging studies using tractography (Lambert et al., 2012) confirmed the functional subdivisions of the STN, although this was not supported by other imaging or meta-analysis data (Keuken et al., 2013; Alkemade, Schnitzler & Forstmann, 2015). According to lesion studies in rodents, projections from the medial prefrontal cortex to the STN are crucial for 'cognitive'/motivational functions such as reward processing (Baunez & Gubellini, 2010; Chudasama, Baunez, & Robbins, 2003; Dias, Robbins, & Roberts, 1996; Eagle & Baunez, 2010; Eagle et al., 2008).

Evidence from magnetic resonance imaging data also suggests connections between associative cortical areas such as the inferior frontal cortex and the supplementary motor

cortex and the STN (Aron, Behrens, Smith, Frank, & Poldrack, 2007). Therefore, the STN is not only involved in the control of motor function but also plays a role in cognition and limbic functions. Most critically, the STN receives input from key cortical areas including the motor cortex, the SMA, the dorsal premotor cortex, the dorsolateral prefrontal cortex, the anterior cingulate cortex and the inferior frontal cortex (Afsharpour et al., 1985; Monakow et al., 1978; Nambu et al, 1997; Parent & Hazrati (1995). The STN projects to both the GPi and SNr and also has connections with the pedunculopontine nucleus (Mesulam, Geula, Bothwell, & Hersh, 1989; Pahapill & Lozano, 2000).

1.1.2 The pedunculopontine nucleus

The pedunculopontine tegmental nucleus (PPN) is located in the brainstem and is subdivided into pars dissipata (PPNd) and pars compacta (PPNc). The PPNd includes the rostrocaudal part and the PPNc includes the caudal portion (Mesulam et al., 1989; Pahapill & Lozano, 2000). The PPN contains GABAergic, glutamatergic and cholinergic neurons (Martinez-Gonzalez, Bolam, & Mena-Segovia, 2011; Wang & Morales, 2009). Glutamatergic and cholinergic neurons are most common in the caudal part of the PPN, whereas GABAergic neurons are in the rostral part (Martinez-Gonzalez et al., 2011). The PPN is involved in transmission of both sensory and motor information and is highly interconnected with the rest of the central nervous system (CNS) (Hazrati & Parent, 1992; Lavoie & Parent, 1994; Saper & Loewy, 1982). Therefore, it receives inputs from the motor cortex, the basal ganglia output nuclei, the STN and the deep cerebellar nuclei (Kang & Kitai, 1990; Saper & Loewy, 1982). Ascending projections from the PPN target the GPi, SNc, associative and intralaminar nuclei of the thalamus; descending projections target the pontine and medullary reticular formation and the spinal cord (Martinez-Gonzalez et al., 2011). Figure 1.5 is a schematic representation of the main connections of the PPN.

The PPN receives excitatory glutatamatergic input from several cortical areas, including the supplementary motor area (SMA), the preSMA, the dorsal and ventral premotor cortex, the frontal eye fields and the medial prefrontal cortex (Matsumura et al., 2000). Evidence suggests that low frequency PPN stimulation produced increased glucose utilization in cortical - such as the dorsal prefrontal, orbitofrontal, medial sensori and

anterior cingulate cortices- and subcortical brain regions - such as the ventral striatum, the thalamus, cerebellum, the midbrain region, the insula, the supramarginal gyrus and the superior temporal gyrus (Ballanger et al., 2009; Costa et al., 2010; Ceravolo et al., 2011). These changes were associated with improved executive function and delayed recall, despite having little impact on motor symptoms (Costa et al., 2010; Ceravolo et al., 2011).
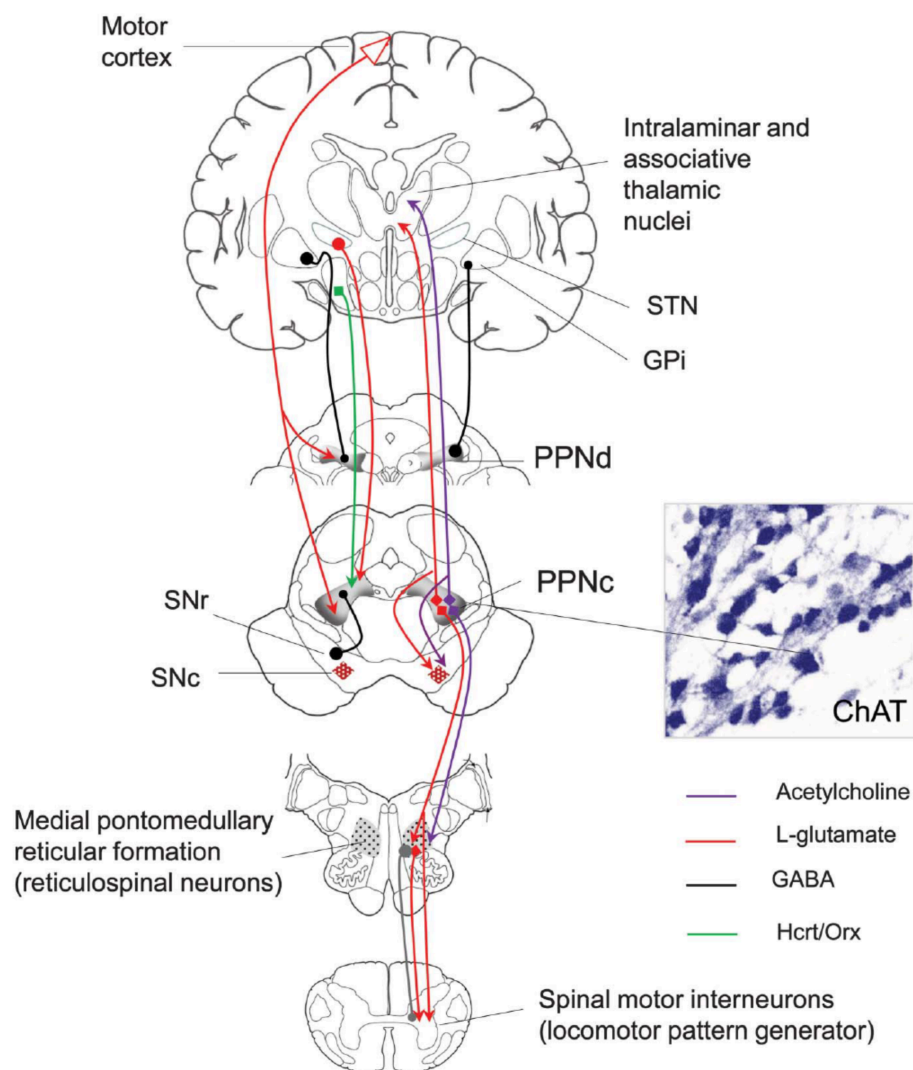
Figure 1.5 Main connections of the pedunculupontine nucleus (PPN). From Benarroch (2013). Neurology, 80(12), 1148-1155.
STN= subthalamic nucleus; GPi= internal segment of the globus pallidus; PPN= pedunculopontine PPNd= pedunculopontine nucleus pars dissipata; PPNc= pedunculopontine nucleus pars compacta; SNr= substantia nigra pars reticulata; SNr= substantia nigra pars compacta; ChAT= choline acetyltransferase; Hcrt/Orx= hypocretin/orexin.

In terms of movement related functions it has been suggested that the PPN may be involved in locomotion (Garcia-Rill, 1991), muscle tone regulation during wakefulness and rapid eye movements (REM) sleep (Garcia-Rill, Homma, & Skinner, 2004) and voluntary movements (Matsumura, 2005; Matsumura, Watanabe, & Ohye, 1997; Okada, Nakamura, & Kobayashi, 2011). Further functions of the PPN include regulation of transition from wakefulness to sleep (McCormick & Bal, 1997) and cortical arousal (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005; Steriade, 2006; Urbano et al., 2012). In PD and atypical Parkinsonism including multisystem atrophy (MSA) and progressive supranuclear palsy (PSP) cholinergic neurons degenerate in the PPN (Hirsch, Graybiel, Duyckaerts, & Javoy-Agid, 1987; Jellinger, 1988; Schmeichel et al., 2008; Zweig et al., 1987). Postural and gait abnormalities are cardinal features of these conditions, and may relate to PPN abnormalities. Evidence also suggests that neural loss in the PPN correlates with the severity of motor symptoms (Rinne, Ma, Lee, Collan, & Roytta, 2008; Zweig, Jankel, Hedreen, Mayeux, & Price, 1989) and PPN lesions produce gait disturbance (Kuo, Kenney, & Jankovic, 2008; Masdeu, Alampur, Cavaliere, & Tavoulareas, 1994). These findings suggest that degeneration of PPN neurons relates to motor symptoms of PD, particularly the gait and mobility problems, however the exact mechanisms are still to be clarified (Pahapill & Lozano, 2000). Research indicates that hyperactivity in the GPi causes inhibition of glutamatergic projections to reticulosoinal brainstem neurons and spinal cord, which in turn results in the muscle tone and locomotion impairments seen in PD (Hamani, Stone, Laxton, & Lozano, 2007; Jenkinson et al., 2009; Matsumura, 2005). Experiments involving GABAergic agonists, lesions or high frequency PPN stimulation in primates support this notion (Jenkinson, Nandi, Aziz, & Stein, 2005; Matsumura & Kojima, 2001; Nandi, Jenkinson, Stein, & Aziz, 2008).

Given the experimental evidence concerning PPN involvement in PD, it was identified as a novel deep brain stimulation target (PPN-DBS) for treating levodopa-unresponsive postural and gait abnormalities, in PD and atypical Parkinsonism. In contrast to patients with STN-and GPi-DBS, who mostly receive high frequency stimulation (>100Hz), patients who have PPN-DBS receive low frequency stimulation (60Hz). The reason for this is that PPN-DBS is a novel approach to treating PD and the exact mechanisms by which it improves symptoms are still to be clarified and therefore low frequency

stimulation is safer from a clinical perspective. Clinical trials looked at the effects of low frequency PPN-DBS alone or in combination with STN-DBS. The results indicated that the greatest improvement in axial symptoms was elicited by a combination of PPN-DBS and STN-DBS for some but not other patients (Hamani et al., 2007; Lozano & Snyder, 2008; Lozano, Snyder, Hamani, Hutchison, & Dostrovsky, 2010; Mazzone et al., 2005; Plaha & Gill, 2005; Stefani et al., 2007). Unilateral PPN-DBS reduced gait freezing and falls in some cases (Ferraye, Debu, & Pollak, 2008; Ferraye et al., 2010; Moro et al., 2010). Additionally, low frequency PPN-DBS induces greater glucose use in orbitofrontal, anterior cingulate and dorsal prefrontal cortex, as well as the left ventral striatum, supramarginal gyrus, right insula and right superior temporal gyrus, which was related to improvement in executive deficits (Ceravolo et al., 2011; Costa et al., 2010). Next, I am going to review Parkinson's disease as the most typical basal ganglia disorder.

1.2 Parkinson's Disease

Parkinson's disease (PD) is a movement disorder characterised by the cardinal motor symptoms of resting tremor, bradykinesia, and rigidity; and additional motor symptoms such as postural instability and gait problems (Gelb, Oliver, & Gilman, 1999). James Parkinson (1817) was the first to diagnose the condition and described it originally as a shaking palsy. PD is the second most common neurodegenerative disease after Alzheimer's disease (Siderowf & Stern, 2003). There are about 120,000 people with PD in the UK (Horsfall, Petersen, Walters & Schrag, 2013). The prevalence is slightly higher for men than women (Pringsheim, Jette, Frolkis, & Steeves, 2014). The evidence showing that PD is one of the most common neurological disorders and that its incidence increases with age (Pringsheim et al., 2014) makes effective treatment of it important. Pathologically PD is characterized by the progressive degeneration of the dopaminergic neurons in the substantia nigra pars compacta (Kish, Shannak, & Hornykiewicz, 1988). Dopamine produced by the substantia nigra pars compacta is the main neurotransmitter for the nigrostriatal tract (Gibb & Lees, 1991). These pathological mechanisms give rise to the cardinal motor symptoms described above (Gelb et al., 1999). In addition to the degeneration of the dopaminergic neurons of substantia nigra pars compacta, other neurotransmitter systems also become affected in PD (Gratwicke, Jahanshahi & Foltynie,

2015). Noradrenergic and cholinergic systems are also compromised, causing non-motor symptoms relating to Parkinson's disease dementia. Furthermore, PD brains reveal specific inclusion bodies, which take the form of globular Lewy bodies (LB) in neural cell bodies or as Lewy neurites (LN) in cellular processes (Forno, 1996; Lewy, 1912; Lowe, 1994; Pollanen, Dickson & Bergeron, 1993). There may be deposits of an aggregated form of the presynaptic protein α-synuclein in the brain of PD patients. PD also causes non-motor symptoms impacting mood, cognition, sleep and autonomic functions (Garcia-Ruiz, Chaudhuri, & Martinez-Martin, 2014). Psychiatric symptoms of PD include depression, anxiety, apathy, fatigue, hallucinations, delusions and medication-induced impulse control disorders such as pathological gambling and hypersexuality. Depression, anxiety and apathy are common in PD and experienced by around 40-60% of patients (Aarsland & Kramberger, 2015). The impulse control disorders can develop in up to 25% of patients on dopaminergic medication (Weintraub et al, 2015). The main motor and other non-motor symptoms of PD are shown in Table 1.1.

Main motor symptoms	Other motor and non-motor symptoms
	Cognitive dysfunction and dementia
Tremor	Depression
	Other psychiatric problems, apathy, anxiety
Rigidity	Hallucinations and delusions
	Sleep problems
Bradykinesia (slowness of movement)	Fatigue
	Dysphonia (low soft voice)
Akinesia (poverty or absence of movement)	Micrographia (small size and difficulty with hand writing)
Balance and walking problems	Masked faces (loss of facial expression and 'poker' face)
	Seborrhoea (excessive greasiness and scaliness of skin)
	Dysphagia (difficulty swallowing and dribbling)
	Autonomic symptoms (postural hypotension, urinary urgency, sweating)
	Sexual problems

Table 1.1 The main motor symptoms and other motor and non-motor symptoms of Parkinson's disease (PD), adapted from Jahanshahi & Marsden (1998). Parkinson's disease: a self-help guide for patients and their carers. London: Souvenir Press Limited.

1.3 Cognition in PD

1.3.1 Mild cognitive Impairment and Dementia in PD

In PD, cognitive deficits are already present during early disease stages as different forms of mild cognitive impairment (MCI) (Aarsland, Bronnick, & Fladby, 2011). On average 27% of PD patients develop MCI (Litvan et al., 2011). The clinical definition of MCI is (1) the recognition of cognitive deficits by the patient and a third reliable source; (2) an insignificant effect upon daily living; (3) the indication that cognitive deficits are not caused by natural aging effects (Geurtsen et al., 2014; Litvan et al., 2011; Petersen, 2004; Petersen et al., 2009). MCI can include deficits in executive function, attention, working memory, language, memory and visuospatial processing (Litvan et al., 2012). In patients with PD, MCI is associated with increasing age, disease duration, and disease severity (Litvan et al., 2011), and mostly affects executive and visuospatial functions, rather than memory deficits that are typically seen in Alzheimer's disease (AD) related MCI (Aarsland et al., 2004). Consequently, MCI in PD is commonly known as PD-MCI. However, the cognitive profile of PD-MCI is heterogeneous and can vary in the cognitive domains that are affected in various combinations (Goldman et al., 2013; Goldman, Weis, Stebbins, Bernard, & Goetz, 2012; Kalbe et al., 2016; Lawrence, Gasson & Loftus, 2016). Different PD-MCI phenotypes may also variably predict further cognitive decline, relate to different pathophysiological substrates and require different therapeutic interventions (Goldman et al., 2018). The exact definition of different PD-MCI subtypes is still evolving. Formerly, cognitive deficits in PD were thought to be subcortical in nature (e.g. psychomotor, executive and working memory deficits) (Pillon, Deweer, Agid & Dubois, 1993), whereas more recently, cortical deficits were also described (e.g. visuospatial, memory and langue deficits) (Litvan et al., 2011; Marras et a., 2013; Sollinger et al., 2010). In general, MCI can be divided into amnestic (memory related) and non-amnestic (not memory related), as well as single-domain and multi-domain subtypes (Goldman, Aggarwal & Schroeder, 2015; Petersen et al., 1999). In PD non-amnestic, single-domain subtype is the most common form of MCI (Litvan et al., 2011).

Research investigating the relationship between specific PD-MCI subtypes and the development of PD-D is limited. However, there is some evidence suggesting that of those

patients who have non-amnestic single-domain MCI (i.e. cognitive deficits that are not related to memory) 69% develop dementia, whereas 63% of those with the non-amnestic multi-domain MCI develop dementia and 40% of those with amnestic MCI develop dementia (Janvin, Larsen, Aarsland & Hugdahl, 2006). On the other hand, research investigating deficits in executive function (Janvin et al., 2005; Levy et al., 2002; Mahieux et al., 1998), verbal fluency (Jacobs et al., 1995; Mahieux et al., 1998), visuospatial function (Mahieux et al., 1998), memory and language (Hobson & Meara, 2004; Levy et al., 2002) suggested that these were all predictive of PD-D. Furthermore, a population-based longitudinal study of incident cases reported that cognitive deficits related to more posterior cortical areas were more likely to predict dementia, compared to cognitive deficits that were related to a frontostriatal pathology (Williams-Gray et al., 2009). In summary, there is a lot of controversy about the prognosis of different subtypes of PD-MCI for PD-D. More detailed investigations are needed to evaluate the exact nature of these subtypes and to what extend they are predictable of PD-D.

Research investigating domain-specific cognitive deficits in PD is inconsistent. Therefore, evidence from studies investigating visuospatial functions in PD patients has reached conflicting conclusions (Brown & Marsden, 1990). While some research found no impairments (Brown & Marsden, 1986; Della Sala, Di Lorenzo, Giordano & Spinnler, 1986; Taylor, Saint-Cyr, Lang & Kenny, 1986), others identified task specific deficits (Ransmayr et al., 1987). Ransmayr and colleagues (1987) used two tasks of visuospatial functions. The first required patients to generate a solution internally, whereas the second task provided different solutions for the patient to choose from. The findings suggested that patients were only impaired on the first task requiring internal control. Therefore, it appears that visuospatial function is only impaired when PD patients are required to internally generate a solution. Furthermore, PD differentially affects certain aspects of memory (Brown & Marsden, 1990). Consequently, studies looking at memory, identified a dissociation between recognition and recall, with recall being impaired and recognition memory spared in early PD (Taylor et al., 1986; Taylor, Saint-Cyr & Lang, 1987; El-Awar et al., 1987) but with recognition also impaired in later stages of the illness (Green et al., 2002). It was suggested that patients would have to engage in effortful retrieval of information which is internally driven when recalling an event, whereas for recognition

they only have to select from given alternatives and therefore memory is not internally driven (Flowers, Pearce & Pearce, 1984; Weingartner, Burns, Diebel & LeWitt, 1984). Again as with visuospatial function, it seems that internally driven memory is more impaired while externally cued aspects of memory are less impaired at least in early PD. Impairments of language have been demonstrated by research using the Boston Naming Test, verbal fluency and verbal learning (Green et al., 2002). However, it is debated whether such language deficits are secondary to executive dysfunction (Litvan et al., 2011).

As already mentioned, MCI is a strong predictor for PD related dementia (PD-D), which has a long-term prevalence of up to 80% of patients followed-up over 20 years (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Aarsland, Tandberg, Larsen, & Cummings, 1996; Hely, Reid, Adena, Halliday, & Morris, 2008). Diagnostic criteria for PD-D include the diagnosis of PD prior to the development of dementia as well as severe impairments in at least two out of four main cognitive domains (memory, attention, visuospatial and executive function); impairments are also required to impact normal functions of daily living and occupational and social functioning (Dubois et al., 2007; Emre et al., 2007). Patients with PD-D commonly have deficits in the domains of executive function, recognition memory, attention and visual perception (Kehagia, Barker & Robbins 2010; Pagonabarraga & Kulisevsky, 2012; Gratwicke, Jahanshahi & Foltynie, 2015), and also have visual hallucinations and cognitive fluctuations (Emre, 2003). PD-D may also be associated with psychiatric symptoms such as anxiety, depression, excessive daytime sleepiness and visual hallucinations (Kehagia et al., 2010; Gratwicke et al., 2015).

The presentation of PD-D is heterogeneous and different factors influence the development of dementia in PD. First, patients' age may influence the development of dementia in PD. Age of onset and disease duration are important factors for PD-D. Patients with young-onset PD who have longer disease durations have decreased risk of developing dementia (Schrag, Ben-Shlomo, Brown, Marsden & Quinn, 1998). Second, executive dysfunction may be associated with dementia in PD. Research investigating this relationship reported that especially deficits in verbal fluency (Levy et al., 2002), abstract

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reasoning (Levy et al., 2002), picture completion (Mahieux et al., 1998) and Stroop performance (Janvin, Aarsland & Larsen, 2005; Mahieux et al., 1998) are predictors for PD-D. However, the extent to which these executive deficits relate to PD-D may be dependent on how long they precede the development of PD-D. For instance, the association between perseveration on the Wisconsin card sorting test (WCST) and the consequent development of PD-D was reported within one year of dementia onset (Woods & Troster, 2003), which does not provide information about the association between early executive deficits and PD-D. Further research indicated that the early cognitive profile in PD patients who eventually develop dementia is different to the typical early executive dysfunction (Williams-Gray, Foltynie, Robbins & Barker, 2007). Williams-Gray et al. (2007) suggested that visuospatial and language deficits may be good predictors of dementia in PD. Further evidence suggested that the pentagon copying on the mini mental state examination (Folstein, Folstein & McHugh, 1975) and semantic fluency are good predictors of PD-D at three and five year follow-up (Williams-Gray et al., 2007; Williams-Gray et al., 2009). Third, the dominant motor symptoms in PD patients may also relate to the development of dementia. PD patients who have axial symptoms such as gait disturbance and postural instability, are more likely to develop dementia early on in the course of the disease (Burn et al., 2006; Foltynie, Brayne, Robbins, & Barker, 2004; Lewis et al., 2005; Williams-Gray et al., 2007), whereas patients with tremor-dominant PD are less likely to develop dementia (Alves, Larsen, Emre, Wentzel-Larsen & Aarsland, 2006). Depression, hallucinations and REM sleep behaviour disorder have been identified as other risk factors for the development of dementia in PD (Williams-Gray et al, 2007; Postuma et al, 2012).

1.3.2 Executive Dysfunction

The most common form of MCI in PD is executive dysfunction (Elgh et al., 2009; Foltynie et al., 2004, see Dirnberger & Jahanshahi, 2013 for review). The findings of a recent meta-analysis suggested that compared to healthy controls, PD patients were impaired on neuropsychological measures of executive function (see Figure 1.6; Kudlicka, Clare, &

Hindle, 2011). Executive function is an umbrella term referring to cognitive processes that control goal-directed behaviours (Lezak, 1982). Different aspects of executive function become impaired in PD. First, evidence from research using tests that require internal control of attention suggests that compared to healthy controls PD patients have deficits shifting their attention internally, whereas such deficits were not present, if patients were provided with an external cue (Brown & Marsden, 1988a, b; Hsieh, Lie & Tai, 1995). Brown and Marsden (1988a) used a cued choice reaction time task and the WCST in a group of PD patients and control participants. While the choice reaction time task involved an external cue that provided information about how the stimulus has to be processed, this was not the case for the WCST. In this case participants had to internally direct their attention towards one attribute of the given stimulus. PD patients' performance was significantly worse compared to the performance of control participants only for the WCST but not the choice reaction time task. Further support for these findings was provided by another study that applied two different computerized versions of the Stroop task. For one version participants were provided with a cue, indicating what attribute of the stimulus was relevant for the response, whereas no cue was given for the second version (Brown & Marsden, 1988b). Again, patients were differentially impaired compared to healthy controls only on the version of the task that required them to redirect their attention internally. Similarly, Hsieh et al. (1995) used a modified version of the Odd Man Out test and reported patients to be only impaired when redirecting attention based on internal cues but not when external cues were provided.

Measures	Hedges' g	Variance	CI	p*
Phonemic fluency	−0.55	0.02	−0.80 − −0.30	0.00
Semantic fluency	−0.75	0.03	−1.07 − −0.43	0.00
Alternating fluency	−0.87	0.15	−1.63 − −0.12	0.02
Digit span backward	−0.46	0.01	−0.67 − −0.26	0.00
WCST categories	−0.68	0.02	−0.97 − −0.39	0.00
WCST total errors	−0.57	0.02	−0.84 − −0.31	0.00
WCST persever. error	−0.69	0.03	−1.01 − −0.37	0.00
WCST cards to 1st category	−0.43	0.03	−0.77 − −0.09	0.01
Stroop interference	−0.54	0.01	−0.77 − −0.32	0.00
Stroop baseline - interference	−0.94	0.05	−1.39 − −0.49	0.00
TMT B	−0.67	0.02	−0.95 − −0.40	0.00

Forrest plot of summary effect sizes

PD patients < controls   PD patients > controls

Figure 1.6 The results of a meta-analysis of performance on standardised tests of executive function in Parkinson's disease (PD), showing effect sizes relative to healthy controls. From Kudlicka, et al. (2011). Mov Disord, 26(13), 2305-2315.
Hedge's g= corrected mean weighted effect size; CI= 95% confidence interval; WCST= Wisconsin Card Sorting Test; TMT B= Trail Making Test, part B. *Two-tailed test.

Second, PD patients have set shifting deficits as demonstrated by studies implementing tasks such as the WCST and the Trail Making Test (TMT) (Taylor & Saint-Cyr, 1995). More recent studies used tasks such as the intradimensional/extradimensional (ID/ED) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Both medicated and non-medicated PD patients were found to have set shifting impairments (Cools, Barker, Sahakian & Robbins, 2001; Owen et al., 1993). It was also indicated that medication might have differential effects for set shifting performance. Owen et al. (1993) reported that frontal lesion patients had deficits in shifting attention away from a previously important stimulus attribute, whereas medicated PD patients had impairments shifting their attention to a previously unimportant attribute and non-medicated PD patients were impaired in both aspects of set shifting. A more recent study reported that set shifting impairments seen in medicated PD patients were different depending on the stimulus salience and may therefore relate to a disproportionate control by bottom-up attention to a salient attribute, rather than a set shifting deficit per se (Cools, Rogers, Barker & Robbins, 2010). More evidence for set shifting impairments in non-medicated PD patients was provided by a study implementing a digit comparison

task (Fimm, Bartl, Zimmermann & Wallesch, 1994). On the other hand, Rowe et al. (2008) used a task during which participants had to switch between the spatial and lexigraphic dimension in a letter search/identification task and found no set shifting deficits independent of medication status.

Third, patients show impaired planning abilities as seen in worse performance on the Tower of Toronto task (Saint-Cyr, Taylor & Lang, 1988). Research using a modified version of the Tower of London task, found differential impairments across the stages of PD (Owen et al., 1992; Owen, Doyon, Dagher, Sadikot & Evans, 1998). De novo patients who were never medicated had no planning deficits. On the other hand, patients who were medicated and had mild or severe motor symptoms had longer response latencies and those patients with severe motor symptoms had reduced accuracy on the computerized version of the Tower of London planning task. Similarly, more recent evidence from a study of future planning showed that medicated patients had difficulties imagining future events (De Vito et al., 2012). Planning deficits in PD may also relate to impairments in prospective memory (Altgassen, Zollig, Kopp, Mackinlay & Kliegel, 2007). Similar to findings from research investigating set shifting, planning impairments may relate to patients' deficits in internal control of attention.

Fourth, PD patients have difficulties inhibiting prepotent responses and also with conflict resolution as seen in impaired performance compared to healthy controls on tasks such as the Go/No Go reaction time task (Cooper, Sagar, Tidswell & Jordan, 1994), the stop signal task (Gauggel, Rieger & Feghoff, 2004; Obeso et al., 2011) and the Simon task (Praamstra & Plat, 2001; Wylie, Ridderinkhof, Bashore & van der Wildneberg, 2010a). Research using the go no go task reported that compared to controls, the patients' ability to inhibit prepotent responses becomes gradually worse with increasing complexity of the decision (Cooper et al., 1994). Praamstra and Plat (2001) reported that interference on incongruent trials of the Simon task was greater in PD patients compared to healthy controls. Patients also made more errors compared to the controls (Praamstra & Plat, 2001; Wylie et al., 2010a). Research using the standard stop signal reaction time task (Gauggel et al., 2004) and the conditional version (Obeso et al., 2011) reported prolonged stop signal reaction times for PD patients compared to age-matched control participants,

suggesting delayed inhibition in PD. A study investigating proactive inhibition in PD using a simple reaction time task with warned and unwarned trials, reported that patients had difficulties releasing proactive inhibition, only when this was driven internally (Favre, Ballanger, Thobois, Broussolle & Boulinguez, 2013). Also, medication did not influence patients' proactive inhibition (Favre et al., 2013).

Finally, research suggests that PD has differential effects on decision-making, depending on the nature of the task. While evidence from studies considering decision-making under uncertainty using the Iowa Gambling task (IGT) did not indicate impaired performance in PD patients (Czernecki et al., 2002; Euteneuer et al., 2009; Mimura, Oeda & Kawamura, 2006; Poletti et al., 2010; Thiel et al., 2003), the results of research investigating decision-making under risk in PD are inconsistent (Brand et al., 2004; Cools, Barker, Sahakian & Robbins, 2003 ; Delazer et al., 2009; Euteneuer et al., 2009). While some studies indicate impaired performance in patients, especially 'on' medication (Cools et al., 2003), others suggest impairments to be equal in medicated and non-medicated patients (Brand et al., 2004; Euteneuer et al., 2009) or no impairment at all (Delazer et al., 2009). Cools et al. (2003) used the Cambridge gambling test and reported that patients were impaired especially when they were on medication. Delazar and colleagues (2009) tested patients on the same task, and found no impairments in patients. Research using the Game of Dice task found impairments that were similar for medicated and non-medicated patients (Brand et al., 2004; Euteneuer et al., 2009).

1.3.3 Dopamine overdose hypothesis

Adverse effects of dopaminergic medication relating to cognitive function in early PD may be explained by the 'dopamine overdose' hypothesis, which was first proposed by Gotham and colleagues (1988). According to the hypothesis, dopaminergic medication increases the pathologically low dopamine levels in the putamen and dorsal striatum, improving the motor symptoms, whereas it overstimulates the ventral striatum, which is not as affected by the dopamine depletion in the early stages of PD. Consequently, while restoring dopamine levels for motor and associative circuits, overdosing the ventral striatum induces impairments of limbic and orbitofrontal circuits producing cognitive deficits. Research using diffusion magnetic resonance imaging supported the notion of

selective degeneration of the dorsal SN in early Parkinson's disease (Du et al., 2012; Vaillancourt et al., 2009). Evidence from research using executive function tasks involving dorsolateral fronto-striatal circuits such as planning and set shifting indicates improved performance on medication (Cools et al., 2001; Gotham et al., 1988; Lange et al., 1992), whereas tests sensitive to limbic and orbitofrontal circuits such as reversal learning (Swainson et al., 2000), conditional associative learning (Gotham et al., 1988), reward learning (Cools, Altmirano & D'Esposito, 2006), probabilistic classification learning on the weather prediction task (Jahanshahi et al., 2010) are impaired on medication in early PD. Figure 1.1 is a schematic presentation of the 'dopamine overdose' hypothesis.

One study was specifically designed to test the hypothesis, by comparing de novo patients and medicated patients on a spatial working memory task and a pattern recognition task (Miah, Olbe Dubbelink, Stoffers, Deijen & Berendse, 2012). While medicated patients performed better on the spatial working memory task, they showed impaired performance for the pattern recognition memory task, which is mediated by the temporal lobes. The effects of dopaminergic medication on executive function differ depending on the receptors that are activated (Brusa et al., 2005). Pergolide, which activates D1/D2 receptors, does not produce deficits, whereas pramipexole activating D2/D3 receptors leads to word fluency and verbal memory impairments (Brusa et al., 2005). Also, dopaminergic overdose is suggested to cause pathological gambling, which may be induced by dopamine agonists and less often by levodopa (Djamshidian et al., 2011).

Cortico-basal ganglia-thalamo-cortical loops:

Effects of medication on dopamine levels in loops:

Impact of dopamine levels on task performance:
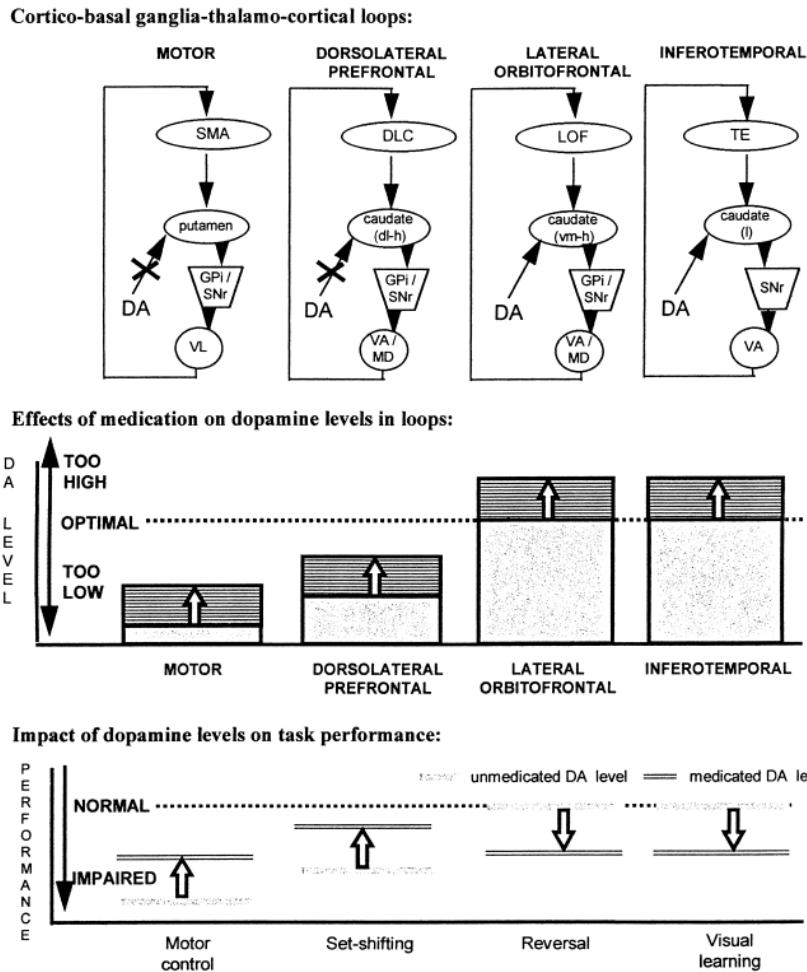
Figure 1.7 'Dopamine overdose' hypothesis and its effects on different fronto-striatal circuits and different aspects of cognitive function. From Swainson et al. (2000). Neuropsychologia, 38(5), 596-612.

Summarising the above it can be stated that PD is associated with cognitive deficits from early stages and increases the risk of dementia. The cognitive deficits can have a heterogeneous presentation and may be influenced by several factors. As cognitive impairment has been shown to be one of the major predictors of quality of life in PD (Schrag, Jahanshahi & Quinn, 2000), when treating the motor symptoms of PD, it is important to ensure that medical or surgical treatment is safe from a cognitive perspective.

1.4 Treatment of Motor symptoms of PD

Therapeutic interventions for PD primarily aim to improve the motor symptoms (Rao, Hofmann, & Shakil, 2006; Rascol, Goetz, Koller, Poewe, & Sampaio, 2002). Non-motor

symptoms are considered individually for treatment according to their nature and severity (Rao et al., 2006).

1.4.1 Dopamine replacement therapy

Initially PD is treated using substances that elevate the pathologically low levels of striatal dopamine. Treatment using dopamine agonists typically precedes treatment with levodopa, but the oral administration of levodopa results in the greatest improvement of the cardinal motor symptoms in PD (Cotzias et al., 1971). However, in the long-term levodopa use may cause major motor complications, such as dyskinesias and on-off fluctuations, and also psychiatric complications. Psychiatric complications can vary in their manifestations. In the past, when levodopa was the main, if not only, treatment for PD patients, psychiatric symptoms such as hallucinations, confusion and delirium occurred. More recently, with the use of dopamine agonists being more common, about 13-25% of patients develop pathological impulsiveness, manifesting as various forms of impulse control disorders (ICDs) (Weintraub, 2008). The ICDs include increased libido and hypersexuality, binge eating, compulsive shopping, pathological gambling and excessive accumulation of unnecessary objects or repetitive meaningless activities ('punding'). The most common risk factors for such ICDs are male gender, age of onset, with younger onset increasing the risk and severity of PD. ICDs are similar to addictive behaviours and support the finding that addiction is a dopamine-mediated behaviour regulated by the ventral striatum (Robbins & Everitt, 2002).

In the long-term, levodopa therapy can induce motor complications such as on-off fluctuations and dyskinesias, which are very disabling and interfere with activities of daily living of patients and have a negative impact on their quality of life (Rahman et al., 2008). These motor complications are present in 80% to 100% of patients medicated with levodopa (Schrag & Quinn, 2000). When patients reach the stage when levodopa produces side effects, such as on-off fluctuations and dyskinesias, then they are often treated surgically if they are suitable candidates for surgery. Deep brain stimulation of the internal segment of the globus pallidus (GPi) and the subthalamic nucleus (STN) leads to improvements of the motor symptoms as shown in randomized controlled trials (Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2012; Williams et al., 2010). In the

next section deep brain stimulation (DBS) will be considered in more detail. This research focuses on the effects of DBS of the STN and not GPi, because the STN-DBS has become the most frequently used target in the surgical treatment of PD worldwide.

1.4.2 Deep Brain Stimulation of the STN

Deep brain stimulation (DBS) is a highly successful method that is commonly used to treat motor symptoms in PD (Deuschl et al., 2006; Follett et al., 2010; Limousin et al., 1998; Weaver et al., 2012; Williams et al., 2010). The patients, who are selected to have STN-DBS surgery, have to fulfil specific criteria to ensure safety (Edwards, Quinn & Bhatia, 2008). These criteria include: (1) Good response to levodopa, but dyskinesias or on-off fluctuations that cannot be managed with different methods; (2) no on-medication gait disturbance; (3) no dementia; (4) no major psychiatric disturbances; (5) age under 70 years.

The surgery involves a stereotactic procedure, during which stimulation electrodes are chronically implanted into the target brain area (Breit, Schulz, & Benabid, 2004). To control the stimulation parameters a programmable pulse generator is implanted in the chest wall (Breit et al., 2004). Figure 1.2 is a schematic presentation of the stimulation electrode and the pulse generator controller. The STN and the GPi were initially identified as stimulation targets as they are hyperactive in PD (Bergman, Wichmann, Karmon, & DeLong, 1994; Filion, 1979). Nigro-striatal dopamine depletion is associated with hyperactivity of the STN and the GPi, which leads to inhibition of the thalamo-cortical projection and the brainstem nuclei. Consequently, patients have difficulties initiating and executing movements (Albin et al., 1989; DeLong, 1990). Despite stimulation of both the STN and GPi improving the cardinal motor symptoms (Weaver et al., 2012), STN-DBS is the most common surgical approach for treating PD (Weaver, Follett, Hur, Ippolito, & Stern, 2005).

A)   B)
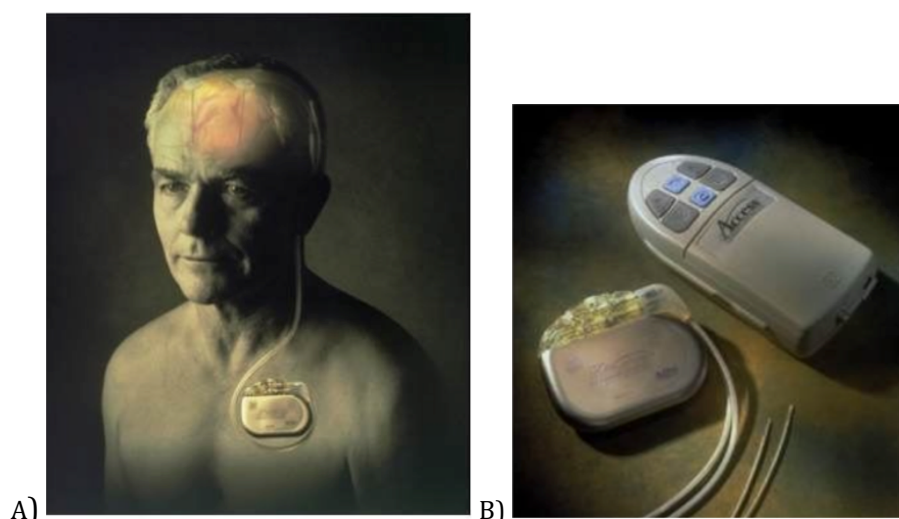
Figure 1.8. A. Schematic representation of the stimulation electrodes and the pulse generators in the brain and B. the pulse generator and the device for altering the stimulation parameters.

STN-DBS allows a significant reduction of dopaminergic medication following surgery, which is not the case for GPi-DBS (Weaver et al., 2005). Considering the side effects that dopamine replacement therapies can have (Calabresi, Di Filippo, Ghiglieri, Tambasco, & Picconi, 2010), such reduction of medication after STN-DBS surgery is useful for reducing on-off fluctuations and dyskinesias, but medication reduction needs to be done gradually over time to prevent apathy (Lhommée et al., 2012). On the other hand, research suggests that adverse events such as cognitive deficits and depression may be somewhat more common following STN-DBS than GPi-DBS (Combs et al., 2015; Follett et al., 2010; Weaver et al., 2012). In the next sections research on the effects of STN-DBS on cognition will be reviewed.

1.5 Effects of subthalamic nucleus deep brain stimulation surgery on cognition

As reviewed above cognitive deficits are common in PD. Therefore, surgical centres screen patients to ensure no severe cognitive deficits or dementia are present prior to surgery. This is usually done using global scales such as the dementia rating scale (DRS) (Smeding et al., 2006) or the mini mental status examination (MMSE) (York, Wilde, Simpson, & Jankovic, 2009). Centres where a neuropsychologist is part of the surgical team also conduct detailed neuropsychological assessment of the patients before and after surgery. In the following sections, the short-term and long-term effects of STN-DBS on cognition will be considered by reviewing the available literature.

1.5.1 Surgical effects on cognition

1.5.1.1 Short-term effects

Findings from studies investigating the short-term effects of STN-DBS on cognition are summarised in Table 1.2. In this section I only review studies that assessed patients pre- and post-operatively and compared patients who received STN-DBS to either a matched PD control group who did not receive STN-DBS or to patients who underwent a different surgical procedure (i.e. GPi-DBS). This focus on controlled studies is to ensure that any changes in cognition detected are actually related to STN-DBS rather than progression of PD.

The results of the controlled studies of cognitive function after STN-DBS listed in Table 1.2 allow a number of conclusions. First, most studies report that STN-DBS did not produce any change in the majority of the measures of cognitive function included in the assessments. Second, the most consistently found deficit across studies is post-surgical impairment of verbal fluency, which was reported in 21 of 26 (80.77%) studies (Alegret et al., 2004; Castelli et al., 2010; Cilia et al., 2007; Daniels et al., 2010; De Gaspari et al., 2006; Gironell et al., 2003; Morrison et al., 2004; Odekerken et al., 2015; Rinehardt et al., 2010; Rothlind et al., 2015; Saez-Zea et al., 2012; Smeding et al., 2006; Tramontana et al., 2015; Weaver et al., 2009; Williams et al., 2010; Williams et al., 2011; Witt et al., 2008; Witt et al., 2013; York et al., 2008; Zahodne et al., 2009; Zangaglia et al., 2009). Both phonemic and semantic verbal fluency are reported to be impaired after surgery compared to pre-operative performance. Third, the other common deficit reported across studies is on the Stroop Colour Word Interference Task, which was impaired post-surgery in 8 of 26 (30.77%) of the controlled studies listed in Table 1.2 (Alegret et al, 2004; Daniels et al., 201; Rothlind et al., 2015; Smeding et al., 2005; Smeding et al., 2006; Tramontana et al., 2015; Witt et al., 2008; York et al., 2008). Fourth, less consistently, deficits on other tests such as similarities (Odekerken et al, 2015; Rothlind et al, 2015), digit symbol substitution (Follett et al, 2010; Rothlind et al, 2015; Williams et al, 2011), symbol search (Rothlind et al, 2015), letter-number sequencing (Rothlind et al, 2015) subtests of various versions of the Wechsler adult intelligence scale (WAIS), and the Trail-making test B (Smeding et al, 2005; York et al, 2008) have been reported. All of these tests would be considered to be tests of 'frontal' function, as they require executive

processes and/or working memory for their completion. Considering that executive deficits are a common feature of PD from the early stages of the illness (Dirnberger & Jahanshahi, 2013; Kudlicka et al., 2011) these results suggest impairment of these executive processes following STN-DBS surgery in a proportion of operated patients. Fifth, deterioration of aspects of verbal or visuospatial memory have been recorded after STN-DBS in a number of these controlled studies (Mikos et al., 2010; Morrison et al., 2004; Rinehart et al, 2010; Rothlind et al, 2015; Smeding et al, 2006;Weaver et al., 2009; Williams et al, 2011). Finally, and most importantly, cognitive decline in the form of MCI or dementia has been documented in a proportion of the operated samples (Castelli et al, 2010; Deuschl et al, 2006; York et al, 2008; Witt et al, 2008; Weaver et al, 2009), with the rate of cognitive decline often over a period of one year follow-up after surgery ranging from 1.6% (Deuschl et al, 2006) to 4% (York et al, 2008) to the high rate of 15% (Castelli et al, 2010).

The evidence described above is informative but needs careful consideration in light of methodological limitations of some studies listed in Table 1.2. Morrison and colleagues (2004) included two patients who had right-sided pallidotomy more than one year prior to their STN-DBS surgery. This procedure can cause long-lasting cognitive deficits (Strutt et al., 2009), which makes the data from these patients invalid. Another study described that three of their STN-DBS patients had already greatly impaired Stroop performance at baseline (Alegret et al., 2004). Evidence suggests that pre-operative cognitive status might influence post-surgical outcome (Hariz et al., 2000; Kim et al., 2013). Therefore it cannot be said for certain what the underlying mechanisms for the deficits found in their study are. The control group included in the study by Smeding and colleagues (2006) performed significantly worse at baseline assessment compared to the patients who were to receive STN-DBS. Thus, this lack of matching at baseline may influence comparisons at follow-up for these samples in this study. Similarly, for the samples recruited by Zahodne and colleagues (2009) at baseline the average disease duration was longer and the UPDRS scores higher for the STN-DBS group compared to the PD control group. This failure to match the operated and control groups at baseline in terms of key variables may influence the validity of the comparisons of the two groups at follow-up. One study described assessment of the STN-DBS patients 1, 6, 12 and 36 months, whereas the control group

only had the 36 months follow-up (Zangaglia et al., 2009). Analysis revealed that the verbal fluency deficit got less across follow-up sessions. Since control data is missing for the intervening assessments it could be argued that this change in verbal fluency across sessions is caused by practice-effects.

Investigators	N	Target, Side Controls	Exclusion criteria	Microelectrode confirmation	Placement verified	Stimulation parameters	Cognitive Tests	Follow-up Months	Cognition Unchanged	Cognition worse
Gironell et al. (2003)*	8 8	STN, B PD Control	Dementia, depression, marked cerebral atrophy	Yes	Yes	NR	digit span, Sternberg paradigm, Benton, RAVLT,ROCF, Stroop, TMT, WAIS arithmetic, TOH, WCST, VF	6	Majority of measures	VF Semantic
Alegret et al. (2004)*	9 7	STN, B APM-csi	Dementia, severe systemic or psychiatric disease, age >75 years, brain atrophy or vascular lesions	Yes	Yes	NR	RAVLT, Stroop, TMT, JLOT, MMSE, phonemic VF	6,12	Majority of measures	VF Phonemic, Stroop
Morrison et al. (2004)	17 11	STN, B PD control	Dementia	Yes	Yes	NR	DRS, NART-R, RMT, BTA, HVLT, BNT, VF, VFDT, JLOT, STDS, OMOT, Stroop	3	Majority of measures	BNT, VF, RMT & HVLT delayed recall

Smeding et al. (2005)	20 14	STN, B Pallidotomy, U	Predominantly unilateral symptoms without severe response fluctuations, severe brain atrophy on CT or MRI, H&Y 4/5 in best on phase, DRS<120, psychosis or depression, previous stereotactic procedure, physical condition making surgery hazardous	Yes	Yes	NR	DRS, VF, NART, PASAT, AVLT,Gron-ingen intelligence test, Stroop, OMOT	6,12	Majority of measures	6 months: Stroop colour-word, TMT-B
De Gaspari et al. (2006)	12 13	STN, B APM-csi	Presence of atypical features, psychiatric disturbances, current treatment with atypical neuroleptics	Yes	Yes	NR	MMSE, VF, Raven's colour matrices, PWL	12	Majority of measures	VF semantic
Smeding et al. (2006)*	103 39	STN, B PD control	Predominantly unilateral symptoms	Yes	Yes	NR	DRS, VF, NART, PASAT,	6	TMT	VF Semantic & phonemic; alternating

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			without severe response fluctuations,, severe brain atrophy, H&Y stage 4 or 5, dementia, psychosis or depression				AVLT, Groningen intelligence test, Stroop, OMOT, TMT, BNT, TMT			stroop, delayed recall AVLT, DRS
Deuschl et al. (2006)	78 78	STN, B PD control	Dementia, major psychiatric illness, no contra-indications	Yes	Yes	NR	DRS	6	-	2 cases of mild cog. Impairment (2.6%); 1 case of moderate cog. Impairment (1.3%).
Cilia et al. (2007)*	20 12	STN, B PD control	Vascular abnormalities, brain atrophy	NR	NR	NR	MMSE, WCST, RPM, VF	12	Majority of measures	Semantic VF
Witt et al. (2008)*	60 63	STN, B PD control	Dementia, psychiatric illness, surgical contra-indications	NR	NR	60 µsec, 130 Hz	DRS, RAVLT, digit span, Benton, Stroop, VF	6	Majority of measures	VF Phonemic & Semantic, Stroop; 5% DBS & 6% con. DRS decline
York et al. (2008)*	23 28	STN, B PD control	Dementia, psychiatric illness, H&Y stage 5, medical	Yes	Yes	NR	MMSE, DRS, Symbol digit modalities test, TMT,	6	-	stroop word/colour -word, VF, TMTB, 1 case with

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							digit span, VF, BNT, RAVLT, BVMT, WCST, Stroop, Clock drawing			dementia (4%)
Zangaglia et al. (2009)	32 33	STN, B PD control	Dementia, psychiatric illness, medical contra-indications	Yes	Yes	NR	MMSE, LMT, verbal span, digit span, CBTT, WCST, RM47, phonemic VF	36	Majority of measures	VF Phonemic & Semantic
Weaver et al. (2009)	60 61 134	STN, B GPi, B PD control	Atypical syndromes, previous surgery for PD, active alcohol or drug abuse, dementia, pregnancy	Yes	Yes	NR	DRS, WAIS, VF, Stroop, WCST, BNT, BVMT, HVLT	6	Majority of measures	VF Phonemic & Semantic, delayed recall, WM, visuomotor speed, 1 dementia in STN-DBS group (1.7%)
Zahodne et al. (2009)	10 12 19	STN, U GPi, U PD control	Dementia	Yes	Yes	NR	VF, digit span backward, BNT, WASI vocabulary	12	Majority of measures	VF Phonemic & Semantic
Follett et al. (2010)	147 152	STN, B GPi, B	Atypical syndromes, previous	Yes	Yes	NR	DRS, WAIS processing speed &	24	Majority of measures	WAIS digit symbol

Study	n	Target	Exclusion criteria			Parameters	Tests	Months	Outcome	Decline
			surgery for PD, active alcohol or drug abuse, dementia, pregnancy				working memory,VF, HVLT, Finger tapping, BNT, WCST, Stroop, BVMT			
Mikos et al. (2010)	11 13 19	STN, U GPi, U PD control	Dementia	Yes	Yes	NR	HVLT, Logical memory test of Wechsler memory scale-III, TMT, Stroop, JLOT, Benton	16	Majority of measures	Verbal recall, processing speed
Castelli et al. (2010)*	27 31	STN, B PD control	NR	Yes	Yes	NR	Raven colour matrices, bi-syllabic words repetition test, CBTT, PAL, TMT-B, NMCS, VF	12	Majority of measures	VF Phonemic, 4 patients (15%) performed significantly worse across the neuropsycho-logical tests
Daniels et al. (2010)	60 63	STN, B PD ontrol	Dementia, major psychiatric illness, surgical	Yes	Yes	130 Hz, 60 μsec	DRS, RAVLT, digit span, Benton, Stroop, VF	6	Majority of measures	VF Phonemic & Semantic, Stroop

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			contra-indications							
Rinehardt et al. (2010)*	20 20	STN, B PD control	Dementia, psychiatric illness	Yes	Yes	1.7 V, 82.5 μsec, 149.3 Hz	MMSE, RBANS	4		Figure copy, line orientation, VF Semantic, digit span, figure recall
Williams et al. (2010)	183 183	STN, B PD control	Dementia	NR	NR	NR	DRS	12	Majority of measures	WASI vocabulary, VF Phonemic & Semantic
Williams et al. (2011)	19 18	STN, B PD Control	MMSE<23, psychiatric complications	NR	NR	NR	MMSE, DRS, RAVLT, BVMT, TMT, Digit span, Stroop, WCST, Clock command	24	Majority of measures	BVMT delayed recall, Symbol digit, Clock command, VF Phonemic & Semantic
Sáez-Zea et al. (2012)*	9 12	STN, B PD control	Presence of other disease, marked functional disability or postural instability, cognitive impairments, psychiatric illness, brain atrophy	Yes	Yes	NR	WMS-III-R, Digit span, TMT, Stroop, WAIS digits, AVLT, BNT, VF, WAIS block design, WCST, WAIS similarities,	6	Majority of measures	VF phonemic

								WAIS digit symbol, arithmetic reasoning		
Schuepbach et al. (2013)	124 127	STN, B PD control	Dementia, depression, psychosis, any medical or psychological problem, interfering with the study protocol	Yes	Yes	NR		DRS	24	DRS	-
Witt et al. (2013)*	31 31	STN, B PD control	NR	NR	NR	NR		DRS, digit span backward, VF, Stroop	6	Majority of measures	VF semantic
Rothlind et al. (2015)*	84 164	STN, B PD control	Dementia	NR	NR	NR		WAIS digit symbol, letter-number sequencing arithmetic, similarities, symbol search, TMT, animal & grocery naming, Stroop, digit span, phonemic VF, BNT, HVLT, BVMT	6	Majority of measures	WAIS-III digit symbol, symbol search, letter-number sequencing & similarities, animal naming, grocery naming, Stroop, BVMT delayed recall, VF Phonemic

Tramontana et al. (2015)*	15 15	STN, B PD control	Dementia, psychiatric illness	NR	NR	NR	JLOT, BNT, VF, digit span, PASAT, WMS-III, WCST, Stroop	12	Majority of measures	12 months: Stroop interference, VF Phonemic
Odekerken et al. (2015)	56 58	STN, B GPi, B	Previous stereotactic surgery, H&Y 5 at best moment of the day, DRS<120, active psychosis, contra-indications for surgical procedure	Yes	Yes	NR	NART, Stroop, TMT, WAIS letter-number sequencing, matrix reasoning & similarities, digit span, WCST, VF, BNT, RAVLT, RBMT	12	Majority of measures	Stroop reading & colour naming, TMT B WAIS-III similarities

Table1.2 Short-term effects of subthalamic nucleus deep brain stimulation (STN-DBS) on cognition based on controlled studies.
PD= Parkinson's disease; STN= subthalamic nucleus; GPi= internal segment of the globus pallidus; B= Bilateral; U= Unilateral; RAVLT= Rey Auditory Verbal Learning Test; ROCF= Rey-Osterrieth complex figure; TMT= Trail making test; WAIS= Wechsler adult intelligence scale; TOH= Tower of Hanoi; WCST= Wisconsin card sorting test; VF= Verbal fluency; DRS= Dementia rating scale; NART= National adult reading test; RMT = Recognition memory test; BTA= Brief test of attention; HVLT-R= Hopkins verbal learning test revised; BNT= Boston naming test; VFDT= Visual form discrimination test; JLOT= Judgement of line orientation test; STDS= Standardized test of direction sense; OMOT= Odd man out test; MMSE= Mini mental status examination; PASAT= paced auditory serial addition task; AVLT= Auditory verbal learning test; PWL= Paired word learning; BVMT= Brief visual memory test; LMT= Logical memory task; CBTT= Corsi's block tapping test; RM47= Raven's matrix 47; PAL= Paired associate learning; NMCS= Nelson modified card sorting test; RBANS= Repeatable battery of neuropsychological status; WMS-III-R= Wechsler memory scale; RBMT= Rivermead behavioural memory test.*studies included in the meta-analysis,

1.5.1.2 A meta-analysis of the short-term effects

To evaluate the short-term effects of STN-DBS surgery in PD on different cognitive domains, a meta-analysis was performed, only including controlled studies that compared patients with STN-DBS to an unoperated PD control group (see Table 1.2). This was done to ensure that reported changes in cognition are related to STN-DBS and not disease progression. The study eligibility criteria were the following: (1) patients with idiopathic PD with STN-DBS; (2) PD control group; (3) interval or ratio data; (4) for both groups reporting neuropsychological data before surgery/ baseline and up to 12 months after surgery/ follow-up; (6) sufficient report of study results for an effect size to be calculated; (7) missing data which could be calculated with previously identified methods in the Cochrane handbook (Higgins & Green, 2008). The neuropsychological tests were categorised into the following nine cognitive domains: cognitive screening; attention and concentration; executive function; psychomotor speed; learning and memory; visuospatial skills; language; phonemic verbal fluency; and semantic verbal fluency. Phonemic and semantic verbal fluency were regarded as separate domains because these were the most consistently found to decline after surgery (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016) and may also be affected differentially (Parsons et al., 2006).

Random effects meta-analytic models were used for the analysis. To compare change from baseline between the two patient groups (STN-DBS versus PD control) the effect size, that is, Cohen's d was calculated for each study. A negative effect size indicates that patients in the STN-DBS group had a larger decline on that cognitive domain at follow-up compared to the PD control group. According to Cohen (1992) an effect size of .20 reflects a small effect, .50 reflects a moderate effect and .80 reflects a large effect. The average weighted effect size the corresponding 95% confidence interval and variance were then calculated. A 95% confidence interval not including zero indicated a significant effect.

Domain	Neuropsychological test	n (STN-DBS)	n (PD control)	K	I²	Q	p
Cognitive screening	Dementia rating scale	213	158	4	0%	0.21	0.98
Attention and concentration	Arithmetic	23	23	7	33%	14.99	0.13
	Corsi's block tapping	27	31				
	Digit span forward	152	187				
	Digit span backward	183	218				
	Number-Letter sequencing	81	114				
	Paced auditory serial addition test	15	15				
Executive function	Card sorting test	154	196	11	61%	45.84	0.003
	Stroop – colour word	306	282				
	Raven's progressive matrices	47	43				
	Trail making test – part B	256	234				
Psychomotor speed	Pegboard task	15	15	10	76%	70.31	<0.001
	Stroop – colour	261	235				
	Stroop – word	275	252				
	Trail making test – part A	203	176				
	WAIS digit symbol coding	104	142				
	WAIS symbol search	84	115				
Learning and memory	Benton visual retention test	60	63	9	19%	24.72	0.21
	Bisyllabic word repetition	27	31				
	Brief visuospatial memory test	106	144				
	Hopkins verbal learning test	82	115				
	Rey auditory verbal learning test	199	142				
	RBANS – immediate memory	20	20				
	RBANS – delayed memory	20	20				
	WMS familiar faces	15	15				
	WMS logical memory	15	15				
	WMS paired associates	15	15				
Visuospatial skills	Judgement of line orientation	44	42	3	45%	5.5	0.14
	Rey-O copy	20	20				
Language	Boston naming test	119	157	3	71%	17.43	0.004
	Animal naming	83	115				
	Grocery naming	84	116				
	WAIS similarities	83	113				
Phonemic Fluency		384	357	11	0%	6.97	0.73
Semantic Fluency		303	244	10	0%	6.95	0.54

Table 1.3 Tests that were included in each cognitive domain and valid sample sizes for each.
STN-DBS=subthalamic nucleus deep brain stimulation; PD=Parkinson's disease; K=number of studies evaluating the cognitive domain; I²= I² statistic; Q=Cochran's Q; WAIS=Wechsler adult intelligence scale; RBANS=Repeatable battery for the assessment of Neuropsychological status; WMS=Wechsler memory scale.

	Average effect size	Effect size variance	95% CI	p
Cognitive Screening	-0.26	0.01	-0.47 to -0.05	0.02
Attention and concentration	-0.17	0.004	-0.34 to -0.01	0.03
Executive function	-0.17	0.003	-0.35 to 0.02	0.08
Psychomotor speed	-0.36	0.002	-0.57 to -0.16	0.0005
Learning and memory	-0.09	0.004	-0.20 to 0.02	0.1
Visuospatial skills	0.28	0.03	-0.07 to 0.64	0.36
Language	-0.31	0.005	-0.58 to -0.04	0.02
Phonemic fluency	-0.46	0.005	-0.61 to -0.31	<0.0001
Semantic fluency	-0.57	0.008	-0.74 to -0.39	<0.0001

Table 1.4 Random effect sizes for the various cognitive domains considered in the meta-analysis.
95% CI=95% confidence interval.

To investigate whether the study samples had a common underlying effect size, the homogeneity of the effect size was computed for each cognitive domain using the Cochran's Q and the I^2. This was done to get information about the cohesiveness of each of the cognitive domains. All analyses were performed using Review Manager 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark).

Twelve controlled studies were considered suitable to be included in the meta-analysis (see Table 1.2 for a list and details of these studies). Table 1.3 presents the particular cognitive domains considered and the specific neuropsychological tests that were used across the studies to tap each of the cognitive domains covered by the meta-analysis. The results of the Cochrane's Q and I^2 tests and the average random effect sizes and their variances and 95% confidence intervals are shown in Table 1.4. Tests of heterogeneity were significant for the domains of executive function (I^2= 61%), psychomotor speed (I^2=76%) and language (I^2=71%). For the remaining domains tests of heterogeneity were not significant.

Random effects analysis yielded significant differences in change from baseline to follow-up between STN-DBS and control patients on several cognitive domains (see Table 1.3). With the exception of semantic verbal fluency (d= -0.57; 95% CI= [-0.74, -0.39]) and phonemic verbal fluency (d= -0.46; 95% CI= [-0,61, -0.31]) which showed moderate effect sizes, the effect sizes in the other domains ranged from -.36 to -.17 and were small by Cohen's (1992) criteria psychomotor speed (d= -0.36; 95% CI= [-0.57, -0.16]), language (d= -0.31, 95% CI= [-0.58, -0.04]), cognitive screening (d=-0.26; 95% CI= [-0.47, -0.05]), attention and concentration (d= -0.17; 95% CI= [-0.34, -0.01]). Therefore, while in all these domains the STN-DBS group had greater decline at follow-up compared to the PD control group, only the effect sizes for the semantic and phonemic verbal fluency are notable (see Figure 1.9).

Measures	Cohen's d	Variance	95% CI	p	Forrest plot of summary effect sizes
Cognitive screening	-0.26	0.01	-0.47;-0.05	0.02	
Attention and Concentration	-0.17	0.004	-0.34;-0.01	0.03	
Executive function	-0.17	0.003	-0.35;0.02	0.08	
Psychomotor speed	-0.36	0.002	-0.57;-0.16	0.005	
Learning and memory	-0.09	0.004	-0.20;0.02	0.1	
Visuospatial skills	0.28	0.03	-0.07;0.64	0.36	
Language	-0.31	0.005	-0.58;-0.04	0.02	
Phonemic fluency	-0.46	0.005	-0.61;-0.31	<0.0001	
Semantic Fluency	-0.57	0.008	-0.74;-0.39	<0.0001	

Figure 1.9 The Forest plot of the results of the meta-analysis of the performance on standardised tests of different cognitive domains by Parkinson's disease (PD) patients with deep brain stimulation of the subthalamic nucleus (STN-DBS), showing effect sizes relative to unoperated PD patients in controlled studies. Cohen's d= corrected mean weighted effect size; CI= 95% confidence interval.

1.5.1.3 Long-term effects

In this section evidence from studies investigating the effects of STN-DBS on cognition in long-term that is two years or more after surgery is reviewed. The research reviewed above in Table 1.2 included PD control groups that were matched with the surgery group in terms of disease duration and symptoms in most studies, which provides more reliable information about the short-term effects of surgery as distinct from progression of the illness. In contrast, it is difficult to use control groups in long-term studies as most of the 'control group' patients subsequently had surgery as well. Table 1.5 lists all the studies, which have reported the long-term effects of STN-DBS on cognition in PD.

Most of the studies listed in Table 1.5, which examined longer-term changes in cognition after STN-DBS over periods ranging from 2 to 10 years indicate that a certain percentage of PD patients presented with global cognitive decline and dementia following STN-DBS surgery. The rates across these studies range from 0% (Contarino et al, 2007; Kim et al, 2013; Tramontana et al, 2015; Jiang et al, 2015) to 32% (Merola et al, 2014). This is quite a wide range of values for cognitive decline after STN-DBS, which probably reflects operation of several factors. First, the rate of cognitive decline and dementia in unoperated PD is variable and depends on a number of factors such as age of onset of PD, with late-onset cases more likely to develop dementia than those with young-onset PD (Aarsland et al., 2001; Emre et al., 2007). Also, male gender is another factor associated with development of dementia in PD (Mayeux et al., 1992). Dementia is also associated with the akinetic-rigid type of PD rather than the tremor-dominant disease (Elizan et al., 1986; Emre et al., 2007). Thus, differences across the samples of the studies listed in Table 3, in the proportion of old-onset versus young-onset PD, akinetic-rigid versus tremor-dominant PD, and male versus female patients are likely to have influenced the percent of cognitive decline following surgery. Second, the studies listed in Table 1.5 probably differed in terms of the cognitive selection criteria applied to their samples and whether or not the patients had a comprehensive cognitive screening and neuropsychological assessment prior to surgery which would have detected cases of dementia or those with MCI on the cusp of further cognitive decline. Third, the highest prevalence of dementia across these studies was 32 %, which does not exceed the prevalence of dementia in the general PD population over similar periods of time

(Aarsland et al., 2003). This suggests that the cognitive decline or dementia observed in a proportion of the operated cases may be attributable to the progression of PD rather than specifically related to the surgery. However, in the absence of many controlled long-term follow-up studies of cognition after STN-DBS this conclusion is provisional.

Investigators	N	Follow-up Years	Cognitive tests	Criteria for cognitive decline and dementia	% Dementia/ Cog. Decline	Comments
Follett et al. (2010)	147 STN-DBS,B 152 Gpi-DBS, B	2	DRS, WAIS processing speed & working memory, semantic and phonemic VF, HVLT, BNT, WCST, Stroop, BVMT	Not provided	Not provided	Visuomotor speed worse after STN-DBS than GPi-DBS
Williams et al. (2011)	19 STN-DBS, B 18 PD controls	2	MMSE, DRS, RAVLT, BVMT, SDMT, TMT, WAIS digit span, Stroop, semantic & phonemic VF, BNT, WCST, clock drawing	Dementia: DSM-IV-TR MCI: =< 2 standard deviations below age corrected mean on at least one cognitive domain	32%	STN-DBS: PD-D in 32%, PD-MCI in 21%; PD Control: PD-D in 16%, PD-MCI in 17%. Sig. Decline in symbol digit, semantic & phonemic fluency, & clock command
Schuepbach et al. (2013)	124 STN-DBS, B 127 PD controls	2	DRS	Not provided	Not provided	No worsening of global cognition, when compared to a PD control group.
Tramontana et al. (2015)	15 STN-DBS, B 15 PD controls	2	Purdue Pegboard, JLO, BNT, semantic & phonemic VF, WAIS digit span, PASAT, WMS-III, WCST, Stroop	Not provided	0%	Stroop reading & colour naming as well as Phonemic verbal fluency was sig. worse compared to PD control group
Funkiewiez et al. (2004)	70 STN-DBS, B	3	DRS, WCST, phonemic and semantic VF	Changes > 1 standard deviation	7.6%	Mean DRS unchanged; but decline in 7.6%; declined VF
Aybek et al. (2007)	59 STN-DBS, B	3	BNT, Stroop, figure drawing, famous faces recognition, digit span, RAVLT, semantic & phonemic VF, TMT, WAIS code & similarities, Piaget's reasoning task	DSM-IV criteria	28%	Decline in memory, inhibition, attention and constructive praxis

Study	Sample		Tests	Criteria	%	Outcome
Zangaglia et al. (2009)	32 STN-DBS, B 33 PD controls	3	MMSE, LMT, verbal span, digit span, CBTT, WCST, Raven's matrices, phonemic VF	DSM-IV	6.2%	1 case dementia & 1 case MCI indicative of executive dysfunction. Significant decline in MMSE
Weaver et al. (2012)	70 STN-DBS, B 89 Gpi-DBS, B	3	DRS, WAIS-II attention, working memory, visuomotor speed, VF, Stroop, WCST, BNT, BVMT, HVLT	Not provided	Not provided	STN-DBS caused faster DRS decline than GPi-DBS
Kim et al. (2013)	36 STN-DBS, B	3	MMSE, TMT, Korean BNT, Rey-Kim Memory Battery, Stroop, semantic & phonemic VF	Not provided	5.5%	MMSE score declined significantly
Odekerken et al. (2016)	64 STN-DBS, B 64 Gpi DBS, B	3	Stroop, TMT, letter-number sequencing, semantic and phonemic VF, RAVLT	Significant decline on composite score	84%	84% of patients in the STN-DBS group had cognitive decline compared to 68% in the GPi-DBS group
Rodriguez-Oroz et al. (2005)	49 STN-DBS, B 20 Gpi-DBS, B	4	Adverse events questionnaire	Mild: easily tolerated Moderate: when causing some interference with daily functioning severe: when incapacitating	24%	Multicentre study 12/49 cognitive decline; 4 mild, 7 moderate, 1 severe
Krack et al. (2003)	49 STN-DBS, B	5	DRS	DSM-IV criteria for dementia	6.1%	Mean DRS unchanged; but dementia in 6.1%
Schupbach et al. (2006)	37 STN-DBS, B	5	DRS	Not provided	Not provided	Patients declined significantly on DRS
Contarino et al. (2007)	11 STN-DBS, B	5	MMSE, digit span, CBTT, RAVLT, Raven's progressive matrices, phonemic VF, WCST	DSM-IV criteria for dementia	0%	None

Gervais-Bernard et al. (2009)	23 STN-DBS, B	5	DRS	Not provided	13%	Three patients had cognitive impairment. Mean change on DRS was not significant
Jiang et al. (2015)	11 STN-DBS, B	5	MMSE, MoCA	Not provided	0	Cognition unchanged
Merola et al. (2014)	174 STN-DBS, B (23% MCI)	>5	Raven's colour matrices, bi-syllabic words repetition, CBTT, PAL, WMS, TMT B, phonemic & semantic VF	MCI= Level-I MDS criteria PD-D= MDS criteria	>40% MCI 32% PD-D	After 3 years: 14% PD-D After 5 years: 24% PD-D After >5 years:32% PD-D
Fasano et al. (2010)	20 STN-DBS, B	8	MMSE, CBTT, digit span, RAVLT, Raven's progressive matrices, MWCST	DSM-IV	5%	1 case with dementia; sig. decline in VF, episodic memory, MWCST
Zangaglia et al. (2012)	30 STN-DBS 17 PD controls	8	MMSE, verbal span, digit span, CBTT, RAVLT, LMT, Raven's progressive matrices, Weigl sorting test, FAB, phonemic & semantic VF, visual selective attention, Rey Complex Figure copy	DSM-IV	16.7%	PD-D in 16.7% in surgical group and 17.6% in control group; phonemic verbal fluency decreased compared to medicated patients; phonemic VF worse in STN-DBS group compared to medicated control group
Aviles-Olmos et al. (2014)	41 STN-DBS, B	8	DRS	DSM-IV	17.1%	After 5 years: 17.1% PD-D After 8 years: 16.7% PD-D
Castrioto et al. (2011)	18 STN-DBS, B	10	Not provided	Clinical examination and formal neuropsychological assessment	17%	Clinical examination & neuropsychology
Janssen et al. (2014)	26 STN-DBS, B	10	MMSE, Stroop, phonemic & semantic VF, CVLT,	Not provided	4%	1 case showed cognitive decline at 10 year follow-up; Performance on Stroop interference, CVLT and VF decreased

Table 1.5 Studies reporting the long-term effects, 2 years or longer of subthalamic nucleus deep brain stimulation (STN-DBS) on cognition, listed in the order of year of publication.

PD= Parkinson's disease; STN= Subthalamic nucleus; GPi= Internal segment of the globus pallidus; DBS= Deep brain stimulation; B= Bilateral; DRS= Dementia rating scale; DSM= Diagnostic and statistical manual of mental disorders; MCI= Mild cognitive impairment; VF= verbal fluency; MWCST= Modified Wisconsin card sorting test; PD-D= Parkinson's disease related dementia; MMSE= Mini mental status examination; CVLT= California verbal learning test; DRS= Dementia rating scale; WAIS= Wechsler adult intelligence scale; HVLT= Hopkins verbal learning test; BNT= Boston Naming test; BVMT= Brief visual memory test; RAVLT= Rey Auditory Verbal Learning Test; SDMT= Symbol digit modalities test; TMT= Trail making test; Judgement of line orientation test; PASAT= paced auditory serial addition task; WMS= Wechsler memory scale; CBTT= Corsi's block tapping test; MoCa= Montreal cognitive assessment; PAL= Paired associate learning; LMT=Logical memory test.

A number of the studies listed in Table 1.5 on the long-term effects of STN-DBS on cognition were in fact controlled (Follett et al., 2010; Schuepbach et al., 2013; Tramontana et al., 2015; Weaver et al., 2012; Williams et al., 2011; Zangaglia et al., 2009; Zangaglia et al., 2012), but some of them (e.g. Williams et al, 2011) had methodological limitations. Zaganglia and colleagues (2009) identified no difference between the STN-DBS and PD control groups in terms of cognitive decline three years after surgery. On the other hand, Williams and colleagues (2011) reported after two years follow-up that 32 % of the STN-DBS group had PD-D compared to 16 % in the control group. Williams et al. (2011) stated that patients in the STN-DBS group were significantly older, had longer disease duration and higher levodopa dosage at baseline compared to the PD control group, which may have confounded the outcome, since baseline levodopa dosage and age correlate with post-surgical cognitive decline (Daniels et al., 2010; Kim et al., 2013; Zahodne et al, 2009; Smeding et al, 2011). Pre-operative cognitive status also influences post-operative cognitive status. In one of the studies with the largest samples and long-term follow-up, the sample included cognitively intact PD patients and a subgroup of patients who had MCI prior to surgery (Merola et al., 2014). Analysis showed that after five years after surgery, more than 40 % of the patients developed MCI and 32 % developed PD-D. Rodriguez-Oroz and colleagues (2005) compared patients with STN-DBS to those with GPi-DBS. Findings suggested that cognitive decline was more common in the STN-DBS group four years after surgery. Combs et al. (2015) reached a similar conclusion, from a meta-analysis of the results of 42 studies reporting the effects of DBS of the STN and the GPi on cognition, with 9 studies being on GPi-DBS. While the effect sizes for STN-DBS on verbal fluency both semantic and phonemic, attention/concentration, executive function and cognition screening were noted to be significant, GPi-DBS only produced effect sizes that approached significance for attention/concentration and verbal fluency.

In summary, the results of the studies listed in Tables 1.2 and 1.5, suggest that with the exception of decline in verbal fluency and tests of executive function such as the Stroop and a proportion of cases showing cognitive decline in the long-term at rates similar to what would be expected from the progression of the illness, it can be concluded that STN-DBS is a relatively safe surgical procedure from a cognitive point of view.

1.5.2 Effects of stimulation of the subthalamic nucleus on cognition

The literature reviewed above assessed the effects of STN-DBS on cognition by assessing PD patients before and after DBS surgery on a battery of neuropsychological tests. The next sections will summarise research investigating the effects of STN stimulation, focusing on studies which have used a STN-DBS on versus off methodology.

1.5.2.1 Inhibition

Inhibitory control is a component of executive function and is required for last minute suppression of action when priorities or circumstances change. It has been proposed that the fronto-striato-subthalamic-pallidal pathways play a role in habitual and goal-directed inhibition (Jahanshahi et al, 2015a). Table 1.6 provides an overview of all the investigations that have examined the effect of acute STN stimulation on inhibition and their main findings. As evident from Table 1.6, the available evidence is inconsistent. Some aspects of response inhibition are impaired by STN stimulation, whereas other features are unchanged or even improved with stimulation. (For detailed review see Jahanshahi, 2013).

Examination of Table 1.6 shows that a variety of tasks have been used to investigate the effects of STN-DBS on inhibitory control including the Stroop, random number generation, the anti-saccade task, the Simon effect task, the go no go reaction time (RT) task, and the stop signal task. Research with the interference condition of the Stroop suggests that performance of patients becomes worse with stimulation on than when DBS is off. On the Stroop interference task patients make significantly more errors indicative of failure to inhibit the habitual response of reading the colour words when instructed to name the colour of ink they are printed in (Jahanshahi et al., 2000a; Schroeder et al, 2002; Witt, Kopper, Deuschl, & Krack, 2006).

While the Stroop is a standardized neuropsychological test, most research looking at response inhibition used experimental paradigms. A study using the Simon task, a task requiring response selection under conflict, which necessitates inhibition of irrelevant stimulus features in order to select the correct response, showed that STN stimulation produced two contrasting effects (Wylie et al., 2010b). They examined the entire reaction

time (RT) distribution. In the fastest part of the RT distribution, when PD patients were tested on STN stimulation they produced an increased number of errors, reflecting fast premature response captured by the irrelevant stimulus feature and failure of inhibition of the incongruent response relative to DBS off. By contrast, for the slowest part of the RT distribution, STN-DBS significantly reduced the magnitude of the 'Simon' interference effect and improved the efficiency of inhibition of the incongruent response. This suggests that STN-DBS had a differential impact on inhibition of incongruent responses depending on response latencies. A recent study also used the Simon task and investigated not only the effects of acute STN stimulation but also compared stimulation of the dorsal and ventral portion of the STN (van Wouwe et al., 2017). The researchers mapped the DBS contacts onto the ventral and dorsal subregions of the STN using MRI and CT data. The results suggested that acute STN stimulation improved the patients' reactive inhibition. Therefore, patients were better at suppressing action impulses during non-congruent trials when they were on STN stimulation relative to when stimulation was off. Moreover, increased reactive inhibitory control was specifically triggered by stimulation of the dorsal STN relative to ventral STN stimulation. These findings indicate that STN stimulation-induced reactive inhibitory control may be related to the dorsal STN.

Findings from research implementing the Go-No-Go task (GNGT) are inconsistent (Ballanger et al., 2009; Hershey et al., 2010; Hershey et al., 2004; van den Wildenberg et al., 2006; Georgiev et al, 2016). This inconsistency may be partly explained by the different percentage of go and no-go stimuli in these tasks, which alters the prepotency of the response and the difficulty of withholding it. For instance, van den Wildenberg et al. (2006) used a target frequency of 50% and found no effects of STN-DBS on action restraint. Hershey and colleagues (2004) administered the GNGT with a high target frequency of 83%, which creates greater prepotency of the 'go' response and hence requires greater cognitive control for action restraint on no-go trials. They found that STN-DBS was associated with higher commission errors and reduced discriminability. In fact, in the Hershey et al. (2004) study a target frequency of 50% was also used and the no-go accuracy and discriminability worsened with STN-DBS only for the high frequency target condition when the stimulators were switched on. This suggests that action

restraint on the GNGT becomes only impaired by STN-DBS when higher levels of cognitive control are required. This proposal is further strengthened by the results of two more recent studies that also used higher target frequencies of 87% (Hershey et al., 2010) or 80% (Georgiev et al., 2016) and found that STN-DBS impaired action restraint relative to DBS off. Georgiev et al (2016) also included blocks of GNGT trials with 50% or 20% go trials and concluded that STN stimulation affected discriminability only for the high target frequency when the go response was most prepotent but not for the GNGT tasks with go frequencies of 50% or 20%. By contrast, Ballanger and colleagues (2009) used a GNGT that had a go frequency of 40% and their results showed that STN stimulation produced greater commission errors indicative of decreased action restraint, which contradicts the idea that negative effects of STN stimulation on action restraint only occur for conditions requiring high cognitive control. Interestingly, Hershey and colleagues (2010) also examined the differential effects of STN-DBS through the ventral and dorsal electrode contacts and concluded that only stimulation of the ventral part of the STN caused deterioration of action restraint on the GNGT, which may also partly account for the differences in findings for target frequencies in terms of the precise location of the active electrode contacts across studies. To identify the contact location as being ventral or dorsal the authors used MRI and CT data.

Similar to the findings with the GNGT, there is evidence from studies of the effect of STN-DBS on random number generation (RNG), that these may be 'load' dependent or vary according to the extent of cognitive control required. RNG is an attention-demanding cognitive task that engages several executive processes, including the need to suppress habitual counting in order to generate numbers in a random fashion (Jahanshahi et al., 1998; Jahanshahi et al, 2000a). RNG is commonly paced and participants are required to synchronize their generation of random numbers with a pacing stimulus. The speed of the pacing stimulus alters the attentional demands of RNG, with faster rates being more attention demanding and resulting in less random output and more habitual counting (Jahanshahi et al, 2000a, 2006). Evidence suggests that randomness and the ability to suppress habitual counting during RNG remains stable or even improves with acute STN stimulation for slow-paced RNG (Jahanshahi et al., 2000b; Williams et al., 2015), whereas it decreases in fast-paced versions of the task (Thobois et al., 2007; Williams et al., 2015).

These findings further suggest that acute STN stimulation may have differential effects on tasks that require inhibitory control depending on task difficulty and the demands for cognitive control as reflected by the ability to engage in action restraint depending on the prepotency of the response in GNGTs or the speed of pacing stimuli, which alter the attentional demands of RNG.

A task commonly used to assess the effects of STN-DBS on response inhibition is the stop signal reaction time (RT) task (Greenhouse et al., 2011; Mirabella et al., 2012; Obeso et al., 2013; Ray et al., 2009; Swann et al., 2011; van den Wildenberg et al., 2006). During the Stop signal reaction time task (Logan & Cowan & Davis 1984) participants are presented with a stop signal at different delays following a go signal, which instructs them to inhibit the prepotent response to the go stimulus. The stop signal reaction time (SSRT) is an estimate of the time taken for reactive inhibition, inhibition in response to an external stimulus. The SSRT can be obtained by subtracting the average stop signal delay from the mean go RTs. To control for 'baseline' effects, Ray and colleagues (2009) excluded all PD patients, who had significantly longer SSRTs in the stimulation off condition compared to a healthy control group, from the analysis. Data from the remaining participants revealed a prolongation of SSRT when stimulation was switched on, suggesting delayed inhibition with STN stimulation. Obeso and colleagues (2013) also reported that inhibition as measured by the SSRT was impaired/delayed in the stimulation on condition compared to when STN-DBS was off. The patients' SSRTs in the stimulation off condition were not different from those of healthy controls (Obeso et al, 2013). By contrast, two other studies that found positive effects of STN stimulation on the stop signal task (Mirabella et al., 2012; Swann et al., 2011) reported that in the stimulation off condition patients performed worse than controls, but that performance was improved and SSRTs were shorter when stimulation was switched on, indicating faster inhibition. Greenhouse and colleagues (2011) examined the differential effects of stimulation through the ventral and dorsal contacts on SSRT and predicted that compared to dorsal stimulation ventral stimulation would produce longer SSRTs. However, unlike the findings of Hershey et al. (2010) with the GNGT, Greenhouse et al. (2011) did not find any differences in SSRT with stimulation of the contacts in ventral versus dorsal STN. In addition to 'baseline' effects, methodological differences across studies may explain some of these inconsistencies on

the impact of STN-DBS on motor inhibition on the stop signal task. First, differences in the specifics of the stop signal tasks, such as the nature of stimuli and responses, proportion of go and stop trials and the relative timing of stimuli would cause variations in task difficulty due to differences in response prepotency. Second, differences in the accuracy of the surgical targeting and positioning of the electrodes in the STN may have an impact on SSRT. Third, there are key sample and procedural differences across studies. Some studies included patients with unilateral (Ray et al., 2009) or bilateral STN-DBS (van der Wildenberg et al., 2006; Swann et al., 2012; Mirabella et al., 2012; Obeso et al., 2013) and unimanual (Ray et al., 2009; Mirabella et al., 2012; Obeso et al., 2013) or bimanual versions of the stop signal task were employed. The movement participants had to perform also differed across studies, with some using reaching (Mirabella et al., 2012) or manual key press (van der Wildenberg et al., 2006; Ray et al., 2009; Obeso et al., 2013). Finally, studies differed in whether they assessed patients on (van der Wildenberg et al., 2006; Ray et al., 2009; Swann et al., 2011; Obeso et al., 2013) or off medication (Mirabella et al., 2012).

There is also some research on the effect of STN-DBS on proactive inhibition. While reactive inhibition is related to stopping responses that are already triggered in response to go stimuli, proactive inhibition relates to responding with restraint to achieve goals. A real-life example of this would be not eating cake when trying to lose weight. Obeso and colleagues (2013) used the conditional version of the stop signal reaction time task to investigate reactive and proactive inhibition. The conditional stop signal reaction time task differentiates between 'critical' trials, for which participants are required to inhibit the response when presented with the stop signal, and 'non-critical' trials, for which participants are requested to ignore the stop signal and produce the response. Obeso et al. (2013) used the response delay effect (RDE) as a measure of proactive inhibition. This RDE is the difference between RTs on 'critical' and 'non-critical' Go trials, and reflects proactive action restraint on 'critical' go trials in anticipation of stop signals. PD patients had a higher RDE and therefore showed more proactive inhibition when tested on STN stimulation, compared to when DBS was off, although the difference was not significant. A second study used a warned and unwarned simple RT task to assess proactive inhibition (Favre et al., 2013). On the warned trials patients received an external cue

indicating that a stimulus instructing a response is about to appear, whereas proactive inhibition had to be released internally on the unwarned trials. Results of this study also suggested that STN stimulation improves the patients' ability to release proactive inhibition.

In conclusion, the existing evidence suggests that reactive and proactive motor inhibition and action restraint are differentially affected by STN stimulation, with the prepotency of the response and degree of cognitive control required being an important factor. The ability to suppress a prepotent motor response assessed with tasks such as the gonogo and the stop signal RT tasks evaluates motor impulsivity. However, impulsivity is a multidimensional construct and various forms of impulsivity exist (Evenden, 1999), some of which relate to the decision-making process and will be considered in the next section.

Investigators	N	Medication Status	Task	Worse with STN-DBS	Unchanged with STN-DBS	Improved with STN-DBS
Jahanshahi et al. (2000b)	13 STN-DBS	Off	Stroop, RNG	Stroop interference task		RNG
Schroeder et al. (2002)	10 STN-DBS	Off	Stroop	Stroop interference task		
Hershey et al. (2004)	24 STN-DBS	Off	Go no Go RT task	Go no Go RT with high target frequency	Go no Go RTs with low target frequency	
Witt et al. (2006)	23 STN-DBS	On	Stroop	Stroop interference task		
Van den Wildenberg et al. (2006)	17 STN-DBS 15 Vim-DBS	On	Go no Go RT task, Stop signal RT task		Go no Go RTs	Stop signal RT task
Thobois et al. (2007)	6 STN-DBS	Off	Random number Generation	Fast-paced RNG		
Ballanger et al. (2009)	7 STN-DBS	Off	Go no Go RT task	Go no Go RT		
Ray et al. (2009)	16 STN-DBS	On	Stop signal RT task	Stop Signal RT task		
Yugeta et al. (2010)	32 STN-DBS	On	Anti-saccade task, Memory guided saccades		Anti-saccade task	Memory guided saccades
Wylie et al. (2010b)	17 STN-DBS	On	Simon task	Simon task-fast responses		Simon task-slow responses
Hershey et al. (2010)	10 STN-DBS	Off	Go no Go RT task	Go no Go RT-with ventral STN-DBS		

Greenhouse et al. (2011)	20 STN-DBS	On	Stop signal RT task	Stop signal RT task-DBS of ventral vs. dorsal contacts		
Swann et al. (2011)	15 STN-DBS 15 controls	On	Stop signal RT task			Stop signal RT task
Mirabella et al. (2012)	10 STN-DBS 13 controls	Off	Stop signal RT task			Stop signal RT task
Favre et al. (2013)	11 STN-DBS 14 PD controls	On	Warned and unwarned Simple RT task			Release of proactive inhibition in unwarned simple RT
Obeso et al al. (2013)	15 STN-DBS	On	Conditional stop signal RT task	Conditional stop signal RT task		
Williams et al. (2015)	15 STN-DBS	On	Random number geenration	Fast-paced RNG	Slow-paced RNG	
Georgiev et al. (2016)	20 STN-DBS 10 PD controls 10 controls	On	Go no Go RT task with 80%, 50%, 20% go trials	Go no go RT with high target frequency (80%)	Go no Go RT with low target frequency (50%, 20%)	
Van Wouwe et al. (2017)	12 STN-DBS 22 controls	Off	Simon task		Reactive inhibitory control	

Table 1.6 Acute effects of subthalamic nucleus (STN) stimulation on tasks involving inhibition or action restraint.
STN-DBS= Subthalamic nucleus deep brain stimulation; PD= Parkinson's disease; RNG= Random number generation; RT= reaction time.

1.5.2.2 Decision-making

Studies investigating the effects of STN stimulation on experimental tests of decision-making are presented in Table 1.7. The results are inconsistent and STN stimulation made performance on some of the decision-making tasks worse compared to DBS off (Antoniades et al., 2014; Cavanagh et al., 2011; Coulthard et al., 2012; Evens et al. 2015; Florin et al., 2013; Frank, Samanta, Moustafa Ahmed, & Sherman, 2007; Green et al., 2013; Oyama et al., 2011; Pote et al., 2016; Rogers et al., 2011; Seymour et al., 2016; Zaehle, Wagenbreth, Heinze, & Galazky, 2017); whereas performance on other tasks improved (Boller et al., 2014, Brandt et al., 2015, Evens et al., 2015, Seinstra et al., 2016, Seymour et al., 2016) or remained unchanged (Brandt et al., 2015, Castrioto et al., 2015, Djamshidian et al., 2013, Evens et al., 2015, Fumagalli et al., 2015, Seinstra et al., 2016, Seymour et al., 2016; Zaehle et al., 2017). This inconsistency most probably reflects the specific processes involved in the various decision-making tasks used and the particular forms of impulsivity tapped by them. Reflection impulsivity refers to an inability to slow down the decision-making process in order to collect a sufficient amount of information before making a choice. This aspect of impulsivity can be assessed by the beads task or probabilistic decision-making tasks described below. Another form of impulsivity relates to delayed gratification, that is the ability to wait for larger later rewards rather than choosing smaller immediate rewards and can be assessed with the delayed or temporal discounting task. Finally, risk-taking relates to choosing options with a high reward prospect but also a higher likelihood of leading to a negative outcome and can be assessed with the balloon task, the Iowa gambling task or the game of dice.

Frank and colleagues (2007) used a probabilistic decision-making paradigm to assess reflection impulsivity. The task consisted of high (choice between stimuli both of which were associated with high or low probability of reward) and low conflict (choice between two stimuli with one having high probability of reward and the second having low probability of reward) trials. Stimulation caused patients to respond with faster RTs in high conflict trials only, suggesting impulsive decision-making. These findings indicate that STN stimulation induces impulsive decision-making causing patients to make rushed decisions especially in high conflict conditions and further support the proposal/hypothesis that stimulation has a negative impact on performance of tasks that

require higher levels of cognitive control. Additionally, the results suggest that detrimental effects of STN stimulation were specific to win/win situations, where both stimuli were associated with a high probability of reward and had motivational salience. Other studies reported similar effects of STN stimulation on high conflict decision-making processes (Cavanagh et al., 2011; Coulthard et al., 2012). More recently, Seymour and colleagues (2016) assessed 22 PD patents with STN-DBS on a temporal discounting and an instrumental learning task, using the DBS on-off methodology. During the instrumental learning task participants had to repeatedly choose between four options, each having different probabilities of financial reward and loss. The probabilities of financial reward and loss for each option were unrelated and slowly changed across trials, requiring participants to constantly update probabilistic information. The results indicated that instrumental learning was significantly worse following STN stimulation due to decreased outcome sensitivity for both rewards and losses. By contrast, the temporal discounting was not altered by STN-DBS. It was concluded that STN-DBS modulates sensitivity to outcome value during instrumental learning and decision-making.

Evidence from studies investigating the acute effects of STN stimulation on other tasks such as a saccadic choice reaction time (RT) task (Antoniades et al., 2014), the moving dots task (Green et al., 2013; Pote et al., 2016) and a status quo task (Zaehle et al., 2017) also suggest that acute STN stimulation alters decision-making in PD. Antoniades et al. (2014) reported that in contrast to healthy controls, on the saccadic choice RT task, six PD patients with STN-DBS on did not show increased RTs as target probability decreased. The prolongation of RT with the decrease of the target probability is a normal behavioral adjustment, which was observed with STN stimulation off but not on. Green et al. (2013) examined the effect of task difficulty by altering the level of stimulus coherence on the 'moving-dots' task. They reported that STN stimulation reduced the effect of task difficulty on RTs and accuracy, relative to STN-DBS off. By contrast, with a 50% coherence version of the moving dots task, Pote and colleagues (2016) reported that compared to DBS off, STN stimulation induced fast responses with increased errors and lower response thresholds, when patients were instructed to decide as quickly as possible, suggesting that impulsivity induced by STN stimulation is limited to situations when

acting under speed pressure. Zaehle and colleagues (2017) used a tennis line judgement paradigm to assess the patients' susceptibility to a default bias, which is the preference for a default option, with increasing perceptual difficulty. The task required patients to judge whether a dot intersects one of two tennis line (IN) or not (OUT), by accepting or changing the default response. The results suggested that acute STN stimulation decreased the patients' decision accuracy for easy decisions but increased accuracy for difficult decisions. These results are inconsistent with previous findings that reported that acute STN stimulation impairs processing on more difficult tasks (Georgiev et al., 2016; Hershey et al., 2004; Williams et al., 2015; Wylie et al., 2010b). Furthermore, Zaehle and colleagues (2017) compared patients who showed baseline impulsivity to patients who did not. The results indicated that STN stimulation had a differential effect for the two groups. For impulsive patients acute STN stimulation increased the default bias, whereas it decreased the default bias for non-impulsive patients, relative to when stimulation was off.

Further research indicates that acute STN stimulation increases risky decision-making on the Iowa Gambling task (IGT) (Oyama et al., 2011; Evens et al., 2015) and can induce loss-chasing behaviour (Rogers et al., 2011). On the loss-chasing game patients were asked to choose between gambling to recover a certain loss, with the risk of doubling it, or quitting the game. With STN stimulation on patients were more likely to chase larger losses, compared to when stimulation was switched off (Rogers et al., 2011). Florin and colleagues (2013) used a calculation task, for which participants were asked to choose their preferred compensation. They could choose between a tournament condition that was associated with higher compensation but also higher risk of no compensation and the piece-rate condition that was associated with lower compensation and lower risk-levels. Patients were asked to choose based on their actual calculation performance. Relative to when stimulation was switched off, patients with STN stimulation were more likely to choose the tournament condition irrespective of their poor performance on previous trials. Thus, STN stimulation was considered to inflate the patients' self-estimation and as a result increased their risk-seeking behaviours.

During the 'game of dice' task participants have to predict the outcome of a dice roll by selecting from high probability and low payoff or low probability and high payoff options. Two studies with this task found that PD patients made less risky decisions with STN stimulation on compared to the off stimulation condition (Boller et al., 2014; Brandt et al., 2015). The 'deal or no deal' task is used to assess decision-making under uncertainty. Initially participants choose one of 26 briefcases containing an unknown monetary reward. During 9 trials participants are then asked to take away a specified number from the remaining briefcases, revealing their value and removing them from the game. After each draw a 'banker' makes an offer to buy the unopened briefcase that was chosen at the beginning. The participant could either accept the offer and take the reward or keep on playing. Brandt and colleagues (2015) reported that patients with STN stimulation on took smaller rewards relative to when stimulation was off, reflecting increased risk aversion. This study also used a framing paradigm to assess patients' gambling behaviour on a fixed reward, depending whether it was perceived as a gain or loss. Therefore, the same monetary reward was framed as either a loss or a gain. The results suggested that STN stimulation did not influence the patients' risky decision-making. The inconsistencies between studies of decision-making under risk and uncertainty relates to differences in the task properties. The Iowa gambling task and the loss-chasing game require more cognitive control and self-reflection and are associated with greater gains and losses than the game of dice. Additionally, during the deal or no deal task participants are not aware of the size of possible rewards and might be less likely to take risk.

By contrast to some of the above findings, other evidence exists implying no or even positive effects of STN stimulation on other aspects of decision-making. A research study that used the beads task to assess the effects of STN stimulation on reflection impulsivity in PD, suggested that stimulation does not influence the level of information accumulation and the decision-making process (Djamshidian et al., 2013). This may be due to different properties of the task used. In contrast to the probabilistic decision-making tasks described above, the beads task does not involve a learning-phase or any reward-related motivational salience. Also, unlike the saccadic choice RT and the moving dots tasks, the beads task does not have an 'acting under time pressure' component.

Research investigating the effects of acute STN stimulation on delayed gratification in PD used different forms of the delay-discounting task. During the delay-discounting task participants are asked to make binary decisions and choose between sooner smaller rewards and later larger rewards. Studies with such tasks consistently reported that patients with STN stimulation on did not differ in terms of discounting or devaluation of later larger rewards relative to when stimulation was switched off (Evens et al., 2015; Seinstra et al., 2016; Seymour et al., 2016).

In conclusion, the effects of acute STN stimulation on decision-making to a large extent appears to be dependent on the specific processes involved and the particular forms of impulsivity tapped by the task. Some of these decision-making processes become impaired and others remain unchanged or even improve with STN-DBS. Similarly, while some forms of impulsivity such as delayed motor inhibition is affected by STN-DBS, other forms such as delaying gratification do not appear to be.

Investigators	N	Medication Status	Task	Worse with STN-DBS	Unchanged with STN-DBS	Improved with STN-DBS
Frank et al. (2007)	17 STN-DBS 15 PD controls	On	Probabilistic decision-making task	Probabilistic decision-making under high conflict		
Oyama et al. (2011)	16 STN-DBS 16 PD controls	On	Iowa Gambling Task	Iowa Gambling Task		
Rogers et al. (2011)	22 STN-DBS	Off	Loss-chasing game	Higher values in loss-chasing experiment		
Canvanagh et al. (2011)	14 STN-DBS	On	Probabilistic decision-making task	Reinforcement learning and choice conflict task		
Torta et al. (2012)	21 STN-DBS	Off	Cambridge gamble task, BIS, QDQ, SPSRQ		Cambridge gamble task, SPSRQ	BIS
Coulthard et al. (2012)	11 STN-DBS 11 PD controls	On/Off	Probabilistic decision-making and information integration task	Probabilistic decision-making		
Djamshidian et al. (2013)	27 STN-DBS 34 PD controls 18 controls	On	Beads task		Beads task	
Florin et al. (2013)	30 STN-DBS 29 PD controls	On	Addition task with tournament option	Risk-seeking in addition task		
Green et al. (2013)	8 STN-DBS	On	Moving dots task	Reaction time did not slow down with task difficulty.		
Boller et al. (2014)	18 STN-DBS	On	Game of Dice task			Game of Dice
Antoniades et al. (2014)	6 STN-DBS 6 controls	On	Saccadic choice RT task	Reaction time of saccadic movement did not slow down		
Fumagalli et al. (2015)	11 STN-DBS 11 PD controls	On			Moral decision-making	

Castrioto et al. (2015)	20 STN-DBS 24 controls	On/Off	Iowa Gambling Task		Iowa Gambling Task	
Evens et al. (2015)	33 STN-DBS 33 PD controls 34 controls	On	Iowa Gambling Task, delay discounting task	Iowa Gambling Task	Delay discounting task	Incentive salience attribution, devaluation of delayed rewards
Brandt et al. (2015)	15 STN-DBS 15 PD controls 15 healthy controls	On	Game of Dice task, Framing paradigm, Deal or no deal task		Game of Dice, Framing Paradigm	Deal or No Deal task
Pote et al. (2016)	12 STN-DBS	On	Moving dots task	Faster reaction times and more errors under speed instructions.		
Seymour et al. (2016)	22 STN-DBS	On	Reward-based instrumental learning task, inter-temporal choice task	Reward-based instrumental learning task – decreased sensitivity to decision values for rewards and losses; more impulsive responding	Inter-temporal choice task	
Seinstra et al. (2016)	40 STN-DBS	On/Off	Inter-temporal choice task		Inter-temporal choice task	
Zaehle et al. (2017)	18 STN-DBS	On	Tennis line judgement paradigm	Easy decisions		Difficult decisions

Table 1.7 Acute effects of subthalamic nucleus (STN) stimulation on decision-making.
STN-DBS= Subthalamic nucleus deep brain stimulation; PD= Parkinson's disease; BIS= Barrat impulsiveness scale; QDQ= Quick delay questionnaire; SPSRQ= Sensitivity to punishment and to reward questionnaire.

1.5.2.3 Learning and memory

Studies investigating the effects of STN stimulation on learning and memory are listed in Table 1.8. A diverse range of tasks, including visual conditional associative learning (Jahanshahi et al, 2000a; Mollion et al., 2011; Ventre-Dominey et al., 2016), probabilistic learning (Coulthard et al., 2012; Frank et al, 2007), reversal learning (Funkiewiez et al, 2006), reward-based learning (van Wouwe et al 2011) and probabilistic classification learning on the weather prediction task (WPT) (Wilkinson et al., 2011) have been used. While most of these tasks involve declarative memory and learning through provision of feedback or reward; others such as the WPT taps into non-declarative procedural memory and learning.

Most research on the tasks employed suggests that STN stimulation either does not influence learning and memory (Coulthard et al., 2012; Frank et al., 2007: Funkiewiez et al., 2006; Weiss et al., 2014; Wilkinson et al., 2011) or improves it (Funkiewiez et al., 2006; Halbig et al., 2004; Mollion et al., 2011; van Wouwe et al., 2011; Wilkinson et al., 2011; Ventre-Dominey et al., 2016) (see Table 1.8). By contrast, on a visual conditional associative learning task (VCLT), during which patients learned 6 arbitrary associations between abstract shapes and colours, patients performed worse when stimulation was on compared to when they were tested off stimulation, making more errors and requiring more trials to reach criterion (Jahanshahi et al., 2000). These results suggest that STN stimulation may induce learning impairments on this task, by requiring a larger number of trials to learn arbitrary associations between colours and abstract designs. On the other hand, more recent evidence suggests that VCLT is improved with STN stimulation (Mollion et al., 2011; Ventre-Dominey et al., 2016). However, the latter studies used a paradigm that required participants to learn associations between two colour cues and directions. Therefore, the cognitive load involved was lower than for the task used by Jahanshahi et al. (2000b), which suggests that the effect of STN stimulation on performance on the VCLT may be load-dependent.

Investigators	N	Medication Status	Task	Worse with STN-DBS	Unchanged with STN-DBS	Improved with STN-DBS
Jahanshahi et al. (2000b)	13 STN-DBS	Off	Conditional associative learning task	Conditional associative learning		
Halbig et al. (2004)	12 STN-DBS	On	WPT	Declarative memory Of cue-outcome associations		Probabilistic classification learning on the WPT
Funkiewiez et al. (2006)	22 STN-DBS	Off	Reversal task with extinction phase		Reversal Task	Extinction task
Frank et al. (2007)	17 STN-DBS 15 PD controls 27 controls	On	Probabilistic reinforcement learning task		Positive or negative feedback-learning	
Canvanagh et al. (2011)	14 STN-DBS	On	Probabilistic reinforcement learning task	Reinforcement learning and choice conflict task		
Wilkinson et al. (2011)	11 STN-DBS 13 controls	Off	WPT		Overall probabilistic classification learning on the WPT	Implicit learning of weak cue outcome associations
Van Wouwe et al. (2011)	12 STN-DBS	On	Probabilistic reward-based learning task			Reward-based decision-learning
Mollion et al. (2011)	12 STN-DBS 10 controls	On	Conditional associative learning task			Conditional associative learning
Coulthard et al. (2012)	11 STN-DBS 11 PD controls	On/Off	Probabilistic learning task		Reward-based learning	
Weiss et al. (2014)	13 STN-DBS 9 PD controls 21 controls	On	WPT		WPT	

| Ventre-Dominey et al. (2016) | 24 STN-DBS 31 PD controls 21 controls | On | Conditional associative learning | Conditional associative learning |

Table 1.8 Acute effects of subthalamic nucleus (STN) stimulation on learning and memory.
STN-DBS= Subthalamic nucleus deep brain stimulation; PD= Parkinson's disease; VCLT= visual conditional learning task; WPT= weather prediction task.

Halbig and colleagues (2004) administered a version of the WPT that involved a non-declarative probabilistic classification learning phase followed by a declarative multiple choice task to evaluate conscious awareness and knowledge of the cue-outcome associations. During the WPT participants learned associations between four geometrical shapes and two possible outcomes: sunshine or rain. Each of the geometrical shapes had a specific probability of being associated with one of the outcomes. The results indicated that STN stimulation differentially affected the two types of memory. While non-declarative procedural learning on the WPT was improved, declarative knowledge of the cue-outcome associations was impaired with STN stimulation on relative to when stimulation was switched off. By contrast, Wilkinson et al. (2011) found that while acute STN stimulation did not influence overall learning on parallel versions of the WPT, nevertheless learning of weak and strong cue-outcome associations were differentially affected by STN stimulation. STN stimulation led to improved procedural/implicit learning of weak cue-outcome associations, but had no effect on learning of strong cue-outcome associations which are more likely to be acquired through explicit/intentional learning. Similar to the results of Wilkinson et al. (2011), Weiss et al. (2014) reported no effect of STN-DBS on overall learning on the WPT, but just a transient mid-stage dip in learning followed by recovery.

In their study, Funkiewiez and colleagues (2006) administered a reversal learning task with an extinction phase. While the performance on the reversal task did not change with STN stimulation, performance on the extinction phase improved when patients were tested on stimulation. This suggests that STN stimulation did not influence switching between responses and perseverations but it did have an effect on completely inhibiting previously learned stimulus-response associations. The positive effect of STN stimulation on the extinction phase of this reversal task may either relate to changes with stimulation in the requirement of cognitive control or alternatively the inhibitory processing of previously learned stimulus-response associations that is necessary for the extinction phase.

Findings from several studies investigating the effects of STN stimulation on probabilistic learning through positive or negative feedback suggests that stimulation induces either

no effect or improves learning. Frank and colleagues (2007) used a probabilistic reinforcement learning task in which the associations between the stimuli and probability of reward had to be learned in an initial learning phase. They identified no effect of STN stimulation on this initial learning phase. Similar conclusions were drawn by others using the same or similar probabilistic learning tasks (Cavanagh et al., 2011; Coulthard et al., 2012). By contrast, Van Wouwe and colleagues (2011) used a probabilistic reward-based learning task adapted from Haruno and Kawato (2006) to assess reward prediction errors and stimulus-action-dependent reward prediction during early and later phases of learning stimulus-action-reward associations. They predicted that STN stimulation would have beneficial effects for later learning phases reflected by increased levels of stimulus-action dependent reward prediction, which was supported by their findings.

As with the other cognitive domains, findings of the impact of acute STN-DBS on learning and memory are inconsistent, most likely because of the varied nature of the tasks used, which tapped different aspects and processes of learning and memory. In summary, conditional associative learning of 6 arbitrary associations which requires greater cognitive control appears to be impaired with STN-DBS (Jahanshahi et al, 2000), whereas probabilistic classification learning on the WPT, particularly of weak cue-outcome associations (Halbig et al, 2004; Wilkinson et al, 2011), the extinction phase of a reversal learning task (Funkiewiez et al, 2006), as well as certain types of reward-based probabilistic learning (van Wouwe et al, 2011) are improved with STN stimulation compared to DBS off.

1.5.2.4 Working memory and cognitive control

Studies investigating the effects of acute STN stimulation on working memory and cognitive control are listed in Table 1.9. Jahanshahi and colleagues (2000b) assessed the effect of STN stimulation on two visual working memory tests, the missing digit test and the paced visual serial addition test (PVSAT). The results indicated that the performance of the patients on these tests of working memory improved with STN stimulation compared to DBS off. Support for such an improvement has also been provided for spatial working memory, digit ordering and an emotional n-back task by other groups (Merkl,

Roeck, Schmitz-Huebsch, Schneider, & Kuehn, 2017; Mollion et al., 2011; Pillon et al., 2000; Ventre-Dominey et al., 2016), although another study found no effect of STN stimulation on the same spatial working memory tasks (Ventre-Dominey et al., 2014).

Importantly, Hershey and colleagues (2004, 2008) reported that stimulation of the STN produced differential effects on a spatial delayed response task depending on the working memory load. When the working memory load was high stimulation impaired performance compared to STN-DBS off, whereas in the low memory load condition performance was unchanged by STN stimulation. This load-dependency of stimulation effects would also account for the results from a study that used an auditory delayed-match-to-sample task (Camalier, Wang, McIntosh, Park, & Neimat, 2017). Camalier and colleagues (2017) reported that patients who were presented with an auditory distractor performed worse on STN stimulation relative to when stimulation was off, whereas patients who were not presented with a distractor performed better on stimulation relative to the off stimulation assessment. Presence of the distractor increased the cognitive load. Therefore, as noted above with the GNGT (Hershey et al., 2004; Georgiev et al., 2016) and random number generation (Williams et al., 2015), STN-DBS has differential effects on tasks involving working memory, action restraint and inhibition depending on the cognitive load. This is also consistent with the finding that performance on a working memory n-back task concurrently with a force tracking task in a dual task condition does not only worsen when STN stimulation is switched on, but that the impairment induced by STN stimulation under dual task conditions increases with the increase of working memory load and hence task difficulty (Alberts et al., 2008). Therefore, similarly to other cognitive domains, whether or not STN stimulation induces an impairment in working memory depends on the demands for greater cognitive control.

Investigators	N	Medication Status	Task	Worse with STN-DBS	Unchanged with STN-DBS	Improved with STN-DBS
Jahanshahi et al. (2000b)	13 STN-DBS	Off	PVSAT, Missing digit			Missing digit, PVSAT
Pillon et al. (2000)	63 STN-DBS	Off	Spatial working memory, digit ordering			Spatial working memory, digit ordering
Hershey et al. (2004)	24 STN-DBS	Off	Spatial delay response task	Spatial delayed response task – two cues	Spatial delayed response task- one cue	
Page & Jahanshahi (2007)	12 STN-DBS	On	Pegboard and finger tapping dual task		Pegboard and finger tapping dual task	
Hershey et al. (2008)	49 STN-DBS	Off	Spatial delayed response task	Spatial delayed response task		
Alberts et al. (2008)	8 STN-DBS	Off	n-back task and force tracking , dual task	n-back task and force tracking , dual task		
Mollion et al. (2011)	12 STN-DBS 10 controls	On	Spatial and non-spatial visual working memory tasks			Spatial and non-spatial visual working memory tasks
Ventre-Dominey et al. (2014)	13 STN-DBS 11 controls	On	Spatial and non-spatial working memory tasks		Spatial and non-spatial working memory tasks	
Ventre-Dominey et al. (2016)	24 STN-DBS 31 PD controls 21 controls	On	Spatial and non-spatial visual working memory tasks			Spatial and non-spatial visual working memory tasks

Camalier et al. (2017)	28 STN-DBS 28 controls	On	Auditory delayed-match-to-sample task	Auditory delayed-match-to-sample task with distractor	Auditory delayed-match-to-sample task without distractor
Merkl et al. (2017)	16 STN-DBS	On/Off	Emotional n-back task		Emotional n-back task

Table 1.9 Acute effects of subthalamic nucleus (STN) stimulation on working memory and cognitive control.
STN-DBS= subthalamic nucleus deep brain stimulation; PVSAT= Paced visual serial addition task.

1.5.2.5 Language

Studies of the acute effects of STN-DBS on language are listed in Table 1.10, including those that have investigated such stimulation effects on semantic and phonemic verbal fluency. With two exceptions (Schroeder et al, 2003; Wojtecki et al., 2006), the results of these studies are consistent in showing that acute STN stimulation does not significantly alter performance on verbal fluency tasks (Jahanshahi et al, 2000a; Okun et al, 2009; Pillon et al, 2000; Romann, Beber, Olchik & Rieder, 2017; Witt et al, 2004). While Shroeder et al. (2003) reported that high frequency stimulation made phonemic verbal fluency worse relative to DBS off, Wojtecki and colleagues (2006) noted that high frequency stimulation impaired performance relative to *low* frequency stimulation. However, performance during neither of the stimulation conditions differed compared to the off stimulation assessment.

Linguistic tasks that require inhibitory control such as picture-word interference or the inhibition section of the Hayling Sentence Completion test remain unchanged or improve respectively following stimulation (Castner, 2007a). Castner and colleagues (2007b) used a lexical decision task to assess controlled and automatic semantic priming. To differentiate between automatic and controlled priming processes the authors implemented short and long stimulus onset asynchronies respectively. The results indicated that controlled semantic priming improves with STN stimulation relative to when stimulation is switched off, indicating improved attentional processing, whereas this is not the case for automatic semantic priming, which reflects non-strategic automatic processing (Castner et al., 2007b). From these findings it may be suggested that STN stimulation improves executive aspects of language, such as the controlled and strategic inhibition of automatic responses (Castner, 2007b).

On the other hand, STN stimulation may lead to deficits on tasks tapping semantic processes of language. Castner and colleagues (2008a) administered a noun-verb production task, where participants were given a verb or a noun and asked to produce a related second verb or noun. Stimulation only induced impairments in the noun-noun and verb-verb-conditions but not in the verb-noun and noun-verb conditions. This deficit increased with the number of lexical options, suggesting that semantic tasks with greater

number of lexical options, which compete with each other and renders response selection more difficult and places higher demands for cognitive control are impaired with STN stimulation. In another study patients completed a homophone meaning generation test. Homophones are words that have the same pronunciation as other words but have a different meaning and some cases are spelled differently, for example ate and eight. The homophone meaning generation test assesses the ability to switch between the different definitions of homophones. PD patients with STN-DBS had greater difficulties to generate homophone meanings compared to when stimulation was switched off (Castner et al., 2008b), reflecting a semantic switching deficit (Castner et al., 2008b) and further supporting the proposal that a higher demand for cognitive control is associated with stimulation-induced deficits.

More recent research implementing less demanding tasks assessing the semantic aspects of language such as sentence comprehension, metaphor comprehension, word association and lexical decision tasks indicated that STN stimulation does not have an impact on patients' performance (Schulz et al., 2012; Silveri et al., 2012; Tremblay et al., 2015). Silveri and colleagues (2012) also administered an action/object naming task and reported that STN stimulation improved performance. These findings further suggest that the stimulation-induced semantic deficits may be limited to linguistic tasks requiring response selection under competition/conflict which demand greater cognitive control.

As evident from Table 1.10, with exceptions (Schroeder et al, 2003; Wotjecki et al., 2006) the majority of studies, which examined the acute effects of STN stimulation on semantic or phonemic verbal fluency reported no differential effect of acute STN stimulation (Jahanshahi et al., 2000, Morrison et al., 2004; Okun et al., 2009; Pillon et al., 2000; Romann et al., 2017; Schulz et al., 2012; Tremblay et al., 2015). Similarly, spontaneous language production remains stable with stimulation (Batens et al., 2015; van Lier et al., 2016). These findings indicate that acute STN stimulation does not produce major changes in language production, other than impairing more complex semantic properties of language, such as word selection under conflict/competition, further supporting the key importance of extent of cognitive control required in determining the effects of STN stimulation on cognition.

Investigators	N	Medication Status	Task	Worse with STN-DBS	Unchanged with STN-DBS	Improved with STN-DBS
Jahanshahi et al. (2000a)	13 STN-DBS	On	Verbal fluency		Semantic/Phonemic verbal fluency	
Pillon et al. (2000)	63 STN-DBS 13 GPi-DBS	On	Verbal fluency		Semantic/Phonemic verbal fluency	
Schroeder et al. (2003)	7 STN-DBS	On	Verbal fluency	Phonemic verbal fluency		
Morrison et al. (2004)	17 STN-DBS 11 PD control	On	Verbal fluency		Semantic/Phonemic verbal fluency	
Witt et al. (2004)	23 STN-DBS	On	Verbal fluency		Semantic/Phonemic verbal fluency	
Wojtecki et al. (2006)	12 STN-DBS	On	Verbal fluency	Phonemic verbal fluency worse with high frequency DBS		Phonemic verbal fluency improved with low frequency DBS
Castner et al. (2007a)	18 STN-DBS 21 controls	On	Picture-word interfere task, Hayling test		Picture-word interference	Inhibition section of Hayling test
Castner et al. (2007b)	18 STN-DBS 19 controls	On	Lexical decision task		Automatic semantic priming	Controlled semantic priming in lexical decision task
Castner et al. (2008a)	8 STN-DBS 15 controls	On	Noun/verb generation task	Noun-noun & Verb-verb generation	Noun-verb generation	
Castner et al. (2008b)	17 STN-DBS 21 controls	On	Homophone meaning generation task	Homophone meaning generation		

Okun et al. (2009)	22 STN-DBS 23 Gpi-DBS	On	Verbal fluency	Semantic/Phonemic verbal fluency	
Schulz et al. (2012)	12 STN-DBS	On	Sentence comprehension, verbal fluency	Sentence comprehension and verbal fluency	
Silveri et al. (2012)	12 STN-DBS 14 controls	On	Verb/noun reading, action/object naming	Verb and noun reading	Action and object naming
Batens et al. (2015)	10 STN-DBS	On	Spontaneous language production task	Spontaneous language production	
Tremblay et al. (2015)	10 STN-DBS	On	Metaphor comprehension, lexical decision, word association, verbal fluency	Metaphor comprehension, lexical decision, word association, verbal fluency	
Van Lier et al. (2016)	18 STN-DBS	On	Spontaneous language production task	Spontaneous language production	
Romann et al. (2017)	16 STN-DBS	On	Phonemic verbal fluency	Phonemic verbal fluency	

Table 1.10 Acute effects of subthalamic nucleus (STN) stimulation on language functions.
STN-DBS= subthalamic nucleus deep brain stimulation.

1.6 Effects of pedunculopontine nucleus deep brain stimulation on cognition

Pedunculopontine nucleus deep brain stimulation (PPN-DBS) is a relatively new approach for treating the axial symptoms in PD. Research investigating the clinical benefits in terms of motor symptoms is inconsistent. While some literature suggests beneficial effects (Mazzone et al., 2005; Plaha & Gill, 2005; Stefani et al., 2007), others reported contradicting results (Ferraye et al., 2010; Moro et al., 2010; Scelzo et al., 2017). This section reviews the existing body of literature looking at the effects of PPN-DBS on cognition. Considering that PPN-DBS is a novel approach for treating PD and not as common as STN-DBS, research into this surgical application is limited. However, some evidence suggests beneficial effects of PPN-DBS for cognition (see Table 1.11).

Zanini and colleagues (2009) assessed language functions in 5 PD patients who had previously undergone STN-DBS, prior to PPN-DBS surgery, six and twelve months after surgery. The results suggest that grammatical aspects of language were improved. On the other hand, Pinto et al. (2014) found speech degradation in a series of PD patients twelve months after PPN-DBS surgery and Brusa and colleagues (2009) identified minimal improvement of verbal fluency in one PSP patient after PPN-DBS. From the given evidence it is difficult to say how PPN-DBS affects language functions in patients. Further cognitive domains found to improve following PPN-DBS include working memory (Costa et al., 2010), attention (Thevathasan et al., 2010) and executive functions (Ceravolo et al., 2011). However, these studies investigated the effects of acute low frequency PPN stimulation, rather than looking at the surgical effects. Also, the majority of studies tested patients, who were treated with PPN-DBS in combination with DBS of a different target (Ceravolo et al., 2011; Costa et al., 2010; Pinto et al., 2014; Thevathasan et al., 2010; Zanini et al., 2009). Therefore, it is uncertain whether cognitive effects are purely caused by PPN-DBS. Recently a case of a patient with PD-D was described (Ricciardi et al., 2015). According to the description, PPN stimulation improved cognition globally compared to when stimulation was switched off. However, it is important to mention that this patient had cognitive declines four years after surgery (Ricciardi et al., 2015). From the research above it becomes apparent that more research looking at larger samples and more extensive cognitive assessment is needed.

Investigators	N	DBS Side	Follow-up months	Neuropsychological tests	Motor symptoms	Cognition domains
Zanini et al. (2009)	5 PD	Bilateral PPN Bilateral STN	6,12	Story generation task	UPDRS-III improved	Grammatical aspects of language improved
Brusa et al. (2009)	1 PSP	Unilateral PPN Right	4,6,9	CVLT, phonemic VF, TMT, digit span	UPDRS-III modestly improved	Minimal verbal fluency improvement
Costa et al. (2010)	5 PD	Bilateral PPN Bilateral STN	3	Modified card sorting test, phonemic VF, RPM, RAVLT, Rey's complex figure test, digit span, corsi's block tapping, TMT	UPDRS-III improved	Significant working memory improvement
Thevathasan et al. (2010)	11 PD	Bilateral PPN Unilateral PPN Bilateral ZI	2-38	Simple reaction time task, digit vigilance task, choice reaction time task	Gait and balance improved	In attention test speed but not accuracy of reaction improved
Ceravolo et al. (2011)	6 PD	Bilateral PPN Bilateral STN	12	CVLT, digit span, TMT, phonemic VF, BNT	UPDRS-III improved	Executive functions improved
Pinto et al. (2014)	7 PD	Bilateral PPN Bilateral STN	12	Speech task	NA	Speech degradation
Ricciardi et al. (2015)	1 PD-D	Unilateral PPN	6, 48	MMSE, RPM47, RAVLT, digit span, VF, nouns naming, copying, MFTC, Stroop	UPDRS-III improved slightly	Improvement of global cognition.

Table 1.11 Effects of pedunculopontine nucleus deep brain stimulation (PPN-DBS) on cognitive functions.
PD= Parkinson's disease; PD-D= Parkinson's disease dementia; PSP= Progressive supranuclear palsy; PPN = Pedunculopontine nucleus; STN= Subthalamic nucleus; ZI= zona incerta; UPDRS= Unified Parkinson's disease rating scale; CVLT= California verbal learning test; VF= Verbal fluency; TMT= Trial making test; RPM= Rey's

progressive matrices; RAVLT= Rey auditory verbal learning test; BNT= Boston naming test; MMSE= mini mental status examination; MFTC= Multiple features target cancellation.

It has been suggested that the basal ganglia together with the frontal cortex are involved in inhibitory processing and the fronto-striatal circuits form a network for habitual and goal directed inhibition (Jahanshahi et al., 2015b). Thus, the basal ganglia mediate the inhibition necessary for action cancellation during stop signal tasks. A race between stop and go processes involved in such a task reflects the race between different neural pathways (Aron & Poldrack, 2006; Schmidt, Leventhal, Mallet, Chen, & Berke 2013). Schmidt and colleagues (2013) investigated the neural correlates of the competing 'go' and 'stop' processes in rats and hypothesised that additional midbrain structures may also influence successful action cancellation. According to their proposal, the PPN and the parafascicular cortex (Pf) might serve as accelerating mechanisms for the stop STN-SNr pathway and may also decrease striatal activity.

1.7 Decision-making models

Research has shown that cortical areas and the basal ganglia are involved in decision-making (Chevalier, Vacher, Deniau, & Desban, 1985; Deniau & Chevalier, 1985; Medina & Reiner, 1995; Redgrave, Prescott, & Gurney, 1999; Schall, 2001; Shadlen & Newsome, 2001; Smith, Bevan, Shink, & Bolam, 1998). It was proposed that the process of decision-making comprises two main stages (Ashby & Spiering, 2004; Shadmehr & Holcomb, 1997). During the acquisition or learning stage, appropriate responses are developed through external reward. During this phase, a reward-maximising combination between behavioural states and actions is established (Sutton & Barto, 1998). Both the basal ganglia and the cortex are involved in this process (O'Doherty et al., 2004; Samejima, Ueda, Doya, & Kimura, 2005; Schultz, Dayan, & Montague, 1997). During the second 'proficient' phase action selection or decision-making takes place. Thus, the current behavioural state is analysed until enough evidence is provided to produce an appropriate response (Gold & Shadlen, 2001, 2002).

More recently, Rangel, Carerer and Montague (2008) suggested that decision-making has 5 stages. The first stage is the representation stage, during which the problem that requires decision-making is presented by considering the different options and actions that can be taken. During the second, valuation stage subjective values are assigned to the different options in order to choose the option with the highest value. During this stage, the value estimation is achieved by considering cost, based on several factors, including probability, delay in reward acquisition and effort required. The third stage involves action execution, followed by the outcome evaluation and learning stages, which may result in modification of the valuation stage. These 5 stages depend on different cognitive processes (Ryterska, Jahanshahi & Osman, 2014). Therefore, stage 1 requires the ability to produce representations of physical or abstract objects; stage 2 relies on the ability to represent subjective value of an object and to consider different forms of cost; stage 3 relies on the ability to execute one action while inhibiting others; stage 4 relies on the ability to estimate the outcome value in consideration of the expected value; and stage 5 relies on the ability to update representations of decision problems based on previous outcomes in order to improve future outcomes. According to Rangel and colleagues

(2008) not all stages described above are required to take place during decision-making, but impairment of one stage can have an impact on the remaining stages. If the impaired stage is not required for a certain decision problem, normal decision-making is still possible.

Research, investigating the neural mechanisms of decision-making, suggests that during decision-making processes cortical areas representing alternative responses increase their firing rate, reflecting the collection of evidence supportive of a certain response (Schall, 2001; Shadlen & Newsome, 2001). From these data, models were developed indicating that cortical neurons associated with certain stimuli are connected with those representing different actions and that these cortical connections encode stimulus-action mapping (Shadlen & Newsome, 2001; Wang, 2002). Consequently, such models imply that the process of decision-making is encoded within cortical areas only.

However, most experimental tasks provide several response options requiring action selection. This concern was addressed by Redgrave and colleagues (1999), who described it as a conflict resolution between different activated brain areas competing for behavioural expression and suggested that the basal ganglia act as a central switch analysing the salience of the different actions. The basal ganglia receive signals from different brain regions (Parent & Hazrati, 1995) and cause tonic inhibition of areas involved in motor execution, which subsequently reduces cortical control over actions. When the activity of the output nuclei is reduced, cortical targets are disinhibited and action selection takes place (Chevalier et al., 1985; Deniau & Chevalier, 1985). This idea is known as the selection hypothesis of the basal ganglia, which has been tested by several computational models (Brown, Bullock, & Grossberg, 2004; Gurney, Prescott, & Redgrave, 2001a, 2001b; Humphries & Gurney, 2002).

Evidence from single-cell recordings of the cortex suggests that activity in certain sensory cortical regions reflects evidence accumulation. In the case of a direction of motion discrimination task this would be the middle temporal visual area (MT). This cortical activity is noisy reflecting uncertainty (Britten, Shadlen, Newsome, & Movshon, 1993; Kim & Shadlen, 1999). This noise increases the likelihood of a decision made on the basis

of cortical activity at a certain time point to be inaccurate. According to the hypothesis described by Gold and Shadlen (Gold & Shadlen, 2001, 2002) activity in the MT reflects the encoding of evidence for a certain direction and that a decision should be made at a time point when the mean evidence is the highest. This suggests that evidence is accumulated over time. However, the hypothesis does not specify when a selection mechanism stops the evidence collection and chooses the response with the highest evidence. The race model describes a simple solution for this problem (Vickers, 1970). The model assumes that an action is selected as soon as a certain evidence threshold is reached. However, this model is not ideal when a decision is made between two or more alternative actions.

The more effective approach would be to calculate the difference between the accumulated evidence for two alternatives and decide as soon as this difference reaches a certain threshold. This approach is described by the drift diffusion (Ratcliff, 1978) or random-walk model (Laming, 1968; Stone, 1960). This model may be statistically explained by the sequential probability ratio test (SPRT) (Barnard, 1946; Wald, 1947) in the case of two alternatives or by the multihypothesis SPRTS (MSPRT) (Baum & Veeravalli, 1994; Dragalin, Tertakovsky, & Veeravalli, 1999) in case of more than two alternatives. These allow the implementation of relative evidence for the given alternatives into the regulation of the decision threshold and reduce decision-making time to a minimum for a fixed accuracy (Bogacz & Gurney, 2007).

Based on empirical evidence that the STN sends several excitatory projections to the output nuclei of the basal ganglia (Parent & Smith, 1987), theoretical works proposed that the STN is involved in integrating the evidence for alternative choices to compute the conflict and regulate the decision threshold accordingly (Mink, 1996; Frank, 2006; Bogacz & Gurney, 2007). Moreover, Frank (2006) hypothesised that the STN acts as a temporary brake, which prevents premature responses when decision-making has to be performed in high conflict situations. This 'hold your horses' temporary braking function of the STN allows time for enough information to be accumulated before a decision is made and thus prevents quick impulsive responding. Therefore, disruption of STN activity with STN-DBS would interfere with the temporary braking function of the STN

and result in fast and impulsive responses. Assessment of patients with PD with bilateral STN-DBS on a probabilistic decision-making task under conflict provided evidence for this model by showing that on trials with high conflict between choice of stimuli both of which were associated with high reward values, patients with PD and STN stimulation on failed to slow down and had significantly faster RTs than with STN stimulation off and unoperated PD patients and healthy controls (Frank et al., 2007). Figure 1.10 is a schematic presentation of how the decision threshold is adjusted.

Figure 1.10 Evidence accumulation in the subthalamic nucleus over time and decision threshold in in risky and fast or safe and slow responses. From Bogacz et al. (2010). Trends Neurosci, 33(1),

More recently, it has been proposed that the decision-making process includes an 'urgency' signal that increases over time to adjust neural activity to become closer to the initiation threshold (Churchland, Kiani & Shadlen, 2008; Cisek, Puskas & El-Mur, 2009; Ditterich, 2006; Thura, Beauregard-Racine, Fradet & Cisek, 2012). Therefore the 'urgency' signal would result in an accuracy criterion that decreases over time. These 'urgency-gating-models' take into account dynamic changes in the environment and allow quicker responding to such changes, resulting in higher reward rates relative to decision-making models that involve a constant criterion (Miller & Katz, 2013; Thura et al., 2012). Support for such 'urgency-gating-models' was provided by premotor and

primary motor cortex recordings of monkeys, making decisions in constantly changing situations, suggesting that neural activity combines rapid estimates of evidence with growing urgency (Thura & Cisek, 2014). Furthermore, recent evidence from the same research group indicated activity of the GPe and GPi is implicated in the decision-making process by providing an urgency signal that changes the extent to which sensory information influences the activity of the premotor and motor cortex (Thura & Cisek, 2017).

A further idea about the role of the STN of some relevance to decision-making is the proposal based on empirical data from the electrophysiological study in primates that the STN implements a switch from automatic to controlled processing, based on signals that it receives from the pre-supplementary motor area (pre-SMA) (Hikosaka & Isoda, 2010). Imaging data from an fMRI study using a decision-making task with varying speed instructions suggested that the pre-SMA and the striatum have increased activity when patients were instructed to make quick responses (Forstmann et al., 2008). Forstmann et al. (2008) reported that the activity in the pre-SMA is related to decision threshold modulation and increased activity of the striatum relates to disinhibition of cortical motor regions enabling faster and sometimes premature responding when decisions have to made quickly. Another fMRI study that used a cued-trials task-switching paradigm (Mansfield et al., 2011) to investigate the roles of the striatum, the pre-SMA and the STN in decision threshold modulation also supports these findings. The task that was used in this study was separated into three subtasks with binary decisions. Between trials participants were presented with cues indicating whether the next trial involves the same subtask (repeat cues) or switches to a different subtask (switch cues) inducing different levels of cautiousness. Results suggested that repeat cues produced a lower decision threshold compared to switch cues. This was reflected by increased activity in the pre-SMA when the decision threshold was lowered in both repeat and switch cue trials. On the other hand, striatal activity only increased in relation to a decreasing threshold for the repeat cue trials, suggesting that the pre-SMA biases the striatum to decrease the threshold under conditions requiring less cautiousness. High decision threshold for switch cues was associated with increased STN activity, suggesting an association with increased cautiousness for these trials.

Evidence from studies investigating decision-making in PD is inconsistent (for review see Ryterska et al., 2014). Research using tasks that assess decision-making under uncertainty or risk, such as the Game of Dice task, or that require outcome prediction, such as the weather prediction task, reported that PD patients had impaired performance relative to healthy control participants (Brand et al., 2004; Euteneuer et al., 2009; Jahanshahi, Wilkinson, Gahir, Dharminda & Lagnado, 2010; Labudda et al., 2010; Shohamy, Myers, Onlaor & Gluck, 2004; Wilkinson, Lagnado, Quallo & Jahanshahi, 2008; Witt, Nuhsman & Deuschl, 2002). Similarly, PD patients are impaired on tasks that require the choice between two options associated with different rewards, such as the Iowa Gambling task (Czernecki et al., 2002; Kobayakawa, Koyama, Mimura & Kawamura, 2008; Mimura, Oeda, Kawamura, 2006). On the other hand, there is some evidence that PD patients perform as well as healthy controls on the same tasks that were initially considered to be impaired (Kobayakawa, Tsuruya & Kawamura, 2010; Labudda et al., 2010; Shohamy et al., 2004), and even on more complex forms of decision-making assessed by dynamic decision-making tasks (Osman, Wilkinson, Beigi, Castaneda & Jahanshahi, 2008; Osman et al., 2014; Witt et al., 2006). Ryterska and colleagues (2014) proposed a possible reason for this inconsistency in findings. They suggested on the base of the 5 stages of decision-making by Rangel et al. (2008) that PD only impairs some but not all stages, and thus leaves decision-making in certain situations unaffected. Therefore, PD would have an impact cost analysis and feedback processing resulting in deficits in the valuation and outcome evaluation stage respectively.

In summary, PD is progressive neurodegenerative disorder that is characterised by its' cardinal motor symptoms and a host of non-motor symptoms including cognitive deficits. These cognitive deficits initially present in the form of mild cognitive impairment and a large proportion of the patients develops dementia in the long-term. Therefore, it is crucial that medical and surgical treatment of PD does not increase the risk of cognitive impairment. STN-DBS is the most successful surgical treatment of PD, leading to significant improvements in motor symptoms and quality of life. There is some evidence that STN-DBS surgery results in decline of some cognitive processes, with the most consistent decline reported for verbal fluency. PPN-DBS is a more recent treatment for

the axial symptoms of PD. Research into the cognitive effects of PPN-DBS is limited, with the existing evidence suggesting beneficial effects for some cognitive domains.

1.8 General Methods

Based on the theoretical works and empirical evidence reviewed above, my first aim was to specifically investigate how stimulation of the STN affects probabilistic decision-making that is not based on previously learned stimulus-action-reward associations and does not involve a component of conflict. My second aim was to investigate the differential effects of STN-DBS surgery and acute STN stimulation on different components of verbal fluency. My third aim was to investigate the effects of acute STN stimulation on visual and verbal conditional associative learning. Finally, considering the limited evidence for the effects of PPN stimulation on cognition, which was derived from patient samples, who mostly also had STN-DBS, I aimed to expand on this by looking at the cognitive effects of PPN-DBS in a sample of patients, who only had PPN-DBS.

1.8.1 Specific Aims and Hypotheses
1.8.1.1 The Subthalamic nucleus (STN) and integration of probabilistic information during decision-making: evidence from the effect of STN-DBS in PD

The first aim of this thesis was to test the role of the STN in probabilistic decision-making when it does not involve reward-based learning and conflict. Decision-making models proposed that the STN integrates probabilistic information for alternative actions and computes conflict to adjust a decision threshold accordingly (Bogacz & Gurney, 2007; Frank, 2006; Mink, 1996). Therefore, probabilistic decisions should be made based on the relative evidence for alternative actions. If STN activity is interrupted decisions should be made based on the absolute evidence for the chosen option. From this it was hypothesised:

1. PD patients with STN stimulation on would make more impulsive decisions compared to when stimulation is switched off and compared to healthy control participants.

2. When STN stimulation is switched on PD patients who receive high frequency stimulation would make more impulsive decisions, compared to patients who receive low frequency stimulation.

1.8.1.2 Dissociable effects of subthalamic nucleus deep brain stimulation surgery and acute stimulation on verbal fluency in Parkinson's disease

The second aim of this thesis was to follow up on the findings, generated across the literature that STN-DBS consistently causes verbal fluency deficits (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). The specific nature of these impairments remains unclear. So far, evidence only looked at semantic and phonemic fluency without taking other factors into account. More specifically, it is unknown, what aspects of verbal fluency are actually compromised. Verbal fluency consists of several processes including search of semantic networks, intrinsic word generation and monitoring of the output. It is important to clarify where the decline in VF performance arises. Troyer, Moscovitch & Wincour (1997) proposed that verbal fluency consists of two subcomponents, namely clustering and switching. Accordingly clustering refers to the number of words belonging to a certain semantic or phonemic subcategory and switching refers to the set shifting between these subcategories. Troyer et al. (1997) further stated that switching would reflect a frontal executive function whereas clustering would reflect a semantic temporal lobe function. Considering that PD mainly affects cognitive functions involving frontal areas, it could be suggested that verbal fluency deficits seen in PD relate to impaired switching but not clustering performance. The research question was what cognitive processes lead to verbal fluency deficits induced by STN-DBS. The following hypotheses were tested:

1. The total number of words on all three verbal fluency tasks would be lower after surgery compared to before surgery.
2. The total number of semantic and phonemic switches would be lower for the category and letter fluency respectively, after surgery compared to before surgery.

3. The average phonemic and semantic cluster size on the category and letter fluency tasks would remain unchanged after surgery compared to before surgery.

4. Acute STN stimulation would have no effect on verbal fluency performance and the total number of words on all three verbal fluency tasks would remain unchanged with STN stimulation on compared to when stimulation was switched off.

5. The total number of semantic and phonemic switches and the average semantic and phonemic cluster size would remain unchanged with STN stimulation on compared to when stimulation was switched off.

1.8.1.3 Effects of STN-DBS on associative learning of verbal and non-verbal information in PD

The third aim of this thesis was to investigate the effects of acute STN stimulation on associative learning for visual and verbal stimuli. Previous research on the effects of STN stimulation on visual conditional associative learning is inconsistent, with some reporting impaired performance with STN stimulation compared to when stimulation was off (Jahanshahi et al., 2000a) and others indicating that patients improved with stimulation on relative to the stimulation off performance (Mollion et al., 2011; Ventre-Dominey et al., 2016). Vriezen and Moscovitch (1990) investigated the effects of different learning instructions on the conditional associative learning task in PD. They administered the same task twice, once learning by trial and error and a second time using corrective feedback. Vriezen and Moscovitch (1990) suggested that the trial-and-error learning instruction would involve frontal networks to a greater extent than the latter. The results indicated that PD patients were only impaired on the task when learning by trial and error but performed normally when learning from corrective feedback. Therefore, the first research question was whether acute STN stimulation has a differential effect on visual conditional associative learning by trial and error and corrective feedback. Research investigating the effects of acute STN stimulation on different cognitive functions, including learning and semantic functions suggested that these largely depend on the on the cognitive load and the level of cognitive control

required. Consequently, tasks with higher cognitive load become impaired with acute STN stimulation (e.g. Jahanshahi et al. 2000a), and tasks with lower cognitive load remain intact or become improved (e.g. Mollion et al., 2011; Ventre-Dominey et al., 2016). Therefore, it could be suggested that this would also apply for a verbal associate learning task. The second research question was whether acute STN stimulation has a differential effect on verbal associative learning of words that are semantically related or unrelated. The following hypotheses were tested:

1. Learning and performance on the trial-and-error learning visual conditional associative learning task would decline with STN stimulation, compared to when stimulation was switched off.

2. Learning and performance on the feedback learning visual conditional associative learning task would remain unchanged with STN stimulation compared to when stimulation was switched off.

3. The total number of correctly learned associations on the verbal paired associate learning task would decline for the 'hard' unrelated pairs only with STN stimulation on compared to when stimulation was switched off, but would remain unchanged for the 'easy' related pairs.

1.8.1.4 Effects of PPN-DBS on cognitive function

The fourth aim of this thesis was to investigate the effects of PPN-DBS on cognitive function. PPN-DBS is a relatively new approach for treating axial symptoms in PD and atypical Parkinsonism such as progressive supranuclear palsy (PSP). While findings concerning its benefits for motor symptoms are inconsistent (Ferraye et al., 2010; Mazzone et al., 2005; Moro et al., 2010; Plaha & Gill, 2005; Scelzo et al., 2017; Stefani et al., 2007), some evidence suggests beneficial effects for certain aspects of cognition. Recent evidence suggests that low frequency PPN-DBS can lead to improvements in executive function, language and working memory (Morita et al., 2014; Stefani et al., 2013). However, most research included patients who had STN-DBS and PPN-DBS. In addition, only one case of a demented patient was described (Ricciardi et al., 2015). Therefore, the first research question was whether patients with either PD or PSP who were implanted with unilateral PPN-DBS would show changes in their cognitive functions

post-operatively compared to pre-operatively. A second question is whether beneficial effects of low frequency PPN stimulation on cognition can be produced in cases of PSP with dementia or PD-D. Due to the limited literature in this field, this study was exploratory in nature and no specific hypotheses were investigated.

1.8.2 Sample recruitment and sample size calculation

Information from previous studies was used to measure the effect size necessary to obtain a statistically relevant sample size in each study. The mean and standard deviation values for the outcomes of interest from previous studies with PD patients who were treated with DBS and PD and healthy control participants were used to obtain µ1 and µ2 to calculate the 'effect size' (d). This allowed us to estimate the power needed at $p = 0.05$. An expected power of 0.8 was used for every power calculation based on the following formula (Cohen, 1992):

$$d = \frac{(\mu1 - \mu2)}{\sigma}$$

Where $\mu1$ represents the mean of group 1, $\mu2$ represents the mean of group 2. σ1 represents the standard deviation of group 1, whereas σ2 represents the standard deviation of group 2, and σ represents the pooled standard deviation of the two groups.

$$\sigma = \sqrt{[(\sigma1^2 + \sigma2^2)/2]}$$

Information from previous studies is derived to obtain the 'effect size' necessary to obtain a statistically significant effect. For Study 1 no previous studies had looked at the effects of acute STN stimulation on the same decision-making task. Therefore, the effect size was based on previous studies that looked at the effects of STN stimulation on similar tasks. Frank and colleagues (2007) included 17 PD patients with STN-DBS, Cavanagh et al. (2011) included 14 PD patients with STN-DBS and Coulthard et al., (2012) included 11 PD patients with STN-DBS with significant results obtained in all three studies. Therefore, in Study 1, 13 PD patients with STN-DBS and a total of 24 healthy controls were included and was considered to provide sufficient power based on these previous studies.

For Study 2, the effect size was based on a previous study that investigated the effects of STN-DBS on both letter and category fluency (York et al., 2008). Following the Cohen

power calculation (1992), observed effect sizes of d = 0.75 and d = 0.82 were obtained from York's repeated-measures letter and category fluency data respectively. The sample size calculation resulted in an N of 18. Therefore, in the first verbal fluency study, 19 PD patients who underwent STN-DBS surgery were included, and in the second verbal fluency study, 22 PD patients with STN-DBS and 9 unoperated PD patients were included. The sample size of unoperated PD patients could not be increased as they were matched with the operated group in terms of disease severity and were future surgical candidates.

For Study 3, the effect size was based on a previous study that investigated the effects of acute STN stimulation on the patients' performance on the visual conditional associative learning task (Jahanshahi et al., 2000b). An observed effect size of d = 0.66 was obtained from the paired mean comparisons. The optimal sample size was estimated as an N of 22. Therefore, in Study 3, 24 PD patients with ST-DBS and 9 unoperated PD patients were included. The sample size of unoperated PD patients could not be increased as they were matched with the operated group in terms of disease severity and were future surgical candidates.

No previous studies examined the effects of PPN-DBS surgery on such an extensive neuropsychological battery of tests. The sample sizes in previous studies are limited and range from single cases to 11 PD patients with PPN-DBS. Furthermore, at our centre, after completion of the surgery on the first series of patients, it became clear that the clinical effects/benefits of PPN-DBS on the motor symptoms were not very impressive and surgery with this target was no longer offered to PD patients. Therefore, in Study 4, the 5 PD and 2 PSP patients, who had PPN-DBS surgery at our center were included. This small sample size is the function of PPN-DBS being a relatively rare treatment approach that is no longer offered at our centre.

1.8.3. Ethics

Ethic approval was obtained from the joint ethics committee of the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery. The project ID number is 01/N040. Patients were provided with information sheets setting out the rationale and aims of each study (please appendices A to C). After reading the

information sheet any questions that patients had were addressed. Informed consent was obtained from all participants (Consent forms can be seen in appendices A to C). On the information sheet, participants are informed that participation is voluntary and that they can withdraw at any time during the study without giving any reason and without any impact on their future clinical care. Furthermore, they are informed that their personal information is treated confidentially and will not leave the Institute and that their results will be only published anonymously, without inclusion of any personal information. Because my study involves patients with PD who have had DBS, which makes them particularly vulnerable I try to make them feel as comfortable as possible and stop as soon as I notice that a participant is in discomfort.

1.8.4 Statistical Analysis

All analyses are done using the statistical package for social sciences version 22 (SPSS Inc., Chicago, Illinois, USA). For power calculation G*Power 3.1.3 software was used. Preliminary data analysis was first completed to check for presence of any outliers (values >2.5 SD from mean) and normal distribution of variables (p value < .05 in Sharpio-Wilks test to indicate non-normality). In cases where data were not normally distributed, non-parametric tests were used.

To determine if the PD STN-DBS and the PD or healthy control groups were matched for age, years of education, and where applicable for global cognition measured on the MMSE and depression scores for Study 1, a one-way ANOVA and for Studies 2 and 3 independent samples t-tests were used. For studies with a mixed repeated measures and between group designs, repeated measures ANOVAs were carried out. For studies with a pure repeated measures design paired t-tests were performed.

Repeated measures ANOVAs were tested for sphericity and the Greenhouse-Geisser correction was used to adjust for degrees of freedom. Post-hoc tests were performed using independent t-tests and paired t-tests where necessary. The significance level used throughout the thesis was $\alpha \leq 0.05$. Although Bonferroni correction overcomes the risk of giving too much weight to what may be differences obtained by chance due to multiple comparisons, it may also increase the risk of a type two error that is accepting the null

hypothesis when it is in fact false. From a clinical point of view, this would be problematic when considering changes in cognition with DBS of the STN, as it would result in important changes to be overlooked. Therefore, Bonferroni corrections were not applied to the results.

Chapter 2. The Subthalamic nucleus (STN) and integration of probabilistic information during decision-making: evidence from the effect of STN-DBS in PD

2.1 Introduction

Due to dopamine depletion in the nigrosrtriatal pathway, the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) become hyperactive in Parkinson's disease (PD) causing inhibition of the thalamo-cortical projection and the brainstem nuclei (Bergman et al., 1994). Consequently, patients have difficulties initiating and executing movements. Deep brain stimulation (DBS) is a highly successful surgical method for treating the motor symptoms of PD, when patients develop drug-induced dyskinesias and on-off fluctuations after long-term levodopa therapy (Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2012; Williams et al., 2010).

A large proportion of the literature suggests that STN-DBS induces deficits in certain cognitive domains particularly in verbal fluency (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). The acute effects of stimulation on cognition have been assessed in experimental tasks implementing the stimulation 'ON vs. OFF' methodology (Jahanshahi, 2013; for reviews see Jahanshahi, et al., 2015a; Jahanshahi et al., 2015b). Evidence from studies investigating decision-making on a range of different experimental tasks is inconsistent, with some suggesting impaired performance induced by STN stimulation (Antonidias et al., 2014; Cavanagh et al., 2011; Coulthard et al., 2012; Evens et al., 2015; Florin et al., 2013; Frank, J. et al., 2007; Green et al., 2013; Oyama et al., 2011; Pote et al. 2016; Rogers et al., 2011; Seymour et al., 2016; Zaehle et al., 2017), whereas others reporting no change (Brandt et al., 2015; Castrioto et al., 2015; Djamshidian et al., 2013; Evens et al., 2015; Fumagalli et al., 2015; Seinstra et al., 2016; Torta et al., 2012) or even improvement (Boller et al., 2014; Brandt et al., 2015; Fumagalli et al., 2015; Torta et al., 2012; van Wouwe et al., 2011; Zaehle et al., 2017).

The goal of a decision process is to choose the alternative with the highest mean evidence (Gold & Shadlen, 2001, 2002). Various models have formulated decision-making as involving two or more stages (Ashby & Spiering, 2004; Rangel et al., 2008; Shadmehr & Holcomb, 1997). In terms of the neural processing underlying decision-making, it has been suggested that decision-making can be divided into three sub-processes (Mazurek et al., 2003). During the first of these processes, sensory areas encode evidence

supporting different alternatives (Britten et al., 1993). This evidence is noisy, requiring a second process where cortical areas representing alternative actions integrate the evidence over time and thereby reduce the noise (Schall, 2001; Shadlen & Newsome, 2001). During the third and final process a neural mechanism measures, whether a decision threshold is reached that supports selection of one alternative and execution of a certain action. Two possible neural mechanisms have been proposed to underlie this third process. Some theories suggest that a decision is made as soon as activity in cortical areas representing a certain action reaches a threshold (Mazurek et al., 2003; Schall, 2001; Shadlen & Newsome, 2001). Others suggest that criterion satisfaction is determined in the basal ganglia (Bogacz & Gurney, 2007; Frank, 2006; Gurney et al., 2001a; Mink, 1996). Mink (1996) proposed that tonic inhibition by the basal ganglia acts as a brake upon cortical and brainstem motor areas. When movement is initiated, basal ganglia output neurons projecting to cortical regions representing the action with the highest level of mean evidence have decreased activity, whereas the remaining output neurons have increased activity to enable behavioural expression of the chosen response. Frank (2006) developed a model of how the STN is involved in the decision-making process. He proposed that the STN controls the decision threshold and that threshold modulation is influenced by the amount of evidence accumulated for the competing alternative responses. The STN acts a temporary 'hold your horses' brake to allow enough information to be integrated before making decisions, to prevent impulsive decisions in high conflict situations. Evidence from experimental studies of PD patients with STN-DBS supports this model (Cavanagh et al., 2011; Frank et al., 2007). Relative to when STN stimulation was switched off, patients with STN stimulation made premature decisions only in high conflict trials. Also, this effect of STN stimulation was only seen in trials where patients had to decide between two alternatives that were associated with a high likelihood of positive outcome. Bogacz and Gurney (2007) suggested that the STN computes conflict of competing actions and modulates the threshold accordingly. Therefore, it integrates the relative evidence for the given options and a decision is made if the difference in evidence reaches a certain threshold. Moreover, the more conflicting the integrated information is the more evidence needs to be integrated before a decision can be made.

PD patients who are treated with STN-DBS initially receive high frequency STN stimulation (<100 Hz), as it leads to the greatest improvement of the cardinal motor symptoms of PD (Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2005; Weaver et al., 2012; Williams et al., 2010). However, recent evidence indicated that low frequency (60 to 100 Hz) STN stimulation has less adverse effects or improves axial symptoms, such as freezing of gait, postural instability or speech impairments, which develop in a proportion of the patients who are treated with STN-DBS 4 to 5 years after surgery (Moreau et al., 2011; Ramdhani, Patel, Swope & Kopell, 2015; Xie et al., 2015; for review Xie et al., 2017). Research investigating the differential effects of high and low frequency STN stimulation on cognition is very limited. Studies investigating the frequency-dependent effects of STN stimulation on phonemic verbal fluency reported that high frequency STN stimulation impaired the patients' performance, relative to when they received low frequency stimulation (Fagundes, Rieder, da Cruz, Beber & Portugez, 2016; Wojtecki et al., 2006). Therefore, it may be suggested that high frequency STN stimulation has a detrimental effect on aspects of cognition whereas low frequency STN stimulation does not. The aim of this study was to investigate the effects of acute STN stimulation on a probabilistic decision-making task that does not involve a learning phase, reward or conflict, and if such effects are frequency-dependent. The following hypotheses were investigated:

1. PD patients with STN stimulation on would make more impulsive decisions compared to when stimulation is switched off and compared to healthy control participants.
2. When STN stimulation is switched on PD patients who receive high frequency stimulation would make more impulsive decisions compared to patients who receive low frequency stimulation.

2.2 Methods

2.2.1 Participants

Thirteen patients (11 males) with a clinical diagnosis of Parkinson's disease based on UK Brain bank criteria were assessed (Hughes, Daniel, Kilford, & Lees, 1992). All patients had quadripolar stimulating electrodes (Medtronic, Minn., USA) chronically implanted into the STN bilaterally, according to procedures previously described (Foltynie et al., 2011). Six patients received high frequency (125 to 160Hz) STN stimulation and seven patients received low frequency (80 to 100Hz) STN stimulation. All patients were rated on the Unified Parkinson's disease Rating Scale (UPDRS: Fahn & Elton, 1987). The mean age was 61.6 (SD=10.04; range 42-73). To control for possible practice and age effects 23 neurologically healthy participants were recruited, of whom eleven (6 males) were matched in age (p>0.05) with the patient group and twelve were younger (8 males). The mean age of the age-matched group was 66.0 (SD=12.28; range 45-82) and the mean age of the young group was 29.3 (SD=4.65; range 24-35). The demographic and clinical information for the study groups are presented in Table 2.1. The stimulation parameters for each patient are presented in Table 2.2.

Group	Age	Gender		Years of Education	MMSE	Digit Span	BDI	SAS	UPDRS STN-DBS	
		M	F						ON	OFF
PD patients	61.6 (10.04)	11	2	13.8 (2.65)	28.7 (2.02)	18.2 (3.74)	8.8 (3.63)	15.0 (5.45)	18.1 (6.85)	37.0 (9.87)
Age-Matched Controls	66.0 (12.28)	6	5	16.5 (2.07)	29.3 (0.90)	18.2 (3.16)	3.7 (3.07)	10.5 (5.28)	-	
Young Controls	29.3 (4.65)	8	4	19.4 (2.72)	29.7 (0.89)	20.4 (3.75)	2.3 (2.18)	5.9 (3.18)	-	

Table 2.1 Demographic and clinical information for the patients with Parkinson's disease (PD), healthy age-matched and young controls.
Values for age, years of education, Mini Mental State Examination (MMSE), Digit span, Beck Depression Inventory (BDI), Starkstein Apathy Scale (SAS) and Unified Parkinson's Disease rating scale (UPDRS) are means and standard deviations (in parentheses).

2.2.2 Design

A 3 Groups x 2 (Stimulation condition/assessment session –STN stimulation on versus off for the PD patients or Time 1 versus Time 2 for the control groups) mixed within subject and between groups design was used. Each participant was assessed on the

probabilistic decision-making task at the 500 ms rate two times. Patients were assessed with their stimulators being switched on and with stimulators switched off in the same session. The order of the stimulation condition was counterbalanced across patients. Control participants were also tested twice to control for practice effects. STN stimulation was switched on and off at least 30 minutes before each part of the assessment started. This time was based on previous research investigating the effects of acute STN stimulation on similar decision-making tasks (Cavanagh et al., 2011; Coulthardt et al., 2012; Frank et al., 2007)

In addition, on 3 separate testing days the patients completed the probabilistic decision-making task at three different rates of presentation of the stimuli: fast (200ms), medium (500ms) and slow (1000 ms). The PD patients were also divided into those receiving high and low frequency stimulation. Therefore, the second part of the study involved a 2 Groups (high versus low frequency stimulation) x 2 Stimulation condition (on versus off) x 3 presentation rates (200ms versus 500ms versus 1000ms) mixed within subject and between groups design.

Patient	Left STN stimulation settings			Right STN stimulation settings		
	Voltage in V	Frequency in Hz	Pulse Width/μs	Voltage In V	Frequency in Hz	Pulse Width/μs
DBS 1	4.0	100	60	3.1	100	60
DBS 2	2.3	80	60	3.0	80	60
DBS 3	2.5	160	60	2.3	160	60
DBS 4	3.4	80	60	3.3	80	60
DBS 5	1.6	130	60	1.8	130	60
DBS 6	1.1	160	60	1.1	160	60
DBS 7	2.5	130	60	2.5	130	60
DBS 8	1.65	80	60	2.2	80	60
DBS 9	2.8	80	60	2.8	80	60
DBS 10	1.9	125	60	1.4	125	60
DBS 11	4.2	80	60	3.2	80	60
DBS 12	3.9	80	60	3.5	80	60
DBS 13	4.1	125	60	3.9	125	60
Mean	2.77	108.46	60	2.62	108.46	60

Table 2.2 Stimulation settings for left and right subthalamic nucleus (STN) in 13 patients with Parkinson's disease (PD).
STN= subthalamic nucleus; V=Voltage; Hz=Hertz; μs=microseconds; DBS=deep brain stimulation.

2.2.3 Neuropsychological assessment

The PD patients and both control groups were screened for global cognition, depression and apathy. The Mini Mental State Examination (MMSE, Folstein, Folstein & McHugh, 1975) was administered to assess global cognitive function. The Beck Depression Inventory (BDI, Beck et al., 1961) and the Starkstein Apathy Scale (SAS, Starkstein et al., 1991) were administered to screen for clinical depression and apathy respectively.

To evaluate working memory, the digit span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III, Wechsler, 1997) was used. To assess processing speed and executive function two subtests of the Delis-Kaplan Executive Function Scale (DKEFS, Delis, Kaplan & Kramer, 2001a, b) were used: From the *Stroop Colour-Word interference* subtest the 'colour naming' condition was administered to assess visual processing speed. During this condition participants were requested to name the ink colours (red, blue, green) of rectangles. The 'interference' condition was administered to assess the ability to produce controlled responding (naming colour of ink) and to inhibit automatic responding (reading words). During this condition participants were requested to name the ink colour of colour-words that were printed in incongruent ink colour (e.g. the word red printed in blue ink). From the *Trail Making Test (TMT)* the 'number sequencing' condition was administered to assess motor processing speed. During this condition participants were requested to connect the letters 1 to 16 in ascending order (e.g. 1-2-3-4). The 'number-letter sequencing' condition was administered to assess switching and set-shifting. During this condition participants were requested to connect numbers and letters 1 to P in alternating order (e.g. 1-A-2-B-3-C-4-D). Raw scores on all subtests were converted into age-corrected scaled scores. To extract the executive component, contrast scaled scores between the 'colour-naming' and 'interference' conditions of the Stroop Colour-Word interference task and the 'number sequencing' and 'number-letter sequencing' conditions of the TMT were calculated. The Stroop Colour-Word Interference task and the TMT were chosen over other tests measuring processing speed and executive function due to certain reasons. Firstly, both tests have a number of subtests including control subtests that allow teasing apart slowing due to cognitive demand of switching (TMT) or response conflict/inhibition (Stroop) from mere motor slowness due to bradykinesia of PD. Secondly the STN has been attributed roles in switching (Hikosaka

& Isoda, 2010) and inhibition (Jahanshahi 2013, 2015), so I selected tests that allowed examining the effect of STN stimulation on set shifting (TMS) and inhibition (Stroop).

2.2.4 Probabilistic decision-making task

Participants were asked to complete a computerized expanded judgement task developed in Matlab (Malhotra, Leslie, Ludwig & Bogacz, 2017). During each trial the participants were instructed to predict if a mouse would run left or right. Each trial included multiple presentations of stimuli of a mouse facing either to the left or the right (Figure 2.1A). The participants were told, "The mouse is more likely to look in the direction it will run, but sometimes it looks in the other direction." The stimuli were selected stochastically such that the probability of mouse looking in the "correct" direction was 0.7. The same randomly pre-generated sequences of stimuli were used for all participants. On each trial, the stimuli were presented until the participant indicated a response by pressing the appropriate right or left buttons of a response box with their right or left index finger respectively. After each response, participants were given feedback (correct or incorrect).

The PD patients performed the task in three conditions differing in the rate of presentation of the stimuli, namely the stimuli were presented every 200 ms, 500 ms, or 1000 ms. In the medium and slow rate conditions, stimuli were presented in the centre of the screen (Figure 2.1A), while in the fast rate condition the mice looking left were presented on the left side of the screen, and vice versa, to make the direction easier to identify within a short period (Figure 2.1B). This might have confounded the results, by causing faster reaction times for the 200 ms presentation rate. Similar to the controls, all patients performed the 500 ms rate first, and then the 200 ms and 1000 ms rates were completed in separate sessions.

Each condition started with practice trials. During piloting we found that some participants had a tendency to respond after seeing only one stimulus. To illustrate the benefit of integrating evidence, in the initial 10 practice trials the participant were asked to wait for a "Go" cue on the screen before pressing a button, the different numbers of stimuli were presented on each trial. In the next 20 practice trials (and in the main

experiment) the stimuli were presented sequentially until the participant pressed a response button. Subsequently, participants completed two experimental blocks of 50 trials, separated by a break of at least 30 seconds. At the end of each block, they were provided with the percentage of correct responses. The percentage of accurate trials and the reaction time in milliseconds were recorded. At an information processing level, the task at hand was supposed to measure to what extend participants integrate information across trials in order to inform their decision. This is achieved by giving the participants the option to choose whenever they feel they received enough evidence, rather than providing them with a speed instruction requesting for a choice to be made as quickly as possible.

2.2.5 Statistical analysis

A series of 3 x 2 repeated measures analysis of variance (ANOVA) was completed to test the effects of study group (PD patients, age-matched controls, young controls) and stimulation condition/assessment session (Stimulation on versus off for PD or Time 1 versus Time 2 for controls) on the reaction times and accuracy scores for the 500 ms rate. To assess the effects of presentation rate, stimulation frequency and stimulation condition on the reaction times and accuracy scores, a series of 3 (rate: 200ms, 500ms, 1000ms) x 2 (Stimulation on versus off) x 2 (High versus low frequency) repeated measures ANOVA was performed for the patient group only. Significant interactions were further investigated using one-way ANOVAs or paired t-tests as a post hoc analysis. A series of Pearson product-moment correlation coefficients were computed to assess the relationships between the DKEFS subtests scaled and contrast scaled scores and the reaction times. As mentioned in the introduction chapter Bonferroni correction was not applied. Despite it overcoming the risk of giving too much weight to what may be differences obtained by chance due to multiple comparisons, it may also increase the risk of a type two error that is accepting the null hypothesis when it is in fact false. From a clinical point of view, this would be problematic when considering changes in cognition with DBS of the STN, as it would result in important changes to be overlooked.
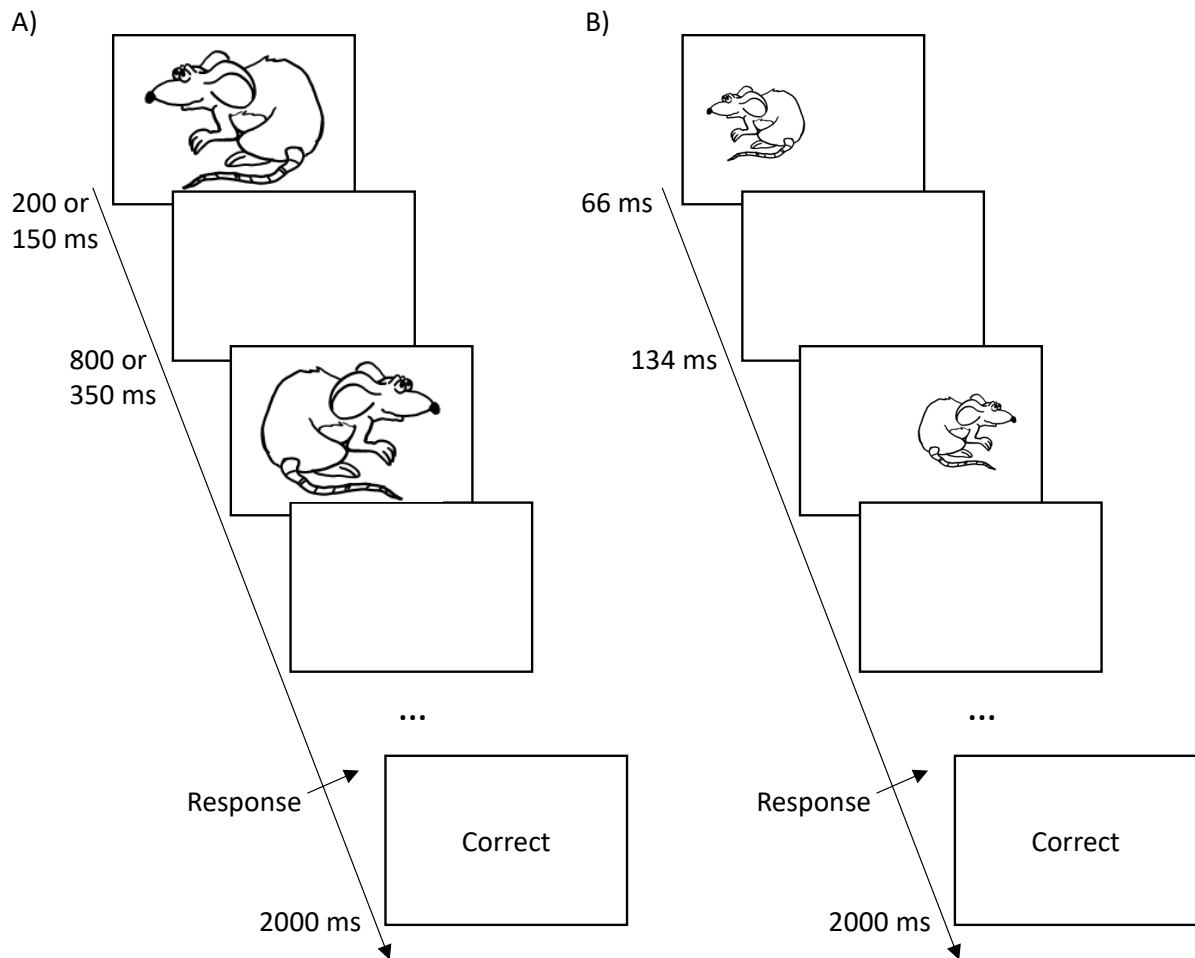
Figure 2.1 Time-line of a single trial. (A) Slow and medium rate conditions. In the slow condition, the stimulus was presented for 200ms followed by 800ms of blank screen, while in the medium condition the stimulus was presented for 150ms and blank screen for 350ms. (B) In the Fast condition, the stimulus was presented for 66 ms followed by a blank screen for 134ms.

2.3 Results

A one-way ANOVA revealed no difference between patients and controls in their MMSE and digit span scores ($p>0.05$). However, they did differ in their years of education ($F_{(2, 33)}=15.52$; $p<0.001$), BDI ($F_{(2, 33)}=15.87$; $p<0.001$), and SAS ($F_{(2, 33)}=11.4$; $p<0.001$). A Tukey's HSD posthoc analysis showed a significant difference in years of education between the patient group and both the age-matched control group ($p=0.029$) as well as the young control group ($p<0.001$) and between the old and young controls ($p=0.029$). Therefore, both control groups had more years of education than the patients. Scores on the BDI were significantly higher for the patient group than both the age-matched control

group (p=0.001) and the young controls (p<0.001), but the control groups did not differ (p>0.05). However, none of the patients had clinical depression. SAS scores were significantly higher for the patients than the young controls (p<0.001) but the patients and the age-matched controls and the two control groups did not differ significantly. To control for any confounding effects, due to significant group differences, years of education, BDI and SAS scores were included as covariates for group comparisons. The BDI and SAS were controlled for, because previous research showed that apathy and depression are associated with cognitive deficits in PD (Starkstein et al., 1992; Tröster et al., 1995).

Considering that depression and apathy are the most common neuropsychiatric symptoms of PD (Aarsland & Kramberger, 2015), it was expected that PD patients would have higher BDI and SAS scores relative to the control participants. It would have been more suitable to compare patients with STN-DBS to a group of unoperated PD control patients, to address such disease-related factors more adequately. However, the restrictions of finding such highly selected patients makes this practically difficult. Apathy and depression in PD involve distinct but overlapping brain networks (Kostić & Filippi, 2011) and whilst apathy might be seen as a core symptom of PD it can appear in the absence of depression (Gallagher & Schrag 2012).

Another factor that is worth mentioning is that the sexes of participants were not well matched across the three study groups, with the PD group consisting of only two females. This could be a confounding factor as male gender is a risk factor for PD-D (Mayeux et al., 1992). However, it was shown that across patients with PD undergoing DBS surgery, 65% are male and only 35% are female (Hariz & Hariz, 2000), and therefore it was practically difficult to recruit an equal number of male and female patients.

A paired t-test revealed a significant difference in the UPDRS scores of the PD patients between the STN stimulation on and off sessions (t(12)=-7.96; p<0.001). Therefore, the UPDRS scores were significantly lower when stimulation was switched on, compared to when stimulation was switched off, indicating significant improvement of the motor symptoms with stimulation.

	PD patients		Age-matched controls		Young controls	
	DBS ON	DBS OFF	Time 1	Time 2	Time 1	Time 2
RT						
200 ms	1933.49 (1232.18)	1715.12 (1036.36)	-	-	-	-
500 ms	2958.52 (1482.54)	3058.72 (1156.25)	2331.61 (1335.07)	2321.21 (1255.47)	3724.57 (2537.26)	3587.52 (2719.92)
1000 ms	3913.77 (2028.08)	3972.55 (2164.79)	-	-	-	-
Accuracy						
200 ms	80.08 (15.02)	77.62 (17.43)	-	-	-	-
500 ms	82.92 (6.46)	82.69 (7.27)	78.55 (9.40)	81.18 (10.22)	84.33 (13.00)	84.17 (12.55)
1000 ms	76.23 (15.76)	75.46 (15.95)	-	-	-	-

Table 2.3 Comparison between Parkinson's disease (PD) patients with subthalamic nucleus deep brain stimulation (STN-DBS) and age-matched and young control participants.
Numbers represent means values standard deviations (in parentheses). Reaction time in milliseconds and Accuracy is presented as percentage correct. PD=Parkinson's disease; RT=Reaction Time.

3.3.1 Effects of presentation rate, stimulation, time and study group

Means and standard deviations of the reaction time and accuracy scores for the three study groups at both assessment sessions are presented in Table 2.3, A repeated-measures ANCOVA comparing the reaction times of PD patients and healthy controls at both assessment sessions, and controlling for years of education, BDI and SAS scores, revealed no significant main effect of group ($F_{(2, 30)}=1.09$; $p=0.857$) or stimulation condition/assessment session ($F_{(1, 30)}=0.28$; $p=0.598$). There was also no significant interaction between group and the stimulation condition/assessment session ($F_{(2, 30)}=0.64$; $p=0.532$). Therefore, during both sessions PD patients did not differ in their reaction times from either of the control groups (Figure 2.2A). The reason for this could be that participants could make a movement whenever they wanted to rather than as fast as possible.

For the PD patients only, a repeated measures ANOVA revealed a significant main effect presentation rate ($F_{(2, 24)}= 12.96$; $p<0.001$). A series of paired t-tests revealed that the patients' reaction times were significantly faster for the 200 ms presentation rate compared to both the 500 ms (ON: $t_{(12)}=-4.1$; $p=0.001$; OFF: $t_{(12)}= -4.64$; $p=0.001$) and 1000 ms presentation rates (ON: $t_{(12)}=-4.28$; $p=0.001$; OFF: $t_{(12)}=-4.62$; $p=0.001$). The

main effect of stimulation condition ($F_{(1, 12)}=0.01$; $p=0.933$) and the interaction between stimulation condition and presentation rate ($F_{(2, 24)}=0.46$; $p=0.636$) were not significant. Therefore, for all three presentation rates, acute STN stimulation did not have an effect on the PD patients' reaction times (Figure 2.3A).

A)

B)
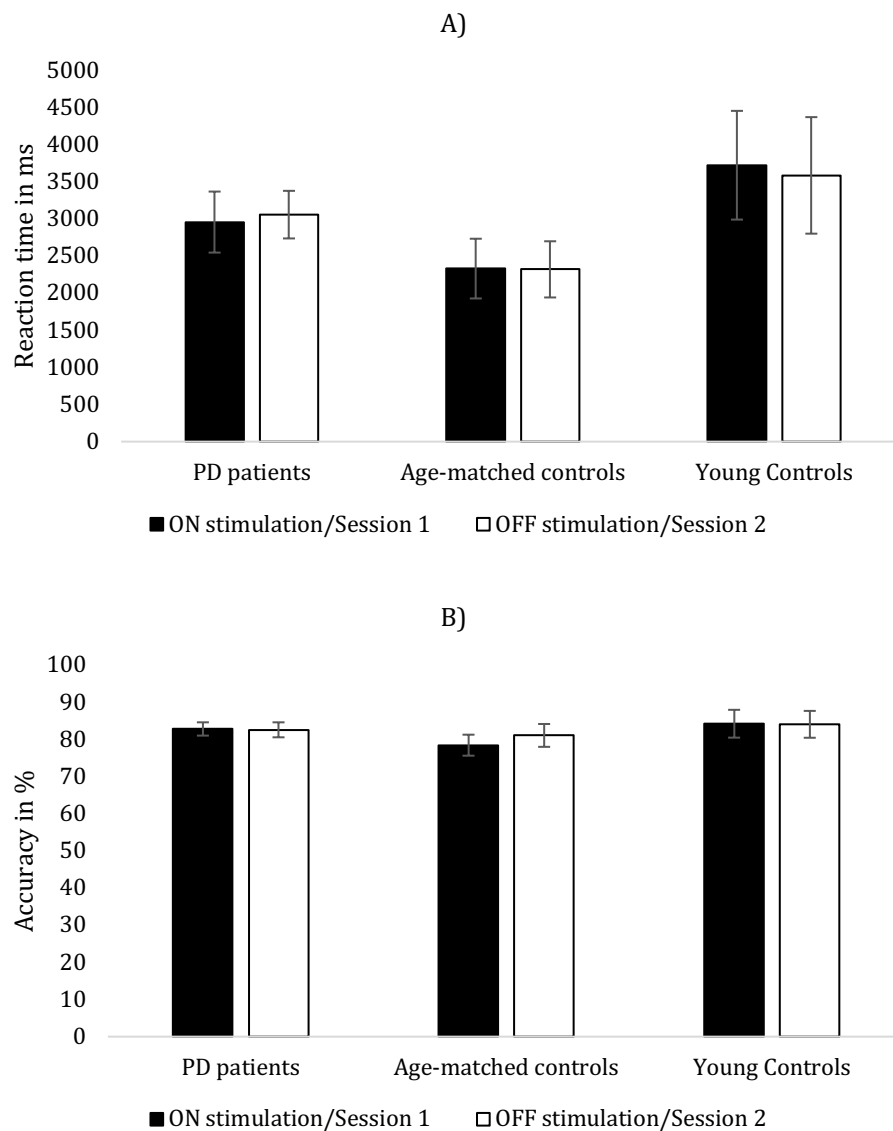
Figure 2.2 The (A) mean reaction time and (B) mean accuracy for the three study groups at the two assessments.
Error bars represent standard errors.

A repeated measures ANCOVA comparing the accuracy scores of PD patients and healthy controls at the two assessments, and controlling for years of education, BDI and SAS

scores revealed no significant main effect of group ($F_{2, 30}$=0.92; p=0.409) or stimulation condition/assessment session ($F_{(1, 30)}$=0.39; p=0.538). There was also no significant interaction between group and stimulation condition/assessment session ($F_{(2, 30)}$=0.61; p=0.549). Therefore, during both sessions PD patients did not differ in their accuracy scores from the two control groups (Figure 2.2B).

A)

B)
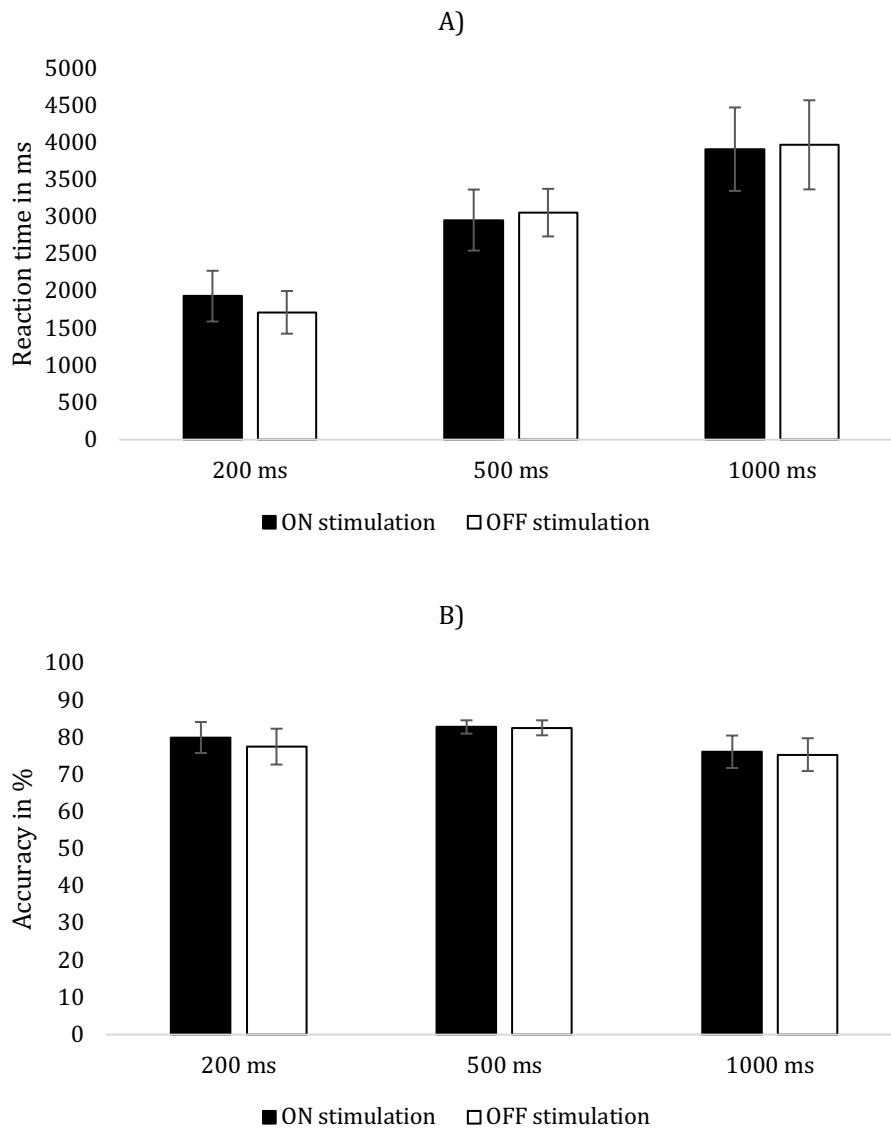
Figure 2.3 The (A) mean reaction time and (B) mean accuracy for the patients with Parkinson's disease (PD) with subthalamic nucleus (STN) stimulation on or off, for the three presentation rates of 200, 500 or 1000 ms.
Error bars represent standard errors.

For the PD patients only, a repeated measures ANOVA revealed no significant main effect of stimulation condition ($F_{(1, 12)}$=0.42; p=0.467) or presentation rate ($F_{(2, 24)}$=2.24;

p=0.129) and no significant interaction between stimulation condition and presentation rate (F(2, 24)=0.17; p=0.846). Therefore, for all three presentation rates, acute STN stimulation did not have an effect on the PD patients' accuracy scores (Figure 2.3B).

2.3.2 Differences between patients with high and low frequency stimulation

Means and standard deviations of the reaction time and accuracy scores for the high and low frequency STN stimulation groups for the on and off stimulation sessions are presented in Table 2.4. The results of a repeated-measures ANOVA comparing the reaction times of the two stimulation frequency groups for the three presentation rates at the on and off STN stimulation conditions indicated no significant main effect of stimulation frequency (F(1, 11)=0.21; p=0.658). Also the interactions between stimulation frequency and stimulation condition (F(1, 11)=0.08; p=0.788), between stimulation frequency and presentation rate (F(2, 11)=0.83; p=0.449) and between stimulation frequency, stimulation condition and presentation rate (F(2, 22)= 1.26; p=0.304) were not significant. Therefore, for all three presentation rates, patients with high and low frequency STN stimulation did not differ in their reaction times (see Figure 2.4A).

	High Frequency DBS		Low Frequency DBS	
	DBS ON	DBS OFF	DBS ON	DBS OFF
RT				
200 ms	1483.57	1533.21	2319.14	1871.04
	(555.33)	(514.65)	(1550.35)	(1365.98)
500 ms	2763.46	2539.91	3125.72	3503.41
	(772.41)	(813.52)	(1956.53)	(1273.75)
1000 ms	4162.09	4061.58	3700.93	3896.23
	(1493.42)	(2124.16)	(2500.62)	(2365.98)
Accuracy				
200 ms	84.67	82.17	76.14	73.71
	(6.35)	(9.81)	(19.46)	(22.11)
500 ms	86.67	82.33	79.71	83.00
	(3.72)	(6.89)	(6.78)	(8.12)
1000 ms	80.17	77.17	72.86	74.00
	(12.69)	(12.77)	(18.32)	(19.17)

Table 2.4 Comparison of reaction times and accuracy for Parkinson' disease (PD) patients with high and low frequency subthalamic nucleus (STN) stimulation for the 200, 500, 1000 ms presentation rates. Values represent means and standard deviations (in parentheses). Reaction time is in milliseconds and Accuracy is presented as percentage. PD=Parkinson's disease; RT=Reaction Time.

The results of a repeated-measures ANOVA comparing the accuracy scores of the two stimulation frequency groups for the three presentations rate for the on and off STN stimulation sessions indicated no significant main effect of stimulation frequency ($F_{(1, 11)}$=0.9; p=0.364). The interactions between stimulation frequency and stimulation condition ($F_{(1, 11)}$=1.24; p=0.289), between stimulation frequency and presentation rate ($F_{(2, 22)}$=0.31; p=0.74) and between stimulation frequency, stimulation condition and presentation rate ($F_{(2, 22)}$=0.42; p=0.662) were not significant. Therefore, for all three presentation rates, patients with high and low frequency STN stimulation did not differ in their accuracy scores (see Figure 2.4B).

A)

B)
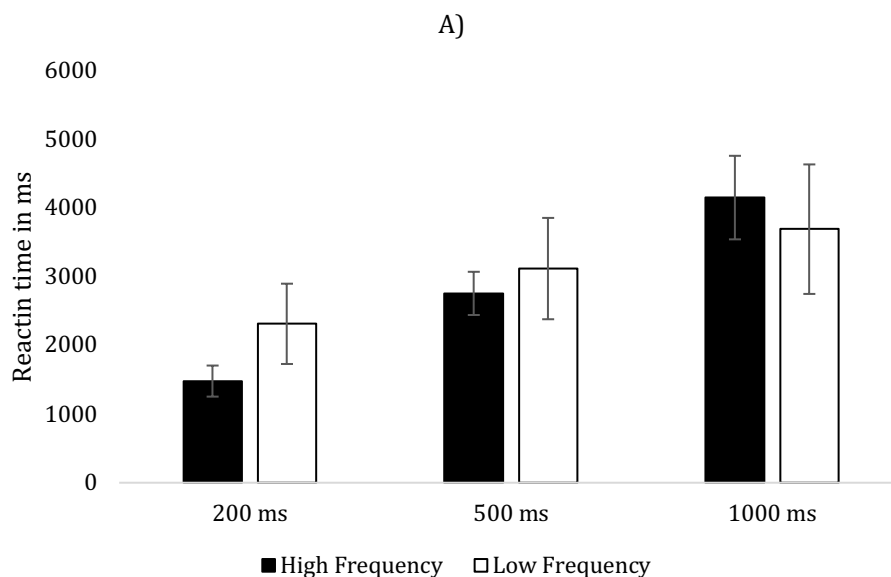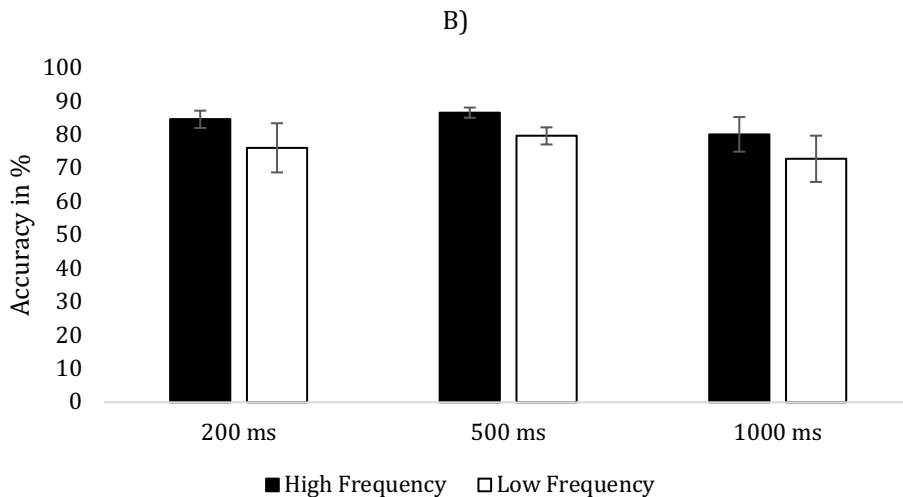
Figure 2.4 The (A) mean reaction time and (B) mean accuracy for the patients with Parkinson's disease (PD) with high and low frequency subthalamic nucleus (STN) stimulation for the three presentation rates of 200, 500 and 1000 ms.
Error bars represent standard errors.

2.3.3 Correlational analysis

The means and standard deviations of the scaled scores on DKEFS subtests for the three study groups are presented in table 2.5. A series of Pearson product-moment correlation coefficients were computed to assess the relationships between the PD patients' reaction times and scaled scores on the DKEFS subtests. When STN stimulation was switched on there were borderline significant positive correlations between reaction time and the contrast scaled score of the TMT ($r(11)=0.53$; $p=0.06$). Increasing reaction time was correlated with increasing TMT contrast scaled scores. When STN stimulation was switched off there were no significant correlations between the reaction time and any of the other measures (all $p>0.05$). For the control groups none of the correlations were significant.

A repeated-measures ANCOVA comparing the different outcome measures of the Stroop colour-word interference task and the TMT for PD patients and healthy controls at both assessment sessions, and controlling for years of education, BDI and SAS scores, revealed a significant effect for the TMT A ($F(2, 30)= 3.82$; $p=0.03$) and the contrast scaled score of the TMT ($F(2, 30)= 6.52$; $p=0.004$), when patients were off stimulation but not when they were on stimulation. Therefore, when STN stimulation was switched off, patients

performed significantly worse on the TMT A and the executive component of the TMT relative to both control groups.

	PD patients		Age-matched controls		Young controls	
	DBS ON	DBS OFF	Time 1	Time 2	Time 1	Time 2
Stroop						
Colour Naming	8.62 (4.13)	7.85 (3.36)	9.91 (2.55)	10.91 (2.70)	9.08 (2.53)	9.75 (1.86)
Interference	9.46 (4.04)	8.23 (4.17)	11.73 (2.41)	12.73 (2.61)	10.17 (3.27)	12.42 (2.47)
Contrast	10.85 (1.86)	10.38 (3.50)	11.82 (1.54)	11.82 (2.36)	11.08 (2.43)	12.67 (2.02)
TMT						
Number	10.00 (3.65)	8.15 (4.28)	11.73 (2.37)	13.27 (2.41)	12.17 (1.47)	12.83 (2.44)
Number-Letter	10.15 (4.01)	9.46 (4.61)	10.91 (2.81)	13.09 (2.17)	11.08 (1.83)	12.00 (2.09)
Contrast	10.23 (2.09)	11.31 (2.06)	9.18 (2.32)	9.82 (0.98)	9.08 (1.38)	9.17 (1.27)

Table 2.5 Scaled scores for the Stroop and Trail Making Test (TMT) for the patients with Parkinson's disease (PD) with deep brain stimulation (DBS) on or off and healthy age-matched and young controls for sessions 1 and 2 (Time1, Time 2).
Values represent mean scaled scores and Standard Deviations in parentheses.

2.4 Discussion

The aim of this Study was to investigate the effects of acute STN stimulation on probabilistic decision-making. For this purpose, 13 PD patients who had STN-DBS for at least 6 months before recruitment, 11 healthy age-matched control participants and 12 healthy younger control participants were assessed on a probabilistic decision-making task. For the 500 ms presentation rate, all participants were assessed two times, the PD patients were assessed once with their stimulation on and another time with their stimulation off, with the order of the stimulation conditions counterbalanced across patients. The control participants were also assessed twice in order to control for practice effects. In addition, in separate sessions, the patients also performed the task at slow and fast rates of 1000 ms and 200 ms respectively, with STN-DBS on and off. The probabilistic decision-making task used was designed to assess decision-making that does not depend on previously learned stimulus-action-reward associations and does not induce conflict. Previous studies implemented tasks consisting of an initial learning phase followed by

the decision-making phase (Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007), whereas the task used in this study required participants to make decisions based on continuously changing information. Based on theories that the STN is involved in modulation of decision thresholds (Bogacz & Gurney, 2007; Frank, 2006), the following hypotheses were formulated: (1) PD patients with STN stimulation on would make more impulsive decisions compared to when stimulation is switched off and compared to healthy control participants; (2) when STN stimulation is switched on PD patients who receive high frequency stimulation would make more impulsive decisions, compared to patients who receive low frequency stimulation.

STN stimulation did not have an effect on the PD patients' reaction times or accuracy for any of the three presentation rates of the decision-making task. These findings are not consistent with the predictions made by the decision-making models of the basal ganglia (Bogacz & Gurney, 2007; Frank, 2006; Mink, 1996). These models suggested that tonic inhibition from the basal ganglia output nuclei puts a brake on cortical and brain stem activity, enabling enough evidence to be accumulated and integrated before an alternative is chosen (Mink, 1996). Moreover, it has been suggested that the STN would be involved in conflict calculation and decision threshold modulation (Bogacz & Gurney, 2007; Frank, 2006). The findings from this study do not support the prediction that the STN is involved in these processes; as patients in the stimulation on or off conditions did not differ from the two healthy control groups in their reaction times. Thus manipulating the output from the basal ganglia with STN stimulation did not influence RTs or accuracy during this decision making task which did not involve stimulus-reward associations or conflict.

Previous research on the effects of acute STN stimulation on decision-making reached contradictory conclusions. While some authors found deficits with STN stimulation on (Antoniades et al., 2014; Canvanagh et al., 2011; Coulthard et al., 2012; Evens et al., 2015; Green et al., 2013; Florin et al., 2013; Frank et al., 2007; Oyama et al., 2011; Pote et al., 2016; Rogers et al., 2011; Seinstra et al., 2016; Seymour et al., 2016; Zaehle et al., 2017), others reported that decision-making remained stable or even improved with STN stimulation on relative to when the DBS was off (Boller et al., 2014; Brandt et al., 2015;

Castrioto et al., 2015; Djamshidian et al., 2013; Evens et al., 2015; Fumagalli et al., 2015; Seinstra et al., 2016; Torta et al., 2012; Seymour et al., 2016; Zaehle et al., 2017). These contradictory findings may reflect differences in methodology and the tasks that were used. Frank and colleagues (2007) were interested in the effects of STN stimulation on decision-making between alternatives that were previously associated with different reward probabilities. Participants were then presented with either high or low conflict stimuli pairs. Results suggested that STN stimulation impaired decision-making in high conflict situations. This was reflected in the PD patients' failure to slow down in high conflict trials when they were tested on STN stimulation, unlike when their stimulation was off or the unoperated PD and healthy controls (Frank et al., 2007). This effect of stimulation was only present in win-win trials when the choice was between two stimuli both of which were associated with high reward probabilities. Similar findings were reported with the same task by Cavanagh et al. (2011), who additionally recorded scalp EGG and showed that STN stimulation reversed the normal increase in theta band activity over the medial prefrontal cortex which is usually associated with raising the decision threshold for high conflict trials, thus suggesting that STN stimulation interferes with the normal ability of the STN to react to decision conflict by modulating the decision threshold (Cavanagh et al., 2011). These findings support the idea that the STN is involved in conflict computation and decision threshold regulation when making decisions associated with high reward value. Another study investigated STN stimulation effects on learning, memory acquisition and information integration in a probabilistic decision-making task (Coulthard et al., 2012). In the task used in this study, stimuli associated with certain actions were presented consecutively, and participants had to update probabilistic information over time. The results indicated that accuracy decreased and reaction times were faster for PD patients when STN stimulation was switched on compared to when it was switched off. This suggests that the STN is important for updating probabilistic information and integrating novel information to regulate the decision threshold.

The present results are not consistent with the above findings. This might be related to differences in properties of the present task compared to the tasks that were used in previous research. Probabilistic decision-making tasks in other studies (Frank et al.,

2007; Cavanagh et al., 2011; Coulthard et al., 2012) were based on previously learned stimulus-action-reward associations, where each stimulus was associated with a certain probability of reward. Our task required participants to continuously update probabilistic information over time and for each trial individually. Therefore, it may be argued that the involvement of the STN in computing decision conflict and threshold modulation is specific to decisions that are associated with a certain reward probability. This idea is further supported by the results of a study which investigated the effects of acute STN stimulation for the PD patients' performance on the beads tasks (Djamshidian et al., 2013). During the beads task participants are requested to guess from which of two cups beads are drawn. One of the cups contains more green and fewer blue beads and the other cup contains more blue and fewer green beads. After each draw of a bead, the participants are asked whether they want to guess the cup or whether they would like to see another bead. If they decide to guess the cup they are informed whether the choice was correct or not. Therefore, similar to the task used in the present study, the beads task has no learning phase and does not involve reward-based decision-making. The results of Djamshidian and colleagues (2013) also indicated that acute STN stimulation did not influence the patients' decision-making behaviour. More recently, empirical evidence suggested that acute STN stimulation has an effect on responsiveness to high reward value (Kojovic et al., 2016). Kojovic and colleagues (2016) used a simple reaction time task that consisted of rewarded and unrewarded trials and reported that acute STN stimulation resulted in increased responsivity to higher reward value. Behaviourally this was reflected by significantly faster movement initiation for high reward values with STN stimulation on relative to when stimulation was switched off. These findings suggested that the STN is involved in reward value estimation. Furthermore, research investigating the local field potentials of STN neurons in PD patients during an effort based decision-task reported that STN activity was related to subjective cost of effort and subjective reward value, but not decision conflict (Zénon et al., 2016). From these results it can be indicated that the STN is involved in computing cost-benefit of decisions rather than decision conflict.

Other previous studies which have reported STN-DBS induced deficits in decision-making have also involved responding under time pressure of speed instructions. For

example, Pote et al (2016) found that on the moving dots perceptual decision-making task, PD patients had significantly faster reaction times and made significantly more errors when acting under speed instructions. Application of the drift diffusion model to the data showed lowering of the decision threshold with STN stimulation on when acting under the time pressure of speed instructions. Thus, time pressure, similar to conflict and reward value seem to be relevant to the effects produced by STN stimulation on decision-making tasks.

The correlational results suggested that the reaction time for the 1000ms presentation rate of the decision-making task was positively associated with the switching and set shifting component of the TMT. Therefore, it could be suggested that this version of the task has a larger executive component relative to the task with the 200 and 500ms presentation rate. Furthermore, the 1000 ms presentation rate required patients to stay attentive and store information in working memory over longer periods of time, and therefore might involve higher levels of cognitive control compared to the 200ms and 500 ms presentation rates. If this was the case it would have been expected that STN stimulation would have induced deficits in task performance as a function of presentation rate. Previous research investigating the effects of acute STN stimulation on inhibitory control and decision-making reported that these were dependent on the extent of cognitive control, with tasks involving more cognitive control becoming impaired with STN stimulation (e.g. Green et al., 2013; Hershey et al., 2004; Obeso et al., 2013; Williams et al., 2016), whereas tasks involving less cognitive control remaining stable or becoming improved (e.g. Djamshidian et al., 2013; Hershey et al., 2004; Williams et al, 2016). This was not the case in the present study. However, considering that on each trial of the current task the target frequency was 70% and that the average accuracy score of the participants was very high, it can be suggested that the cognitive load and control involved in this task were generally not very demanding.

In conclusion, our data suggest that stimulation of the STN did not impair decision making in PD patients, under these restricted experimental conditions. This is not consistent with some of the current decision-making models of the basal ganglia and previous research. These results may be related to the fact that decision-making was not based on previously

learned stimulus-action-reward associations, as it was the case for previous studies reporting that acute STN stimulation induced impulsive decision-making in high conflict situations. The present task did not involve any explicit conflict, reward or time pressure in the decision-making process and therefore the results suggest that the STN is not involved in choice in the absence of conflict, reward or time pressure, factors that may be necessary to engage the STN. This is an important finding which necessitates revision of our concepts about the role of the STN in decision-making to be specific to situations involving conflict, reward or time pressure. This may explain why impulsivity in daily life is not pervasive among PD patients who have had STN-DBS and why only a proportion of patients develop impulse control disorders following surgery under specific situations in the presence of specific triggers.

Chapter 3. Dissociable effects of subthalamic nucleus deep brain stimulation surgery and acute stimulation on verbal fluency in Parkinson's disease

3.1 Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder that causes motor symptoms such as bradykinesia, rigidity, resting tremor and postural instability (Lees, Hardy & Revesz, 2009). However, attention is increasingly paid to the non-motor symptoms of PD, such as depression, cognitive deficits, sleep disturbances and autonomic symptoms (Gallagher, Lees & Schrag, 2010). This increased focus is because consideration of the non-motor symptoms is relevant to the management of the disorder, given that evidence suggests that non-motor symptoms such as depression and cognitive dysfunction are the major predictors of quality of life in PD (Schrag, et al., 2000).

Treatment of PD targets the motor symptoms (Rao et al., 2006; Rascol et al., 2002) and initially involves dopamine-replacement medication, including levodopa and dopamine agonists. When the patients develop long-term side-effects such as on-off fluctuations and dyskinesias they are treated surgically with deep brain stimulation (DBS). DBS of the subthalamic nucleus (STN) is the most commonly used surgical approach for treating PD and leads to significant improvements of the motor symptoms (Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2005; Weaver et al., 2012; Williams et al., 2010). However, three meta-analyses suggested adverse effects of STN-DBS for cognition, with surgery particularly affecting verbal fluency, psychomotor speed, memory, attention, and executive function (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). The most consistent post-operative decline was found for verbal fluency (e.g. Smeding et al., 2006; Witt et al., 2013). This is also supported by the results of the meta-analysis conducted and reported in the Introduction of this thesis.

3.1.1 Verbal fluency and Parkinson's disease

Successful verbal fluency performance requires search of associative networks and information retrieval from memory as well as implementation of several executive functions. Table 3.1 lists the various executive functions involved in verbal fluency. Verbal fluency tasks are used to assess the ability to retrieve information meeting specific search criteria such as words beginning with a particular letter or belonging to a specific semantic category (Lezak, Howieson & Loring, 2004).

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Executive processes involved in verbal fluency
Allocation and sustaining attention
Internal response generation
Selective inhibition of inappropriate words
Switching and set shifting
Self-monitoring of output

Table 3.1 Executive processes involved in verbal fluency.

Lesion studies have established that verbal fluency impairments are seen in patients with frontal lobe (Coslett, Bowers, Verfaellie & Heilman, 1991; Crowe, 1992; Miller, 1995) and temporal lobe lesions (Corcoran & Upton, 1993; Martin, Loring, Meador & Lee, 1990), with letter fluency being more sensitive to frontal lesions (Coslett et al., 1991; Milner, 1964) and category fluency being more sensitive to temporal lesions (Newcombe, 1969). Imaging studies using functional magnetic resonance imaging (fMRI) found associations between letter fluency performance and activation of frontal regions, such as the premotor cortex, dorsolateral prefrontal cortex and Broca's area, and temporal areas, such as the anterior, middle and posterior regions (Cuenod et al., 1995). Additionally, studies implementing positron emission tomography (PET) identified activity in brain areas such as the left dorsolateral prefrontal gyrus and parahippocampal gyrus during performance of a verbal fluency task relative to a word repetition task (Frith, Friston, Liddle & Frackowiak, 1991) and the left dorsolateral, ventrolateral and medial regions of the frontal lobes and the left inferior temporal lobe (Klein, Milner, Zatorre, Meyer & Evans, 1995). Mummery, Patterson, Hodges and Wise (1996) investigated differential brain activation for category and letter fluency using PET. The results indicated that during letter fluency there was increased activity in the precentral gyrus and the middle frontal gyrus relative to activity during the category fluency task, whereas for the reverse contrast they reported increased activity in the left inferior and anterior temporal regions. These findings further support the multifactorial nature of verbal fluency.

Research investigating verbal fluency in PD suggested that non-demented patients are impaired on both letter (Azuma et al., 1997; Flowers et al., 1995; Obeso et al., 2012) and category fluency (e.g. Auriacombe et al., 1993; Cooper et al., 1991; Obeso et al., 2012). According to a meta-analysis impairments of category fluency are greater than those of

letter fluency (Henry & Crawford, 2004). In addition, this verbal fluency deficit is associated with a greater risk of dementia in PD (Jacobs et al., 1995), and is one of the main characteristics of PD dementia (PD-D) and is more severe than impairments seen in patients with Alzheimer's type dementia (Stern et al., 1993; Fenelon, Mahieux, Huon & Ziegler., 2000).

3.1.2 Verbal fluency and subthalamic nucleus deep brain stimulation

Research into the cognitive effects of STN-DBS indicated that patients with PD produce significantly fewer words following STN-DBS surgery compared to their pre-operative performance (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). More recently, the number of studies comparing patients with STN-DBS to control groups consisting of PD patients, who were either unoperated or had DBS to another target has increased (reviewed in the general introduction). The majority of these controlled trials suggested that verbal fluency deficits following STN-DBS surgery were still present when compared to matched PD control groups (e.g. Smeding et al., 2006; Witt et al., 2013). Therefore, the verbal fluency deficits reported in PD patients with STN-DBS cannot be simply explained by disease progression but seem to be associated with the STN-DBS.

Research described above investigated the cognitive effects of STN-DBS as a whole procedure rather than differentiating between 'surgery' and 'acute stimulation' effects. There have been a number of studies that investigated the acute effects of STN stimulation on verbal fluency. Most of these indicated that acute stimulation did not have an effect on either category or letter fluency (Jahanshahi et al., 2000; Morrison et al., 2004; Okun et al., 2009; Okun et al., 2012; Pillon et al., 2000; Tremblay et al., 2015; Witt et al., 2004). Only two studies reported that STN stimulation induced changes in letter fluency performance (Schroeder et al., 2004; Wojtecki et al., 2006). Schroeder and colleagues (2004) reported a decline of letter fluency with STN stimulation compared to when stimulation was switched off. Additionally, they reported reduced activation in the right orbitofrontal cortex and a left fronto-temporal network, which was associated with impaired verbal fluency performance. By contrast, Wojtecki and colleagues (2006) reported that patients produced significantly fewer words on a letter fluency task with high frequency 130 Hz STN stimulation compared to when they were on low frequency

10 Hz stimulation, but that there was no significant difference in performance between the on and off stimulation conditions. These findings suggest that different frequencies may induce differences in letter fluency performance. Okun and colleagues (2009, 2012) compared 'surgery' effects by comparing performance on phonemic and semantic verbal fluency before and after STN-DBS and also examined 'acute stimulation' effects using DBS on versus off methodology. They concluded that verbal fluency deficits after STN-DBS are contributable to surgery rather than acute stimulation, as patients performed worse after STN-DBS surgery compared to the pre-operative assessment, however acute stimulation did not have an effect on verbal fluency performance.

Thus, the results are inconsistent across studies and the exact nature of these STN-DBS induced verbal fluency deficits remains unclear. Troyer, Moscovitch and Wincour (1997) suggested that verbal fluency has two components reflecting different cognitive processes. The first process is clustering which refers to the production of words belonging to the same semantic or phonemic subcategory. The second process of verbal fluency is switching which refers to the shifting between phonemic or semantic subcategories. Both these subcomponents correlate with the total number of words. Therefore, impairment in the production of either switches or clusters can result in impaired verbal fluency performance. According to Troyer and colleagues (1997) switching is related to frontal-lobe function, whereas clustering depends largely on temporal lobe functioning. To assess this hypothesis, they implemented a divided attention approach, where the primary tasks were letter and category fluency and the secondary 'distraction task' was finger-tapping, thought to rely on functions of the prefrontal cortex. The results indicated that under divided attention conditions young and older adults produced less words and switches on the letter fluency task only. The idea that switching relies largely on frontal lobe networks and clustering on temporal networks was further supported by research that investigated these components in patients with focal frontal or temporal lobe lesions (Troyer, Moscovitch, Wincour, Alexander & Stuss, 1998a). The findings indicated that semantic clustering was only impaired in temporal lobe patients and phonemic switching was only impaired in frontal lobe patients. Similar conclusions were drawn by research showing differential impairments in Alzheimer's type and PD dementia, with Alzheimer's type dementia

inducing impairments in clustering and PD dementia inducing switching impairments (Troyer, Moscovitch, Wincour, Leach & Freedman, 1998b). Considering that Alzheimer's type dementia largely involves degeneration of the temporal areas and PD dementia largely affects frontal regions, this further supports the hypothesis that switching recruits frontal and clustering recruits temporal networks.

Only a few studies investigated the effects of STN-DBS on these two components of verbal fluency. De Gaspari and colleagues (2006) assessed a total of 26 patients with PD who underwent STN-DBS surgery on a letter and a category fluency task before and 6 to 12 months after surgery with stimulation being switched on. They reported a significant decline in switching on both verbal fluency tasks after STN-DBS surgery compared to the pre-operative assessment. Similar results were described by Saint-Cyr, Trepanier, Kumar, Lozano & Lang (2000), who followed up 11 patients over 3 to 12 months after surgery, indicating a decline in switching compared to the pre-operative performance. More recently Vonberg, Ehlen, Fromm, Kuhn & Klostermann (2016) investigated the effects of *acute* STN stimulation on switching and clustering. The findings of their study suggested a positive effect of STN stimulation on switching, but there was no effect on the number of clusters that patients produced. The patients produced more switches when STN stimulation was on compared to when stimulation was off. Taken together, the findings of these three studies suggest that STN-DBS surgery might produce a switching impairment, whereas acute stimulation may lead to a mild improvement of switching. Considering that switching is supposed to reflect a function related to frontal regions, the latter finding is unexpected considering that the majority of research reported detrimental effects of acute STN stimulation for tasks that require set shifting (e.g. Jahanshahi et al., 2000a; Schroeder et al., 2002). It is worth mentioning that neither of the studies described above considered phonemic and semantic switches and clusters individually and analysed them together. Also, Vonberg and colleagues (2016) did not analyse data for the letter and category fluency tasks separately, and therefore it cannot be determined whether these changes were specific to one or both fluency tasks. Further differentiation between phonemic and semantic switches and clusters is necessary in order to understand the exact mechanisms of impairment. In addition, it is important to

differentiate between surgical and stimulation effects, by assessing patients before and after surgery as well as ON and OFF stimulation.

The aim of the present study was to investigate the differential effects of STN-DBS surgery and acute STN stimulation on different verbal fluency tasks: phonemic, semantic and switching category. Furthermore, this investigation aimed to clarify what aspects of verbal fluency become impaired, by examining switching and clustering as two components reflecting function in frontal and temporal networks respectively. The following hypotheses were formulated:

1. The total number of words on all three verbal fluency tasks would be lower after surgery compared to before surgery.
2. The total number of semantic and phonemic switches would be lower for the category and letter fluency respectively, after surgery compared to before surgery.
3. The average phonemic and semantic cluster size on the category and letter fluency tasks would remain unchanged after surgery compared to before surgery.
4. Acute STN stimulation would have no effect on verbal fluency performance and the total number of words on all three verbal fluency tasks would remain unchanged with STN stimulation on compared to when stimulation was switched off.
5. The total number of semantic and phonemic switches and the average semantic and phonemic cluster size would remain unchanged with STN stimulation on compared to when stimulation was switched off.

3.2 Methods

3.2.1 Participants and Design
All participants had a clinical diagnosis of Parkinson's disease according to the UK brain bank criteria (Hughes, Daniel, Kilford, & Lees, 1992). Responsiveness to levodopa was assessed and all patients were rated on the Unified Parkinson's disease Rating Scale (UPDRS: Fahn & Elton, 1987) before and after surgery. All operated patients had quadripolar stimulating electrodes (Medtronic, Minn., USA) chronically implanted into

the STN bilaterally, according to procedures described previously (Foltynie et al., 2011). Post-surgical MRI confirmed correct placement of at least one of the contacts in or near the sensorimotor section of the STN. A clinical benefit of STN-DBS observed on the UPDRS in every case (see below), confirmed correct positioning of the electrodes.

3.2.1.1 Sample and design to examine the effects of STN-DBS stimulation and surgery

Nineteen PD patients (12 males) were recruited. All patients were assessed prior and after STN-DBS surgery. Three patients were left-handed, the remaining were right-handed. The mean age was 57.42 (SD=7.5; range 41-69). Prior to surgery all patients had severe disabling PD as shown by a mean UPDRS score of 49.53 (SD=17.91; range 16-86) off medication. All patients showed levodopa responsiveness which was reflected in an average UPDRS score of 10.58 (SD=8.14; range 1-31) on medication. Table 3.2 shows the demographics and clinical features of the sample. All patients had a significant improvement of their motor symptoms with surgery.

Age	Gender		Handedness		Years of education	Disease duration	MMSE	Pre-operative UPDRS		Post-operative UPDRS	
	M	F	R	L				ON Med.	OFF Med.	ON Med.	OFF Med.
57.42 (7.5)	12	7	16	3	13.87 (3.49)	13.47 (3.91)	29.05 (1.08)	10.58 (8.14)	49.53 (17.91)	11.79 (9.29)	21 (13.53)

Table 3.2 Demographic and clinical information for the patients with Parkinson' disease.
Values for age, years of education, disease duration, mini mental status examination (MMSE), and unified Parkinson's disease rating scale (UPDRS) are means and standard deviations in parentheses. Post-operative UPDRS scores assessed on stimulation.

A within subject design was used. All patients were assessed on the verbal fluency tasks twice. Initially within one month prior to surgery on medication and a second time 12 to 24 months after surgery on medication and stimulation.

3.2.1.2 Sample and design to examine the effects of acute STN stimulation

Twenty-two patients (15 males) who had bilateral STN-DBS for at least six months and nine unoperated control PD patients (5 males) were recruited. Four patients in the operated group were left-handed. The mean age was 60.41 (SD=6.01; range 46-70) in the operated group and 59.33 (SD=6.12; range 53-69) in the control group. Patients were

assessed on medication. Table 3.3 shows the demographic and clinical features of both groups. For this study depression and apathy scales were not included as baseline measures as both groups consisted of PD patients, making it less likely that these factors would differ significantly and confound the results.

	STN-DBS	PD Control
Age	60.41 (6.01)	59.33 (6.12)
Gender		
Male	15	5
Female	7	4
Handedness		
Right	18	9
Left	4	0
Years of education	14.27 (2.83)	16.11 (4.43)
Disease duration years	13.27 (4.91)	10.11 (5.02)
MMSE	29.32 (0.72)	-
UPDRS		
ON-DBS/Med.	12.8 (8.53)	18.71(12.48)
OFF-DBS	25.2 (13.07)	-

Table 3.3 Demographic and clinical information for the patients with Parkinson's disease (PD), with and without subthalamic nucleus deep brain stimulation (STN-DBS).
Values for age, years of education, disease duration, and unified Parkinson's disease rating scale (UPDRS) are means and standard deviations in parentheses.

A 2 (study group) x 2 (assessment) mixed between groups-within subject design was used. All patients were assessed on the verbal fluency tasks twice. The operated group was assessed one time with their stimulation switched on and a second time with the stimulation switched off. The order of the stimulation condition, on versus off, was counterbalanced across patients. STN stimulation was switched on or off at least 30 minutes before each part of the assessment. This time was based on previous research investigating the effects of acute STN stimulation on several cognitive functions (e.g. Jahanshahi et al., 2000a). The control group were also tested twice to control for practice effects. Table 3.4 shows the stimulation settings for the operated patients.

Patient	Left STN stimulation settings			Right STN stimulation settings		
	Voltage in V	Frequency in Hz	Pulse Width/µs	Voltage in V	Frequency in Hz	Pulse Width/µs
DBS 1	3.3	130	60	3.3	130	60
DBS 2	3.7	130	60	3.8	130	60
DBS 3	3.6	130	60	3.1	130	60
DBS 4	3.0	130	60	4.1	130	60
DBS 5	3.0	130	60	3.0	130	60
DBS 6	1.3	130	60	1.3	130	60
DBS 7	2.5	185	60	3.5	130	60
DBS 8	3.3	130	60	3.0	130	60
DBS 9	2.6	130	60	3.1	130	60
DBS 10	2.6	130	60	3.0	130	60
DBS 11	2.2	130	60	2.2	130	60
DBS 12	2.5	130	60	3.6	130	60
DBS 13	1.8	130	60	1.9	130	60
DBS 14	1.2	130	62	3.5	130	62
DBS 15	1.35	160	60	1.25	160	60
DBS 16	2.45	140	60	2.2	130	60
DBS 17	1.1	125	60	2.4	125	60
DBS 18	2.9	130	60	2.9	130	60
DBS 19	3.4	130	60	2.95	130	60
DBS 20	2.3	130	60	3.45	130	60
DBS 21	2.3	130	60	2.5	130	60
DBS 22	1.85	130	60	2.15	130	60
Mean	2.47	134.09	60.09	2.83	131.14	60.09

Table 3.4 Stimulation settings for left and right subthalamic nucleus (STN) in 22 operated patients with Parkinson's disease (PD).
 STN= subthalamic nucleus; V=Voltage; Hz=Hertz; µs=microseconds; DBS=deep brain stimulation.

3.2.2 Tasks and Procedures

For the first study three verbal fluency tasks from the Delis-Kaplan Executive Function System (D-KEFS, Delis, Kaplan & Kramer, 2001a, b) assessment were used: letter (phonemic) fluency, category (semantic) fluency and category switching fluency. For the letter fluency task patients were given three different letters (e.g. F-A-S), one at the time and were asked to produce as many words starting with that letter as possible within one minute. For category fluency patients were given two categories (e.g. Animals and Boy's names) one at a time and again were asked to produce as many words belonging to that category as possible within one minute. For category switching fluency patients were given two categories at once (e.g. Fruit and Furniture) and were asked to alternate between words belonging to one or the other category within one minute.

For the second study the tasks involved were almost the same with a slight difference in the category fluency task. Patients were given only one category during each session and were asked to produce as many words as possible belonging to that category within five minutes. The aim of this modification was to determine the time course of word generation on this task over a longer interval. Additionally, parallel forms were used for all verbal fluency tasks because the on and off stimulation assessments in the operated group and the two assessments of the control group took place during one session.

3.2.3 Measures

The words generated by the patient were recorded on a record sheet verbatim and also tape-recorded for later analysis. For each of the verbal fluency tasks, the following measures were obtained: (1) total number of correct words across trials which were transformed into age-corrected scaled scores, (2) average size of phonemic clusters, (3) average size of semantic clusters, (4) total number of phonemic switches, (5) total number of semantic switches. Using the methods set out by Troyer et al, (1997), cluster size was computed in the following way: If a cluster consisted of only one word belonging to a certain subcategory, it was scored as 0; if a cluster consisted of two words belonging to a certain subcategory it was scored as 1; if a cluster consisted of three words belonging to certain subcategory it was scored as 2; and so on. In order to get the average cluster size, all clusters were added up and then divided by the total number of clusters, including clusters consisting of only one word. The average number of switches was obtained by adding up the switches per minute and then dividing it by three in the case of the Letter verbal fluency task and by two or five for the Category verbal fluency task (Troyer et al., 1997). The instructions and scoring sheets that were used to score cluster size and number of switches are presented in Appendix D.

3.2.4 Statistical Analysis

To evaluate the effects of STN-DBS surgery on the total number of words and phonemic and semantic switches produced during the letter and category fluency tasks a series of paired t-tests was done. In cases where assumptions for the paired t-test were violated a Wilcoxon signed rank test was performed instead. As cluster size was a small scale measure, a series of Wilcoxon signed rank tests was done to analyse the effects of STN-

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DBS surgery on phonemic and semantic cluster sizes. One-tailed significance was used for the effects of STN-DBS surgery on total number of words and two-tailed significance was used for effects on the total number of switches and cluster size.

To evaluate the effects of STN stimulation and group on the number of words produced during the three verbal fluency tasks a 2 (study group) x 2 (condition/assessment) x 3 (VF task) repeated measure analysis of variance (ANOVA) was performed. To further investigate any significant interactions, t-tests were performed. To evaluate the effects of STN stimulation on the number of semantic and phonemic switches for the letter and category fluency tasks a series of paired t-tests were performed. In cases where assumptions for paired t-tests were violated a Wilcoxon signed rank test was performed instead. To analyse the effects of STN stimulation on phonemic and semantic cluster sizes for the letter and category verbal tasks a series a series of Wilcoxon signed rank tests were done. As mentioned in the introduction chapter Bonferroni correction was not applied. Despite it overcoming the risk of giving too much weight to what may be differences obtained by chance due to multiple comparisons, it may also increase the risk of a type two error that is accepting the null hypothesis when it is in fact false. From a clinical point of view, this would be problematic when considering changes in cognition with DBS of the STN, as it would result in important changes to be overlooked.

For changes that reached statistical significance Cohen's d was calculated to evaluate the magnitude of the effect and robustness of the change. An effect size of 0.2 is considered a small effect, of 0.5 a moderate effect and of 0.8 a large effect (Cohen, 1992).

3.3 Results

3.3.1 The effects of STN-DBS surgery and stimulation

A paired t-test revealed that patients had significantly lower UPDRS scores during the post-operative assessment compared to their pre-operative off medication assessment. This was the case for when patients were on medication (t(18)=10.99; p<0.001), and off medication (t(18)=7.95;p<0.001). Therefore, the motor symptoms significantly improved from before to after surgery.

3.3.1.1 The effects on the number of correct words

The means and standard deviations for the number of correctly produced words at pre- and post-operative assessments are presented in Table 3.5. A series of paired t-tests revealed significant differences in the number of correct words that were produced between the pre- and post-operative assessments for letter fluency (t(18)=2.76;p=0.007; d=0.65), category fluency (t(18)=3.18;p=0.003; d=0.73), and switching category fluency (t(18)=1.83;p=0.04; d=0.44).

	Pre-operative	Post-operative
Letter Fluency	13.79 (4.18)	11.89 (4.82)
Category Fluency	12.16 (3.5)	9.56 (3.61)
Switching Category Fluency	13.42 (3.58)	11.58 (5.2)

Table 3.5 Comparison of the verbal fluency performance of the patients with Parkinson's disease (PD) before and after surgery.
Values represent means and standard deviations (in parentheses) of the number of correct words (scaled scores) on the three verbal fluency tasks.

Therefore, patients produced less words post-operatively on the letter, category and switching category fluency tasks. Figure 3.1 presents the average scaled scores for the number of correctly produced words for the three verbal fluency tasks.
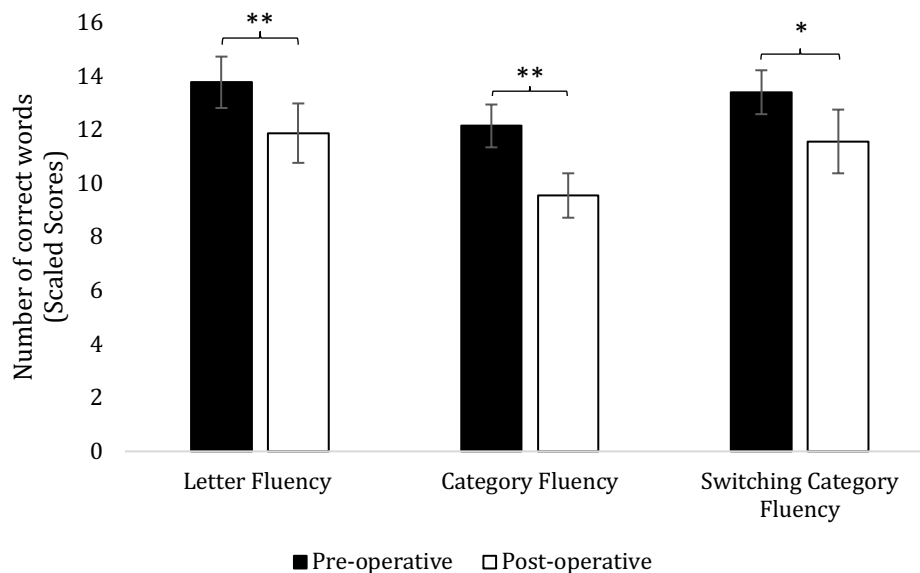
Figure 3.1 Mean number of total correct words (scaled scores) produced on the letter, category and switching category verbal fluency tasks pre-operatively compared to post-operatively.
Error bars represent standard errors. *p<0.05; **p<0.01.

3.3.1.2 The effects of STN-DBS surgery on clustering

The means and standard deviations for the size of phonemic and semantic clusters that were produced are presented in Table 3.6. A series of Wilcoxon signed rank tests indicated no significant changes on the letter fluency task for the sizes of either the phonemic (Z=-1.00; p=0.32) or semantic clusters (Z=-1.24; p=0.21) from the pre- to the post-operative assessment. Therefore, the size of the clusters that the patients produced did not differ between the two assessments.

	Pre-operative	Post-operative
Letter Fluency		
Phonemic Clusters	0.43 (0.19)	0.51 (0.23)
Semantic Clusters	0.11 (0.09)	0.07 (0.08)
Category Fluency		
Phonemic Clusters	0.04 (0.06)	0.06 (0.05)
Semantic Clusters	1.13 (0.83)	0.51 (0.33)

Table 3.6 The average size of the phonemic and semantic clusters on the letter and category fluency tasks before and after surgery.
Values represent means and standard deviations (in parentheses).

On the other hand, a series of paired Wilcoxon signed rank tests revealed significant decrease for category fluency in the size of the semantic clusters (Z=-3.14; p=0.002; d=0.73), but not phonemic clusters (Z=-1.07; p=0.29). Therefore, the size of the semantic clusters decreased post-operatively compared to the pre-operative assessment, whereas the size of the phonemic clusters remained stable. Figures 3.2A and B present the average size of phonemic and semantic clusters that patients respectively produced on the letter and category fluency tasks pre- and post-operatively.

Figure 3.2 The mean size of (A) phonemic clusters and (B) semantic clusters on the letter and category fluency tasks when assessed pre-operatively compared to post-operatively.
Error bars represent standard errors. **p<0.01.

3.3.1.3 The effects of STN-DBS surgery on switching

The means and standard deviations for the number of phonemic and semantic switches are presented in Table 3.7. A series of paired t-tests indicated a significant change in phonemic switches from the pre- to post-operative assessment on the letter fluency task ($t(18)=3.58$; $p=0.002$; $d=0.82$) and the category fluency task ($t(18)=3.93$; $p=0.001$; $d=0.95$), but no difference in the semantic switches on either the letter ($t(18)=1.36$; $p=0.19$) or category fluency tasks ($t(18)=1.09$; $p=0.29$).

	Pre-operative	Post-operative
Letter Fluency		
Phonemic Switches	11.89 (4.29)	9.63 (34.09)
Semantic Switches	14.72 (5.51)	13.43 (5.8)
Category Fluency		
Phonemic Switches	20.76 (6.4)	12.5 (4.82)
Semantic Switches	16.13 (4.68)	11.58 (3.76)

Table 3.7 The average number phonemic and semantic switches on the letter and category fluency tasks before and after surgery.
Values represent mean and standard deviations (in parentheses).

Therefore, the patients produced less phonemic switches post-operatively than pre-operatively on the letter fluency and category fluency tasks but the number of semantic switches did not change on either the letter or category fluency tasks. Figure 3.3A and B

present the average number of phonemic and semantic switches respectively that the patients produced on the letter and category fluency tasks.

Figure 3.3 The mean number of (A) phonemic switches and (B) semantic switches on the letter and category fluency tasks when assessed pre-operatively compared to post-operatively.
Error bars represent standard errors. **p<0.01

3.3.2 The effects of acute STN stimulation

A paired t-test showed that operated patients had significantly lower UPDRS scores when STN stimulation was on compared to when stimulation was off (t(21)=-5.45; p<0.001). Therefore, stimulation improved the motor symptoms of the patients. Patients in the operated and unoperated control groups were matched in terms of severity of motor symptoms as measured by the UPDRS when they were on medication. However, it cannot be stated that they were matched in terms of symptom severity when off medication, as this was not assessed, due to the fact that it would have resulted in discomfort of the patients to not only be off DBS but also medication. Furthermore, the PD patients in both groups were matched in terms of age, disease duration and years of education (p>0.05).

	STN-DBS		PD Control	
	ON	OFF	Assessment 1	Assessment 2
Letter Fluency	11.14	11.05	12.89	12
	(3.9)	(3.56)	(3.33)	(3.94)
Category Fluency	8.36	7.38	9.05	7.38
	(4.07)	(4.5)	(7.36)	(3.62)
Switching Category Fluency	11.77	11.45	11.11	12.89
	(4.07)	(3.75)	(4.14)	(3.59)

Table 3.8 The number of correct words (scaled scores) on the three verbal fluency tasks on and off subthalamic nucleus (STN) stimulation for the patients with Parkinson's disease (PD) who have deep brain stimulation (DBS) and at assessment 1 and 2 for the unoperated control patients.
Values represent means and standard deviations (in parentheses).
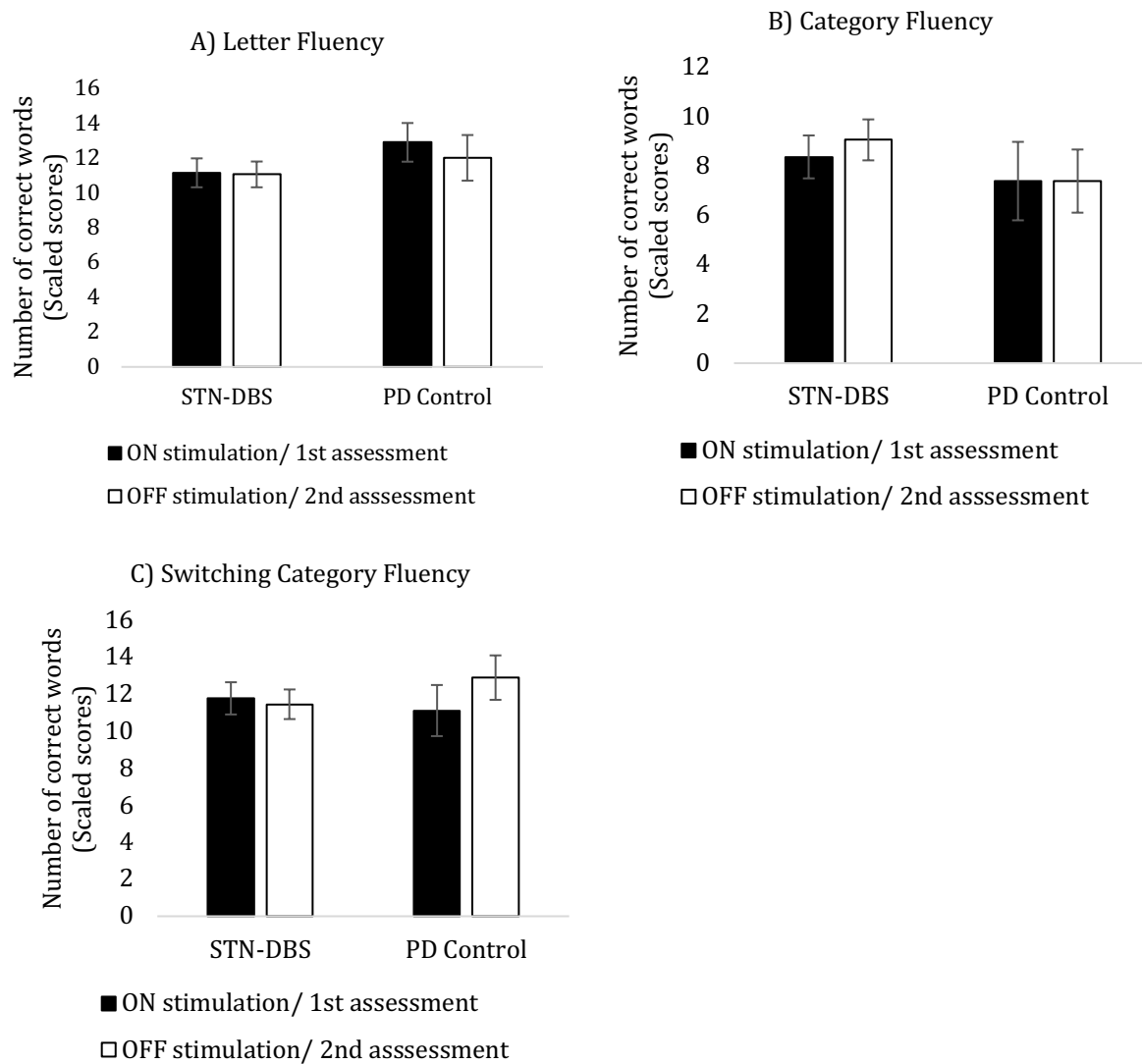
A) Letter Fluency

B) Category Fluency

■ ON stimulation/ 1st assessment
□ OFF stimulation/ 2nd asssessment

C) Switching Category Fluency

■ ON stimulation/ 1st assessment
□ OFF stimulation/ 2nd asssessment

Figure 3.4 Mean number of total correct words (scaled scores) produced on the (A) letter, (B) category and (C) switching category verbal fluency tasks ON and OFF stimulation for the STN-DBS group and at the 1st and 2nd assessment for the PD control group. Error bars represent standard errors.

3.3.2.1 The effect of acute STN stimulation on the number of correct words

The means and standard deviations for the number of correctly produced words for the stimulation on and off assessments for the operated group and at the two assessments for the control group are presented in Table 3.8. A repeated measures ANOVA revealed

no effect of group (F(1, 28)=0.004; p=0.949) or DBS condition/Time of assessment (F(1,28)=0.229; p=0.636). There was also no group x assessment/stimulation condition interaction (F(1,28)=0.063; p=0.804). Therefore, there was no difference in verbal fluency between the groups and acute STN stimulation did not have an effect on the patients' performance (see Figure 3.4).

	ON stimulation	OFF stimulation
Letter Fluency		
Phonemic Clusters	0.58 (0.52)	0.97 (0.91)
Semantic Clusters	0.12 (0.28)	0.13 (0.24)
Category Fluency		
Phonemic Clusters	0.15 (0.31)	0.16 (0.28)
Semantic Clusters	1.06 (0.55)	0.7 (0.47)

Table 3.9 The average size of phonemic and semantic clusters on the letter and category fluency tasks for the patients who deep brain stimulation (DBS), with subthalamic nucleus (STN) stimulation on and off. Values represent means and standard deviations (in parentheses).

3.3.2.2 The effect of acute STN stimulation on clustering

The means and standard deviations for the size of the phonemic and semantic clusters in operated patients with STN stimulation on and off are presented in Table 3.9. A Wilcoxon signed rank test revealed a significant effect of stimulation on the size of semantic clusters during the category verbal fluency task (Z=-2.46; p=0.014; d=0.52). Therefore, patients produced larger clusters when they were on stimulation compared to when they were off stimulation. Figures 3.5A and B show the mean size of phonemic and semantic clusters for the stimulation on and off assessments. There were no effects of stimulation on the sizes of the remaining cluster measures (all p>0.05).
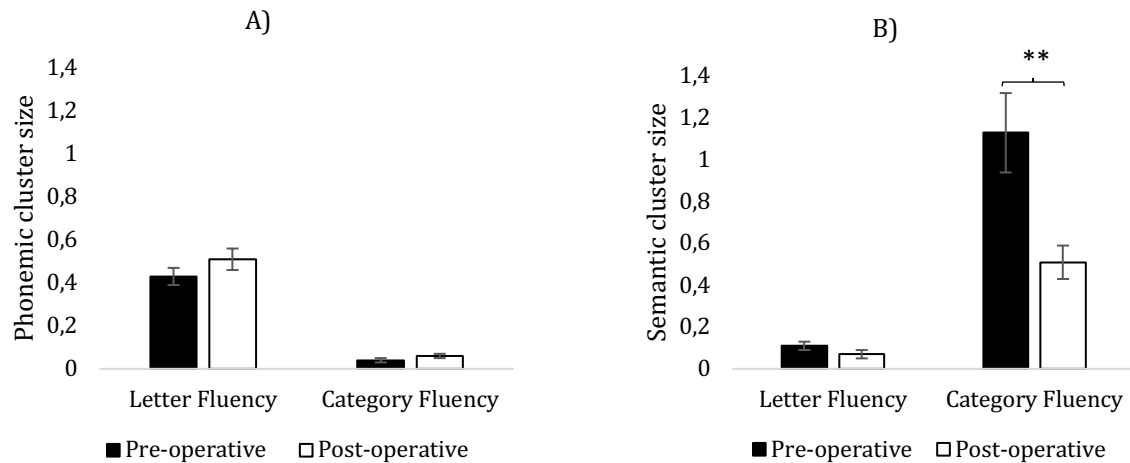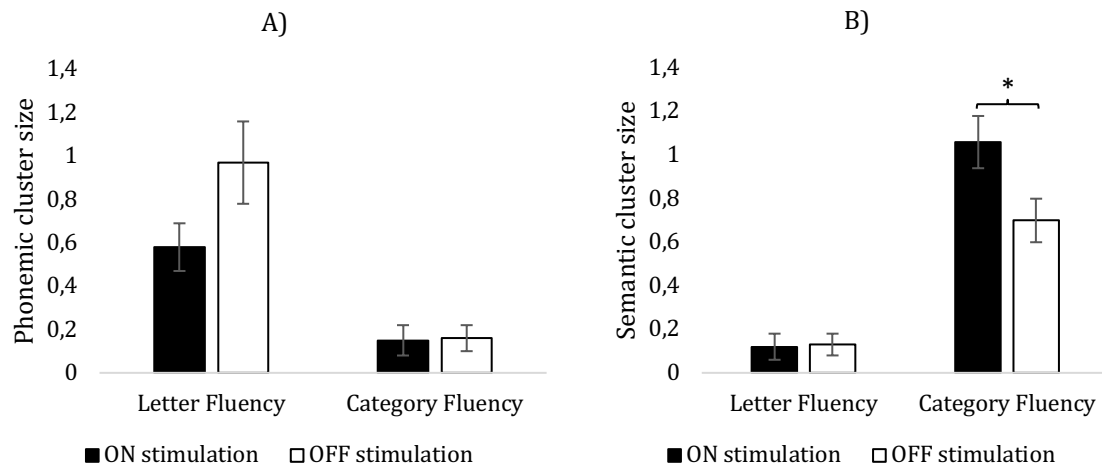
Figure 3.5 The mean size of (A) phonemic clusters and (B) semantic clusters on the letter and category fluency tasks when patients with deep brain stimulation (DBS) were assessed with stimulation ON compared to stimulation OFF.
Error bars represent standard errors. *p<0.05.

3.3.2.3 The effects of acute STN stimulation on switching

The means and standard deviations for the number of phonemic and semantic switches for operated patients with stimulation on and off are presented in Table 3.10. A paired t-test revealed a significant effect of stimulation on the number of semantic switches on the category verbal fluency task (t(21)=-2.51; p=0.02; d=-0.41).

	ON stimulation	OFF stimulation
Letter Fluency		
Phonemic Switches	9.24 (4.79)	7.94 (2.9)
Semantic Switches	11.56 (4.17)	10.91 (3.23)
Category Fluency		
Phonemic Switches	8.75 (2.43)	8.28 (2.47)
Semantic Switches	4.78 (1.57)	5.58 (1.94)

Table 3.10 The number phonemic and semantic switches on the letter and category fluency tasks for the patients who deep brain stimulation (DBS), with subthalamic nucleus (STN) stimulation on and off. Values represent means and standard deviations (in parentheses).

Patients produced fewer semantic switches when stimulation was switched on compared to when stimulation was off. For the remaining switching measures no significant effects were obtained (all p>0.05). Figures 3.6A and B show the mean number of switches that patients produced on the Letter and Category fluency tasks with STN stimulation on and off.
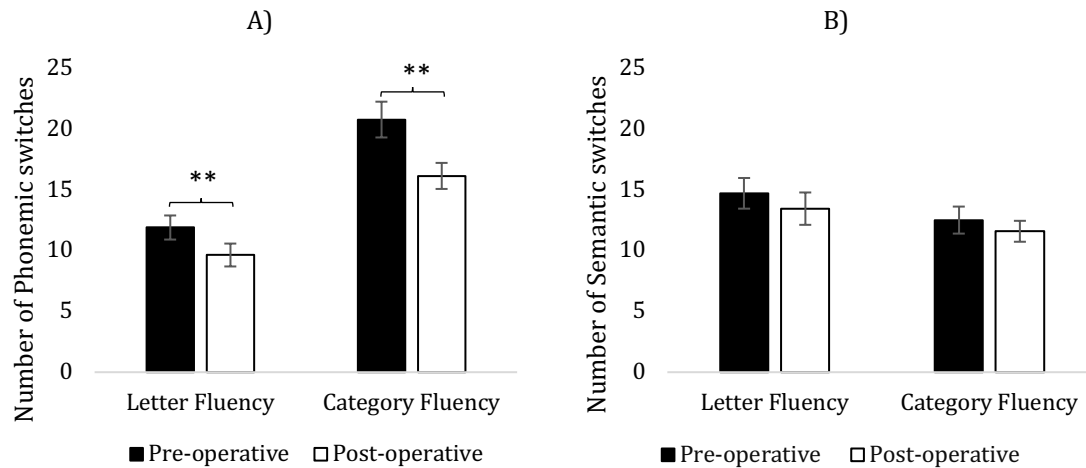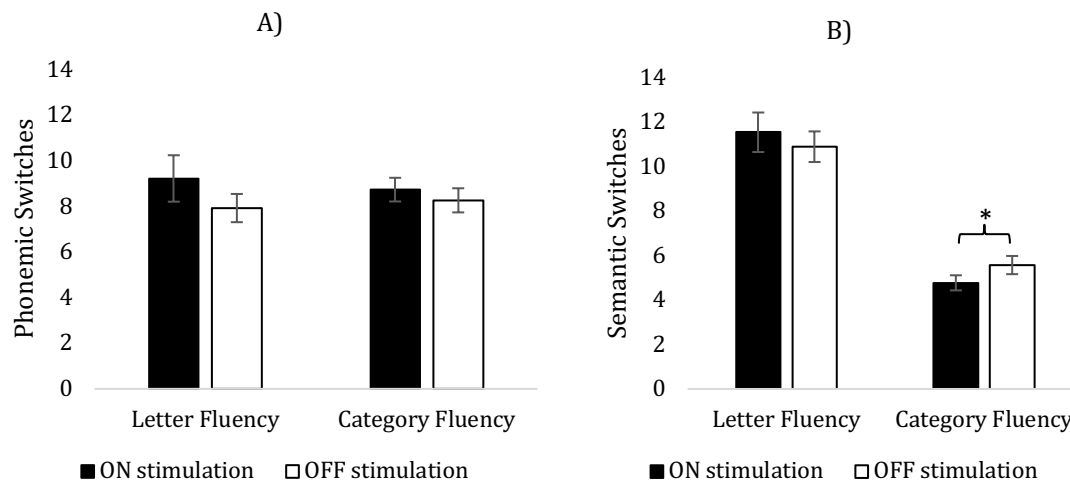
Figure 3.6 The mean number of (A) phonemic switches and (B) semantic switches on the letter and category fluency tasks when patients with deep brain stimulation (DBS) were assessed with stimulation ON compared to stimulation OFF.
Error bars represent standard errors. *p<0.05.

3.4 Discussion

The aim of this study was to investigate the effects of STN-DBS on verbal fluency in more detail, and to tease apart the effects of surgery and acute stimulation and the potential mechanisms of any change. To do so, two separate studies were designed looking at the effects of STN-DBS surgery and acute STN stimulation in two independent samples. The first study consisted of 19 patients with PD undergoing STN-DBS surgery, who were assessed on three verbal fluency tasks (letter fluency, category fluency, switching category fluency) shortly before having surgery and a second time one year or longer after surgery. The second study included 22 patients with PD who underwent STN-DBS surgery at least 6 months prior to recruitment and 9 unoperated matched PD control patients. Patients in both groups had to perform the three verbal fluency tasks twice, the operated group once with their stimulation on and the second time with the stimulation off with the order of the on and off assessments counter-balanced across patients. Furthermore, to investigate the potential mechanisms underlying verbal fluency impairments following STN-DBS surgery, we examined not only the number of correct words generated but also the sizes of phonemic and semantic clusters and the number of phonemic and semantic switches as suggested by Troyer et al. (1997). The hypotheses tested in this study were: (1) The total number of words on all three verbal fluency tasks

would be lower after surgery compared to before surgery; (2) The total number of semantic and phonemic switches would be lower for the category and letter fluency respectively, after surgery compared to before surgery; (3) The average phonemic and semantic cluster size on the category and letter fluency tasks would remain unchanged after surgery compared to before surgery; (4) The total number of words on all three verbal fluency tasks would remain unchanged with STN stimulation, compared to when stimulation was switched off; (5) The total number of semantic and phonemic switches and the average semantic and phonemic cluster size would remain unchanged with STN stimulation, compared to when stimulation was switched off.

3.4.1 The effects of STN-DBS surgery and stimulation - pre- versus post-operative comparisons

Analysis of the effects of STN-DBS surgery on the performance on the letter, category and switching category fluency tasks revealed, as predicted, significant declines in the number of words on all three tasks from before to after surgery. These findings further support previous research indicating that STN-DBS induces a verbal fluency impairment (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). Also, in agreement with previous research (Combs et al., 2015; Parsons et al., 2006), the largest effect was found for category fluency (d=0.73). This implies that the largest impairment is seen for the generation of words requiring information retrieval from semantic memory. Additionally, it suggests that STN-DBS does not only have an impact on the fronto-striatal network but also on networks involving temporal regions. This proposal is supported by research using PET to measure blood flow in different brain targets that receive input from the STN in PD patients with STN-DBS (Schroeder et al., 2003). The results indicated that compared to DBS off, STN stimulation was associated with decreased blood flow in the right orbitofrontal cortex and in the left fronto-temporal network, including the left inferior temporal gyrus and left inferior frontal gyrus, during verbal fluency performance.

As predicted, analysis of the effects of STN-DBS on phonemic and semantic switches showed that patients produced significantly fewer phonemic but not semantic switches on both the letter and category fluency tasks after surgery compared to before surgery. These results suggest that STN-DBS impairs the patients' ability to switch and shift

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attention between phonemic subcategories when completing the letter and category fluency tasks, which may relate to changes in fronto-striatal activity following surgery (Hershey et al., 2003). There is empirical evidence implicating the fronto-striatal circuits in switching and set-shifting (Cools et al., 2001; Owen et al., 1992; Owen et al., 1998; Rogers et al., 2000). Further evidence for the involvement of frontal regions in verbal fluency impairments following STN-DBS in PD has been provided in imaging studies using SPECT-ECD and PET (Cilia et al., 2007; Kalbe et al., 2009). Cilia and colleagues (2007) used SPECT-ECD to investigate the brain perfusion in PD patients, who had a selective decline in category fluency with STN-DBS and reported that this deficit was associated with decreased perfusion in the left dorsolateral prefrontal cortex, anterior cingulate cortex and ventral caudate nucleus. Similarly, Kalbe and colleagues (2009) indicated that STN-DBS induced declines in verbal fluency were related to reduced activity of the left dorsolateral prefrontal cortex, left Broca's area and the right dorsal anterior cingulate cortex. The present results also support the findings of De Gaspari and colleagues (2006), who reported that patients made fewer switches following STN-DBS surgery. However, they did not differentiate between phonemic and semantic switches, and the findings of the present study further suggest that the impairment is specific to phonemic rather than semantic switching.

Analysis of the effects of STN-DBS surgery on the size of phonemic and semantic clusters revealed that there was only an effect on semantic cluster size for the category fluency task. Therefore, patients produced significantly smaller semantic clusters after surgery compared to before surgery. De Gaspari and colleagues (2006) reported cluster size to remain unchanged after surgery. It could be hypothesised that the decrease in semantic cluster size relates to the STN-DBS induced decrease in blood flow in the inferior temporal lobe as reported by Hershey and colleagues (2003). Research investigating the functional anatomy of semantic systems using PET has identified regions of the inferior temporal cortex, specifically the left superior temporal sulcus, left anterior middle temporal gyrus, and frontal cortical areas, specifically the left inferior frontal sulcus, to be involved in word related semantic processing (Vandenberghe, Price, Wise, Josephs & Frackowiak, 1996). Thus, our results showing reduced semantic cluster size during the category fluency task following surgery may suggest that STN-DBS has also an impact on

search and retrieval of information from semantic memory, and that this additional impairment may be the reason for category fluency being more severely impaired after STN-DBS surgery than letter fluency. However, considering that results from Vandenberghe and colleagues are based on healthy participants, this idea needs to be considered carefully and should be further investigated.

3.4.2 The effects of acute STN stimulation-STN-DBS on versus off comparisons

Analysis of the effects of acute STN stimulation on patients' performance on the letter, category and switching category fluency tasks revealed no differences in the number of words produced on any of the three tasks between the ON and OFF stimulation assessments, as predicted. There were also no differences in task performance between the operated STN-DBS group and the matched unoperated PD control group. Our finding that acute STN stimulation has no effect on verbal fluency is in agreement with a large proportion of the previous literature (Jahanshahi et al., 2000a; Morrison et al., 2004; Okun et al., 2009; Pillon et al., 2000; Tremblay et al., 2015; Schulz et al., 2012; Witt et al., 2004). Only two studies reported that STN stimulation produced an impairment specific to letter fluency. Schroeder and colleagues (2003) assessed 7 PD patients with STN-DBS and reported a significant decline in the number of words that patients produced on a letter fluency task when they were on stimulation compared to when stimulation was off. They also used PET to assess changes in brain activity related to changes in task performance and indicated that there was a decrease in blood flow in the right orbitofrontal cortex and in the left fronto-temporal network thought to be associated with verbal fluency. Wojtecki et al. (2006) found a stimulation frequency dependent effect on verbal fluency. They reported that there was a decline in the number of words produced when patients received high-frequency 130 Hz STN stimulation compared to low-frequency 10 Hz stimulation. However, they reported no significant changes between either of the STN stimulation on assessments compared to the off stimulation assessment. From the majority of the previous findings combined with the present results it is clear that acute STN stimulation does not have an effect on verbal fluency performance, but the results of Schroeder et al (2003) suggest that STN stimulation may induce changes in brain activity in fronto-temporal networks implicated in verbal fluency performance. Further information about STN modulation of activity during performance

of verbal fluency tasks was provided by another study. Anzak et al (2013) recorded local field potentials from the electrodes bilaterally implanted in the STN while PD patients performed letter or category fluency or control word repetition tasks. Compared to the control tasks, performance of the verbal fluency tasks was associated with increased gamma band activity in the local field potentials recorded from the left STN which was significantly associated with the total number of words generated and the measure of switching during verbal fluency. The results of Anzak et al (2013) suggest that the surgical effects associated with decline in verbal fluency with STN-DBS may relate to local changes in the STN itself, rather than the inconsistent evidence about the surgical trajectory intersecting the ventricles (York et al, 2009) or the caudate (Yes: Witt et al, 2013; No: York et al, 2009) or positioning of the electrodes in the ventral part of the STN (Witt et al, 2013; Mikos et al, 2011). This proposal is also consistent with the finding that verbal fluency decline was associated with electrodes which were in or adjacent to the motor STN proper (York et al, 2009).

Analysis of the effects of acute STN stimulation on phonemic and semantic switches revealed a significant change in the number of semantic switches patients produced during the category fluency task. Thus, patients produced significantly less switches during category fluency when STN stimulation was on compared to when stimulation was switched off. Previous research investigating the effects of acute STN stimulation on switching performance has looked at letter fluency only and reported that patients produced more switches when stimulation was on compared to the stimulation off assessment (Vonberg et al., 2016). These findings are not consistent with the present results. However, Vonberg and colleagues (2016) did not differentiate between phonemic and semantic switches. It could be argued that the differential effects seen in the present study and Vonberg et al.'s (2016) study can be explained by different underlying mechanisms. Changes reported by them may reflect STN-DBS induced reduced inhibitory control causing patients to switch more often between different phonemic subcategories. And such reduced inhibitory control could be due to reduced fronto-striatal activity (Hershey et al., 2003; Jahanshahi et al., 2015; Schroeder et al., 2003). The results from the present study may relate to a STN stimulation induced modulation of semantic memory retrieval leading to patients remaining within one subcategory for longer before

switching to the next. This may be a function of the decreased activity in the inferior temporal lobes and the fronto-temporal networks seen in patients with STN-DBS (Hershey et al., 2003; Schroeder et al., 2003). Further reasons for these variances in findings may relate to factors such as the exact location of the stimulating electrode contacts in the STN, considering that there is evidence that the electrode position can have an effect on cognitive and more particularly on verbal fluency decline after STN-DBS surgery (Witt et al., 2013; York et al., 2009). Witt et al. (2013) suggested that patients with active electrodes in the ventral portion of the STN developed verbal fluency impairments, whereas patients with active electrodes in the dorsal portion of the STN showed normal verbal fluency. By contrast, York and colleagues (2009) reported that declined verbal fluency performance was associated with electrodes placed closer to the approximate motor STN and more superiorly and posteriorly in the right hemisphere and electrodes placed in the lateral and superior directions in the left hemisphere. However, recent evidence suggested that declined letter fluency was unrelated to electrode position and or number of microelectrode recordings during surgery (Smith, O'Connor, Pappavassiliou, Tarsy & Shih, 2014). Also, Okun and colleagues (2009) compared patients with GPi- and STN-DBS and compared stimulation effects of the ventral and dorsal STN regions and indicated deficits in verbal fluency performance were not associated with stimulation of different areas. Thus, it is not clear whether or not surgical parameters relate to the verbal fluency impairments.

Analysis of the effects of acute STN stimulation on the size of phonemic and semantic clusters revealed a significant change in semantic cluster size on the category fluency task between the stimulation on and off assessment, whereby patients produced larger semantic clusters on stimulation compared to when stimulation was off. This finding is also not consistent with previous findings reporting no differences in cluster size with acute STN stimulation (Vonberg et al., 2016). As cluster size and number of switches are likely to be related measures, our finding of larger semantic cluster size combined with fewer semantic switches during category fluency without a significant change in the total number of words generated with STN stimulation ON relative to OFF, simply suggests that patients may have altered their search/retrieval/generation strategies with STN

stimulation, spending longer generating words belonging to one specific subcategory and engaging in fewer switches between subcategories.

3.4.3 The effects of STN-DBS surgery and acute STN stimulation

The aim of the study was to differentiate between the effects of the STN-DBS procedure as a whole and acute STN stimulation on verbal fluency performance and its subprocesses switching and clustering. This was done to follow up on previous research that also looked at surgery and stimulation effects (Okun et al., 2009; Okun et al., 2012). Okun and colleagues (2009, 2012) reported that the STN-DBS induced verbal fluency impairment was purely related to STN-DBS surgery and that acute stimulation did not result in any further changes. Indeed, the findings of the current study also support this conclusion as there was a significant decline in the number of words patients produced after surgery compared to before surgery but the patients' performance remained unchanged when stimulation was on compared to when it was off, suggesting that impairments in verbal fluency persist even when the STN-DBS is off. However, Okun and colleagues (2009, 2012) did not look at the impact of STN-DBS surgery and acute stimulation on the component processes of verbal fluency, which was also examined in the current study. The results of the present study indicate that verbal fluency impairments following STN-DBS surgery are primarily related to an executive dysfunction evident as a decreased number of phonemic switches on both the letter and category fluency tasks. It may be assumed that this deficit relates to decreased activation of the fronto-striatal network and the key frontal areas that mediate verbal fluency performance as previously reported (Cilia et al., 2007; Kalbe et al., 2009; Schroeder et al., 2003). In addition to this executive component there was a change in the semantic cluster size on the category fluency task only between the pre- and post- operative assessments. Therefore, patients produced significantly smaller clusters after surgery compared to before surgery. This may reflect a deficit in word retrieval from the semantic memory enhancing the decline of word numbers on the category fluency task only. In support of this statement would be findings from studies using PET that suggested decreased blood flow in the inferior temporal lobe (Hershey et al., 2003; Schroeder et al., 2003), which is involved in word-related semantic systems (Vandenberghe et al., 1996). In terms of acute STN stimulation effects the present findings that while stimulation does not change the overall performance on

verbal fluency tasks, it nevertheless modulates the strategies patients use to retrieve information from semantic memory, as patients produced larger semantic clusters and fewer semantic switches on the category fluency task with stimulation on compared to when stimulation was off. In support of this would be findings of Schroeder and colleagues (2003), who reported decreased blood flow in a frontotemporal network with acute stimulation, which might relate to modulated semantic processing.

On the basis of the similarity in the executive processes involved in verbal fluency, the Stroop colour word interference task and random number generation, it has been previously suggested that the STN-DBS induced declines in all these tasks may reflect a deficit in response selection under competition or conflict (Thobois et al, 2007). For random number generation, on each trial there is competition in response selection between numbers 1 to 9. Such a competition in response selection increases by many magnitudes for verbal fluency, when one considers, for example, the potential words beginning with the letter 'F' that are available for selection and retrieval from memory on a letter fluency task. It is possible that STN-DBS surgery interferes with the process of response selection under conflict during letter and category and switching category verbal fluency, similar to the decline documented in fast-paced random number generation (Thobois et al, 2007), or the Stroop Interference task (Jahanshahi et al, 2000a; Witt et al, 2006).

This study had a couple of limitations. First, two different samples were recruited for part one and part two of the study. It would have been even more informative to see the effects of STN-DBS surgery and acute STN stimulation in the same sample as there could have been some variability between the two patient groups. Second, for the second part of the study the PD control group was relatively small and less than half the size of the operated group. However, the two patient groups were matched in terms of age and disease duration and most patients at that disease stage would have surgery which made it more difficult to find a larger group of unoperated PD patients as a control group.

In conclusion, this study was the first to differentiate between the effects of STN-DBS surgery and acute stimulation on verbal fluency performance and also to examine the

effect on surgery and acute stimulation on the clustering and switching processes. The findings indicated STN-DBS surgery and acute stimulation have differential and dissociable effects on verbal fluency. Furthermore, our results showed that impaired performance on different verbal fluency tasks primarily related to an executive dysfunction as reflected as a decrease in the number of phonemic switches and that deficits in semantic memory search and retrieval as reflected by decreased semantic cluster size on the category fluency task also contributed to the greater decline in the number of words produced on this task after STN-DBS surgery. Acute STN stimulation did not significantly alter the number of words generated and the verbal fluency performance of the operated patients did not differ from unoperated PD patients. By contrast, acute STN stimulation modulated semantic processing, as evident in increased semantic cluster size and decreased number of semantic switches on the category fluency task, without significantly influencing the overall verbal fluency performance compared to DBS off. Future research should aim to investigate the effects of STN-DBS surgery and acute stimulation within one sample and also include an unoperated PD control group for the comparison of surgery effect, to ensure that surgery effects found in this research are not caused by disease progression.

Chapter 4. The effects of STN-DBS on associative learning of verbal and non-verbal information in PD

4.1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder (Siderowf & Stern, 2003) and is characterised by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (Kish et al., 1988), which is the main source of dopamine for the nigrostriatal tract (Gibb & Lees, 1991). This pathology results in the major motor symptoms of the disease (Gelb et al., 1999), namely bradykinesia, rigidity, resting tremor and postural instability (Lees et al., 2009). The main focus of clinical management of PD is to improve these motor symptoms, but non-motor symptoms, such as depression and cognitive impairment have been widely recognized, and are considered for clinical management, as they have a major impact on the patients' quality of life (Schrag et al., 2000).

Cognitive deficits are already present in about 30% of the patients during early disease stages, and typically begin as executive dysfunction (Elgh et al., 2009; Foltynie et al., 2004). Executive function includes a variety of cognitive processes that control goal-directed behaviours. As reviewed by Dirnberger & Jahanshahi (2013), in PD several aspects of executive function become impaired including internal control of attention (Brown & Marsden, 1988a, b; Hsieh et al., 1995), set shifting (Taylor & Saint-Cyr, 1995), planning (Saint-Cyr et al., 1988) inhibition of prepotent responses and conflict resolution (Cooper et al., 1994) and decision-making (Brand et al., 2004). Besides executive function, such mild cognitive impairment (MCI), can further affect working memory, language, memory and visuospatial processing (Litvan et al., 2011, 2012). MCI is a strong predictor of PD related dementia (PD-D), which has a long-term prevalence of up to 80 percent (Aarsland et al., 2003; Aarslandet al., 1996; Hely et al., 2008) and is characterised by severe cognitive decline in the domains of memory, attention, visuospatial and executive function (Dubois et al., 2007; Emre et al., 2007; Gratwicke et al., 2015).

As mentioned above clinical management of PD primarily aims to improve the motor symptoms (Rao et al., 2006; Rascol et al., 2002). These are initially treated with dopamine-replacing substances, such as levodopa and dopamine agonists. However, dopamine-replacing therapy can result in long-term side effects such as on-off motor

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fluctuations and dyskinesias at which point patients are commonly treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN), as it results in significant improvements of the motor symptoms (Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2005; Weaver et al., 2012; Williams et al., 2010). However, STN-DBS may cause deficits in certain cognitive domains including executive function, verbal learning, memory and particularly verbal fluency (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016).

4.1.1 Conditional Associative Learning and Parkinson's disease

Conditional associative learning (CAL) tasks involve both planning and learning and therefore rely on executive function (Gotham et al., 1988; Marié et al., 1999). During a conditional associative learning task participants are required to learn the arbitrary associations between several stimuli and responses, by trial-and-error (Petrides, 1985a). Stimuli can be either visual or verbal in nature. According to Levine, Stuss and Milberg (1997) it is important to differentiate conditional associative learning from standard paired-associate paradigms and classical conditional or discrimination learning paradigms. During paired associate learning the correct stimulus pairings are presented together enhancing the strength of the associations. Also, participants are required to only make one response. During conditional or discrimination learning tasks only one stimulus-response pair is reinforced. Responding to other stimuli is reduced through non-reward. On the other hand, in CAL all stimulus-response pairs are reinforced, and participants have to learn a conditional rule, where they have to select a different response for each stimulus (Petrides, 1986).

CAL performance has been found to be sensitive to frontal lobe function. Animal studies of nonhuman primates reported that lesions to the posterior dorsolateral prefrontal cortex (DLPFC) produced CAL performance deficits (Halsband & Passingham, 1982; Halsband & Passingham, 1985; Petrides, 1982; Petrides, 1985b). Also, lesions to the right and left frontal lobes led to CAL impairments in humans (Petrides, 1985a; Petrides, 1990). Studies using functional imaging reported increased cerebral blood flow in the DLPFC, in particular in Brodmann area 8 and the anterior cingulate (Petrides, Alivisatos, Evans & Meyer, 1993) and the cingulate cortex and dorsal premotor area (Mitz et al.,

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1993). From these findings, it can be suggested that CAL performance relates to frontal lobe function and in particular to the DLPFC and premotor cortex. Furthermore, Toni, Krams, Turner and Passingham (1998) used PET to measure cerebral blood flow while participants performed a visuomotor conditional associative learning task. They reported that learning was related with activity within a network that was distributed throughout the ventral extrastriate and prefrontal cortex and was further associated with the basal ganglia and the parahippocampal gyrus. Later, the same group conducted an fMRI study and used a visuomotor control task in addition to the learning task (Toni, Ramnani, Josephs, Ashburner & Passingham, 2001). The results indicated learning-specific activity within a temporo-prefrontal circuit. Interestingly, they found that supportive activity from the hippocampus, parahippocampus and basal ganglia were dependent on the learning stages/phases. Therefore, during early learning stages there was increased hippocampal and parahippocampal activity, whereas during late learning stages there was increased basal ganglia activity. These findings indicate that hippocampal, parahippocampal regions and the basal ganglia are involved in conditional associative learning.

Research on CAL performance of PD patients is inconsistent. Canavan and colleagues (1989) investigated the effects of early PD on participants' performance on a variety of learning tasks. They used one visual-motor and another visual-visual CAL task. During the former patients had to learn the associations of six different colours with six different movements using a handle. During the visual-visual task patients had learn the associations between the same six colours and six different shapes. The results indicated no differences in performance for either of the CAL tasks between the PD patients and age-matched healthy controls. However, the authors reported a minority of older patients who did have impaired task performance. On the other hand, research investigating visuospatial CAL in patients with Alzheimer-type dementia and PD reported that PD patients were impaired when performing the task (Sahakian et al., 1988). This study used a task that became increasingly more difficult by increasing the number of stimulus-response pairs (1 to 8 pairs). Also, they included de novo PD patients as well as medicated patients who were in the later stage of the illness. The results indicated that PD patients in both groups required more trials to reach the criterion and had fewer correct trials for

the 6 and 8 pairs conditions compared to control participants. Lange, Wells, Rossor, Jenner and Marsden (1991) used the same task as Sahakian et al. (1988) did and supported their findings. On the other hand, Gotham and colleagues (1988) tested PD patients on and off medication and reported that patients were impaired on the conditional associative learning task only when they were on medication. Based on these findings they developed the 'dopamine overdose' hypothesis, which states that dopaminergic medication results in *overstimulation* of the ventral striatum which is not dopamine depleted to the same extent as the dorsal striatum in early stages of PD, thus leading to impaired functioning of the limbic and orbitofrontal circuits resulting in cognitive deficits. Another study also used a spatial CAL task and compared the performance of PD patients to that of healthy control participants (Zgaljardic et al., 2007). Their findings indicated that patients produced more errors and required more trials to reach criterion on the task. Therefore, most research suggested that PD patients are impaired on CAL tasks apart from one (Canavan et al., 1989). Nevertheless, even the latter study mentioned that older PD patients did show impaired performance when compared to younger patients or healthy controls. When considering the average age of the patients in the other studies, it may be noted that the patients' age has an effect on the performance of such tasks.

One investigation used a visual CAL task with two different learning instructions (Vriezen & Moscovitch, 1990). Their task included six pairs of numbers (1 to 6) and drawings. In addition to the typical trial-and-error learning instruction that was also implemented by other research studies they also used a feedback learning instruction. For the feedback learning instruction participants were initially told which number was associated with which drawing. The remaining test procedure was the same as for the trial-and-error learning instruction with the difference that when patients selected a wrong drawing, they were told the correct selection i.e. were provided immediate corrective feedback. They used this condition in order to assess whether deficits seen in PD are due to an inability to select the correct response from a number of potential responses or due to impaired trial-and-error learning. Their results suggested that compared to healthy control participants PD patients were only impaired on the trial-and-error learning

version of the task, from which they further concluded that trial-and-error learning depends on the integrity of the fronto-striatal network.

4.1.2 Conditional Associative Learning and subthalamic nucleus deep brain stimulation

There is some research on the effects of STN-DBS surgery on CAL performance. Trépanier et al. (2000) compared PD patients with STN-DBS or GPi-DBS or pallidotomy on several neuropsychological tasks, including a CAL task with 4 arbitrary pairings. The results indicated that PD patients produced more errors on the CAL task following STN-DBS surgery compared to their pre-operative assessment, and they performed worse compared to patients who had had different surgical treatments. The same group also reported more errors and trials to criterion in PD patients with STN-DBS after surgery compared to before surgery (Saint-Cyr et al., 2000). These findings indicate that STN-DBS surgery has a detrimental effect on learning and performance of the CAL task in PD. However, the above studies did not evaluate the effects of acute STN stimulation on CAL task performance and simply compared learning before and after surgical interventions.

Findings of studies investigating the effects of acute STN stimulation on CAL are inconsistent. Jahanshahi and colleagues (2000a) used a visual CAL task, requiring patients to learn arbitrary associations between six colours and six abstract designs, and reported that patients produced more errors and required more trials to reach criterion when they were on stimulation compared to when stimulation was off, indicating a detrimental effect of acute STN stimulation on CAL. On the other hand, more recent evidence suggests that visual CAL was improved when patients were tested on stimulation compared to when stimulation was off (Mollion et al., 2011; Ventre-Dominey et al., 2016). However, the latter studies used a paradigm that required participants to learn associations between two colours and directions. Therefore, the cognitive load involved was lower than for the task used by Jahanshahi et al. (2000a), which suggests that the effect of STN stimulation on CAL task performance may be load- dependent. To date, there has been no study investigating the effects of acute STN stimulation on CAL tasks that use the feedback learning condition. Thus, the aim of this study was to first, investigate the effects of acute STN stimulation on a CAL task with arbitrary colour and

abstract design stimuli including both trial-and-error and feedback learning versions and relative to a verbal paired associate learning task and second to compare patients with STN-DBS to unoperated PD control participants. The following hypotheses were tested:

1. Learning and performance on the trial-and-error learning visual conditional associative learning task would decline with STN stimulation, compared to when stimulation was switched off.

2. Learning and performance on the feedback learning visual conditional associative learning task would remain unchanged with STN stimulation compared to when stimulation was switched off.

3. The total number of correctly learned associations on the verbal paired associate learning task would decline for the 'hard' unrelated pairs only with STN stimulation on compared to when stimulation was switched off, but would remain unchanged for the 'easy' related pairs.

4.2 Methods

4.2.1 Participants

All participants had a clinical diagnosis of Parkinson's disease according to the UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992). Responsiveness to levodopa was assessed and all patients were rated on the Unified Parkinson's disease Rating Scale (UPDRS: Fahn et al., 1987) before and after surgery. All operated patients had quadripolar stimulating electrodes (Medtronic, Minn., USA) chronically implanted into the STN bilaterally, according to procedures described previously (Foltynie et al., 2011).

Twenty-four patients (16 males) who had bilateral STN-DBS for at least six months and nine unoperated control patients (5 males) were recruited. Five patients in the operated group were left-handed, all other participants were right-handed. The mean age was 59.58 (SD=6.53; range 46-70) in the operated group and 59.33 (SD=6.12; range 53-69) in the control group. Patients were assessed on medication. Table 4.1 shows the demographics and clinical features of both groups.

	STN-DBS	PD Control
Age	59.58 (6.53)	59.33 (6.12)
Gender		
Male	16	5
Female	8	4
Handedness		
Right	19	9
Left	5	0
Years of Education	13.05 (2.75)	16.11 (4.43)
Disease duration	13.04 (4.78)	10.11 (5.02)
MMSE	29.35 (0.71)	-
UPDRS		
ON-DBS/Med.	11.94 (8.7)	18.71 (12.48)
OFF-DBS	24.02 (13.41)	-

Values for age, years of education, disease duration, and unified Parkinson's disease rating scale (UPDRS) are mean and standard deviations (in parentheses).

4.2.2 Design

A 2 (study group) x 2 (assessment) mixed between groups-within subject design was used. All patients were assessed on all three associative learning tasks twice. The operated group was assessed once with their stimulation switched on and a second time with the stimulation switched off. The order of the stimulation condition was counterbalanced across patients. STN stimulation was switched on or off at least 30 minutes before each part of the assessment. This time was based on previous research investigating the effects of acute STN stimulation on several cognitive functions (e.g. Jahanshahi et al., 2000a). The control group was also tested twice to control for the effects of repeated administration of the learning tasks. For each testing testing, the order of the trial and error and corrective feedback versions of the visual conditional associative learning tasks was counterbalanced across participants in each group. Table 4.2 shows the stimulation settings for the operated patients.

Patient	Left STN stimulation settings			Right STN stimulation settings		
	Voltage in V	Frequency in Hz	Pulse Width/μs	Voltage in V	Frequency in Hz	Pulse Width/μs
DBS 1	4.5	160	60	2.5	185	90
DBS 2	2.3	130	60	2.8	145	60
DBS 3	3.3	130	60	3.3	130	60
DBS 4	3.7	130	60	3.8	130	60
DBS 5	3.6	130	60	3.1	130	60
DBS 6	3.0	130	60	4.1	130	60
DBS 7	3.0	130	60	3.0	130	60
DBS 8	1.3	130	60	1.3	130	60
DBS 9	2.5	185	60	3.5	130	60
DBS 10	3.3	130	60	3.0	130	60
DBS 11	2.6	130	60	3.1	130	60
DBS 12	2.6	130	60	3.0	130	60
DBS 13	2.2	130	60	2.2	130	60
DBS 14	2.5	130	60	3.6	130	60
DBS 15	1.8	130	60	1.9	130	60
DBS 16	1.2	130	62	3.5	130	62
DBS 17	1.35	160	60	1.25	160	60
DBS 18	2.45	140	60	2.2	130	60
DBS 19	1.1	125	60	2.4	125	60
DBS 20	2.9	130	60	2.9	130	60
DBS 21	3.4	130	60	2.95	130	60
DBS 22	2.3	130	60	3.45	130	60
DBS 23	2.3	130	60	2.5	130	60
DBS 24	1.85	130	60	2.15	130	60
Mean	2.65	134.58	60.08	2.81	136.25	61.33

Table 4.2 Stimulation settings for left and right subthlamic nucleus (STN) in 24 patients with Parkinson's disease who have deep brain stimulation (DBS). STN=subthalamic nucleus; V=Voltage; Hz=Herz; μs=microseconds; DBS=deep brain stimulation.

4.2.3 Task and procedures

4.2.3.1 Visual Conditional Associative Learning Task – Trial-and-error and feedback learning versions

The Visual Conditional Associative Learning task (VCLT; Petrides, 1985; Gotham et al., 1988) was completed in order to assess CAL of non-verbal information. During the task participants were required to learn arbitrary associations between 6 abstract geometric designs and 6 colours (red, black, yellow, green, blue and brown) within maximum of 12 blocks (see Figure 4.1A). The test material consisted of six cards each showing one colour and six cards each showing all six designs displayed in random order. Two versions of the VCLT were completed. In the trial-and-error learning version during each block of trials

the participants were presented with each colour in a predetermined order and asked to indicate which design they thought was associated with that colour (see Figure 4.1B). For each selection, participants were told if they were correct or not. If the selection was wrong the participants continued to choose other designs until they found the correct association. The task was discontinued when the criterion of two consecutive blocks of trials correct was achieved or 12 blocks were completed.

In the feedback learning version the participants were initially shown each colour and the design that was associated with it (see Figure 4.1C). Following this familiarization period, participants were presented on each trial with one of the six colours in a predetermined order and asked to indicate which design they thought was associated with that colour. If the selection was correct, the next trial was initiated and if it was incorrect the participant was told the correct selection and one error was scored. This was continued until the criterion of two consecutive blocks of trials correct was reached or alternatively until 12 blocks of trials were completed.
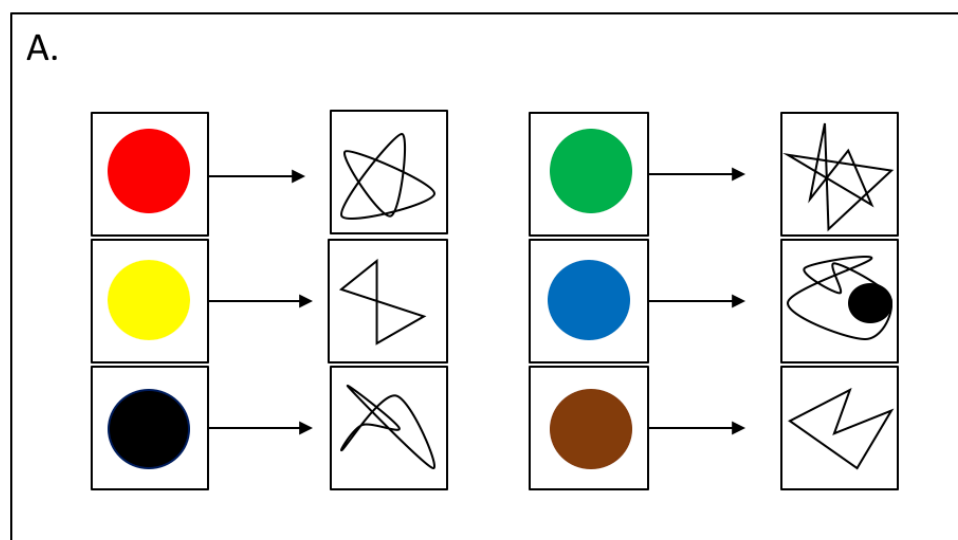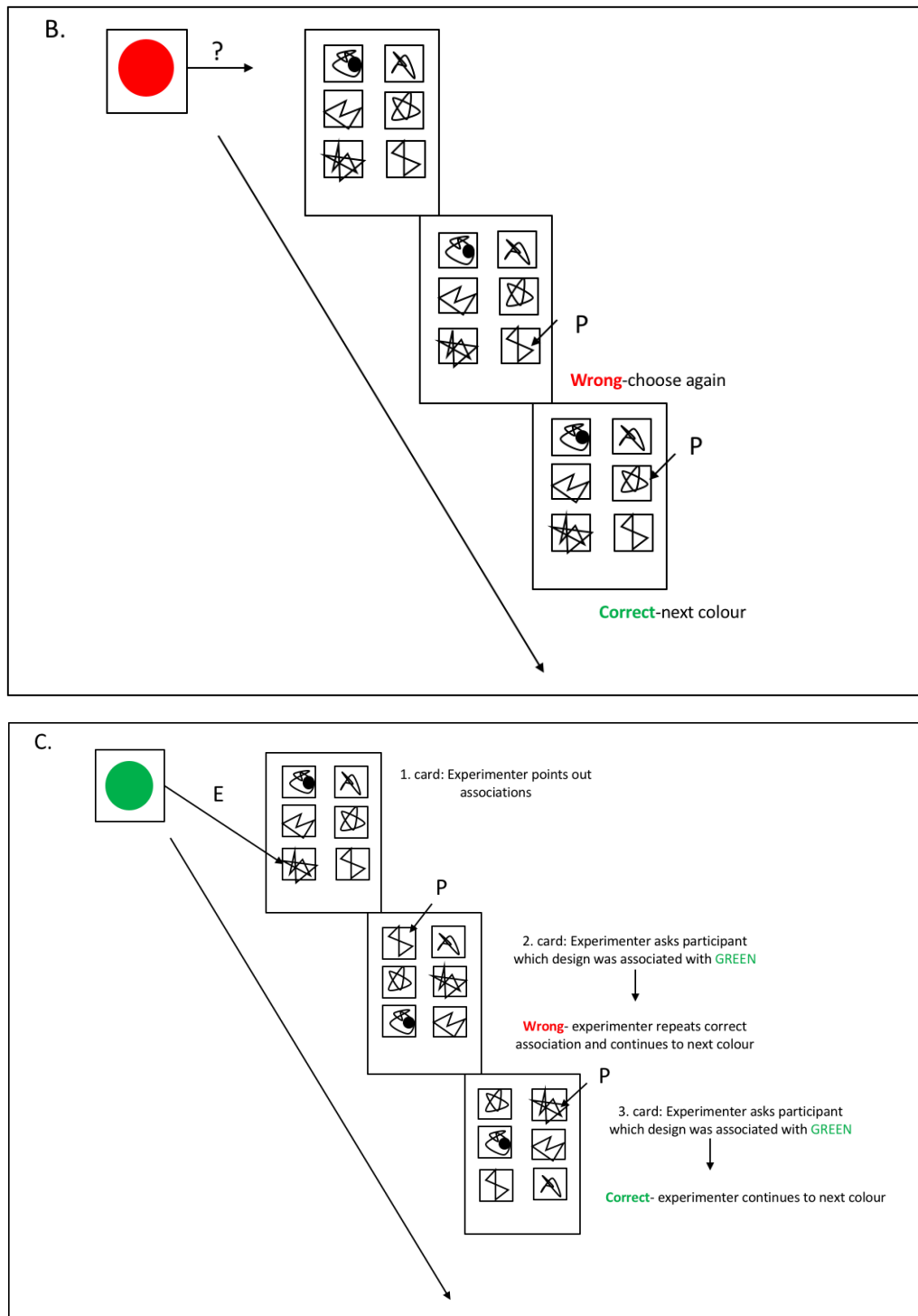
Figure 4.1 The trial-and-error and Feedback learning versions of the visual conditional associative learning task. Part (A) represents example associations for one set of abstract designs; part (B) represents an example course for learning by trial and error and; part (C) represents an example course for learning by corrective feedback.

P= Participant; E=Experimenter

The number of errors, the number of trials that were correct first time, the total number of trials and the number of blocks to criterion were recorded. To make the two versions

of the task comparable, the scoring scheme proposed by Vriezen and Moscovitch (1990) was used. Therefore, for the total number of trials and errors the first error was counted only. Four different sets of designs were used, with the order of the two versions of the test and the order of the design sets being counterbalanced across participants. A previous study tested and established in a sample of young healthy controls that the four different versions of the task were parallel and equivalent in difficulty (Pieters et al, 2004).

4.2.3.2 Paired Verbal Associative Learning Task

The Verbal Paired Associates (VPA) subtest from the Wechsler Memory scale-III (WMS-III, Wechsler 1997) was used to assess associative learning of verbal information. The task consisted of six trials. For each trial participants had to listen to eight pairs of associated words, four pairs consisted of related words (easy items: e.g. baby-cries or rose-flower) and four pairs consisted of unrelated words (hard items: e.g. school-grocery or cabbage-pen). After listening to the list of pairs, participants were told one word at a time and asked to say which word they thought was associated with the given word. This was repeated until they either learned all associations until the third trial or after six trials had been reached. The number of correct answers and the number of trials until all items were learned were scored for easy and hard items separately. To control for possible practice effects, two parallel versions of the task were used.

4.2.4 Statistical Analysis

To analyse the effects of acute STN stimulation in the operated PD group and the practice effects in the PD control group on the different measures of the trial-and-error and feedback learning versions of the visual conditional associative learning task and the verbal paired associative learning task a series of Wilcoxon signed rank tests was performed because the measures for the on and off stimulation or time 1 and time 2 assessments were not normally distributed. To analyse any potential differences in the measures on the trial-and-error and feedback learning versions of the visual conditional associative learning task and the verbal paired associative learning task between the STN-DBS and PD control group a series of Mann-Whitney U tests was performed because the data were non-normally distributed at least in one group. To analyse the differences

in performance between the trial-and-error learning and the feedback learning versions of the visual conditional learning tasks at the different assessments a series of Wilcoxon signed rank tests was performed because the scores on both versions of the task were non-normally distributed. As mentioned in the introduction chapter Bonferroni correction was not applied. Despite it overcoming the risk of giving too much weight to what may be differences obtained by chance due to multiple comparisons, it may also increase the risk of a type two error that is accepting the null hypothesis when it is in fact false. From a clinical point of view, this would be problematic when considering changes in cognition with DBS of the STN, as it would result in important changes to be overlooked.

For changes that reached statistical significance Cohen's d was calculated to evaluate the robustness of the change. An effect size of 0.2 is considered a small effect, of 0.5 a moderate effect and of 0.8 a large effect (Cohen, 1992).

4.3 Results

Patients in the operated and unoperated groups were matched in terms of severity of motor symptoms as measured by UPDRS part III, age, disease duration and years of education (all $p>0.05$). A paired t-test showed that operated patients had significantly lower UPDRS scores when STN stimulation was on compared to when stimulation was off ($t(23)=-5.7$; $p<0.001$). Therefore, stimulation improved the motor symptoms of these patients.

4.3.1 Effects of acute STN stimulation and repeated administration on the Visual and Verbal Associative Learning tasks

The means and standard deviations for the total number of trials, total number of errors, trials that were correct first time and the number of blocks to criterion for both study groups at the stimulation on and off assessments for the operated group and at assessment 1 and 2 for the PD control group are presented in Table 4.3.

	PD STN-DBS group		PD Control group	
	ON stimulation	*OFF stimulation*	*Assessment 1*	*Assessment 2*
VCLT (trial-error learning)				
Total trials	36.33(17.96)	35.00(16.85)	50.00(21.63)	27.33(17.77)
Errors	8.67(10.63)	8.5(8.98)	14.44(11.88)	7.67(14.38)
Trials correct first time	57.46(10.79)	57.88(7.96)	45.67(16.18)	57.22(13.72)
Blocks to criterion	6.67(3.29)	6.54(3.05)	9.11(4.08)	5.22(3.35)
VCLT (Feedback learning)				
Total trials	26.58(24.4)	23.00	30.67(21.93)	15.33(10)
Errors	7.96(14.85)	5.63(11.64)	7.11(10.04)	1.33(2.6)
Trials correct first time	57.42(12.31)	59.88(11.58)	57.56(10.37)	64.11(4.23)
Blocks to criterion	5.63(4.55)	4.91(3.65)	5.67(4.15)	3.22(1.64)

Table 4.3 Comparison of performance on the trial-error and feedback learning versions of the visual conditional associative learning task (VCLT) between the operated (PD STN-DBS) and unoperated patients (PD control) with Parkinson's disease (PD).
Values represent means and standard deviations (in parentheses) for the different measures of the tasks.

A series of Wilcoxon signed rank tests revealed no significant effects of acute STN stimulation on any of the measures on the two versions of the VCLT in the operated group (all p>0.05; see Figures 4.1A and C). However, there were several significant changes from the first to the second assessment in the unoperated control group.
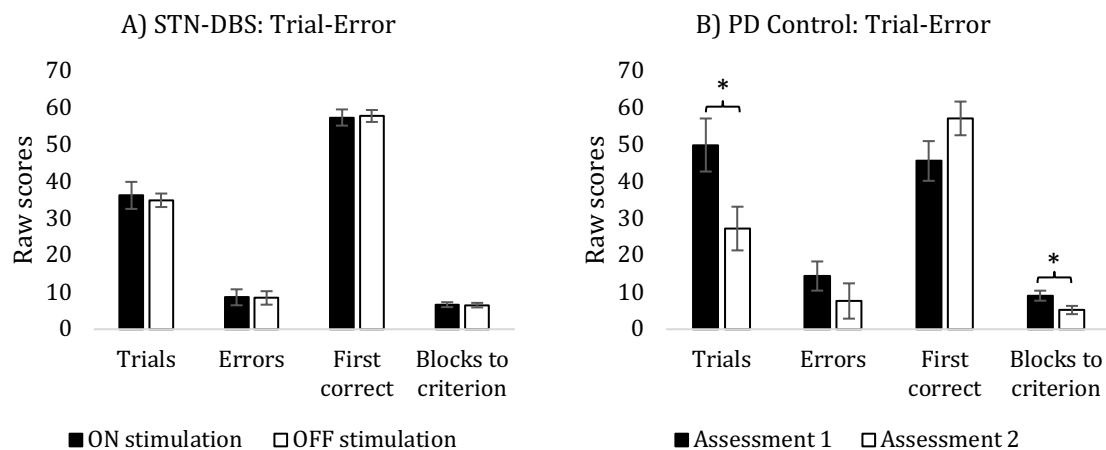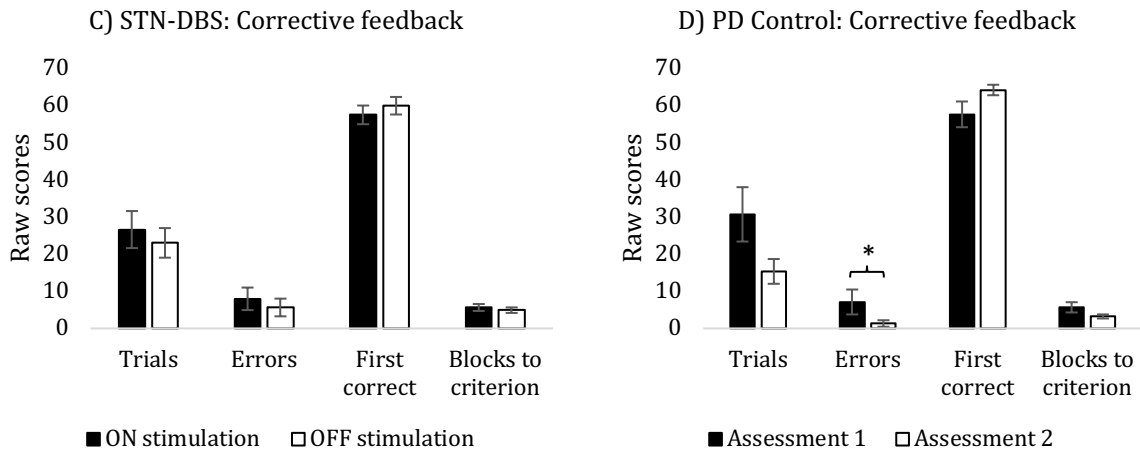
*Figure 4.*2 The mean number of trials, errors, trials correct first time and blocks until criterion was reached on the trial-and-error learning version of the visual conditional associative learning task (VCLT) for (A) the subthalamic nucleus deep brain stimulation (STN-DBS) group with stimulation on and off, and (B) the Parkinson's disease (PD) Control Group at the first and second assessment and on the feedback learning version VCLT for (C) the STN-DBS group with stimulation on and off, and (D) the PD Control group at the first and second assessment.
Error bars represent standard errors.*p<0.05

The unoperated PD control patients had a lower number of trials (Z=-1.99; p=0.046; d=0.89) and a lower number of blocks to criterion (Z=-1.99; p=0.046; 1.28) for the trial-and-error learning version of the task at the second assessment compared to the first assessment (see Figure 4.1B). Also, they produced less errors on the feedback learning version during the second assessment compared to the first assessment (z=-2.02; p=0.043; d=0.67). There was also a change in the number of blocks to criterion that reached borderline significance (Z=-1.89; p=0.058; 0.653). Therefore, control participants reached the criterion within fewer blocks at the second assessment compared to the first assessment (see Figure 4.1D). Figure 4.2 presents the mean number of first correct trials on both versions of the task across 12 blocks for both study groups.

To control for the improvement effect of repeated administration that was observed in the PD control group for the visual conditional associative learning task the above analysis was repeated for those patients who completed the assessment on stimulation first (N=10) and off stimulation first (N=14) separately.

	Task done ON First		Task done OFF First	
	ON stimulation	*OFF stimulation*	*ON stimulation*	*OFF stimulation*
VCLT (trial-error learning)				
Total trials	37.6(13.53)	28.8(8.39)	35.43(21.03)	39.43(20.07)
Errors	9.3(6.07)	5.1(3.45)	8.21(13.19)	10.93(10.92)
Trials correct first time	56.6(6.13)	60.8(3.39)	58.07(13.37)	55.79(9.63)
Blocks to criterion	6.8(1.99)	5.4(1.17)	6.57(1.08)	7.36(3.71)
VCLT (Feedback learning)				
Total trials	29.6(25.54)	14.4(8.1)	24.43(24.28)	29.14(23.04)
Errors	9.5(17.19)	1.0(1.7)	6.86(13.5)	8.93(14.48)
Trials correct first time	56.4(11.03)	64.9(1.66)	58.14(13.51)	56.29(14.22)
Blocks to criterion	6.3(4.69)	3.5(1.35)	5.14(4.55)	5.93(4.43)

Table 4.4 Comparison of the performance on the trial-error and feedback learning versions of the visual conditional associative learning task (VCLT) between the operated patients with Parkinson's disease (PD) who were assessed on and off subthalamic nucleus (STN) stimulation first.
Values represent means and standard deviations (in parentheses) for the different measures of the tasks.

The means and standard deviations for the patient subgroups who completed the tests in the stimulation on and off first are presented in Table 4.4.
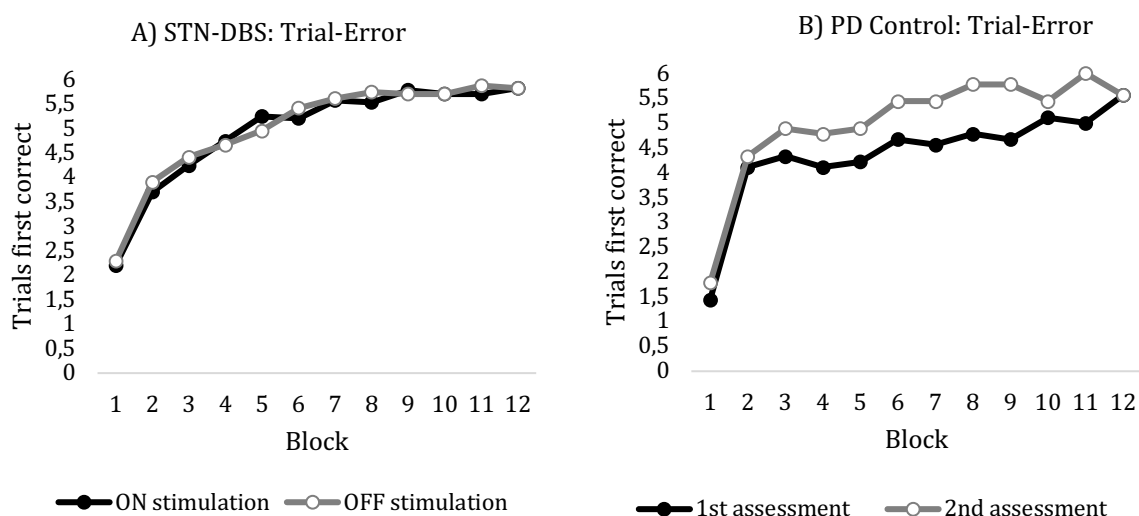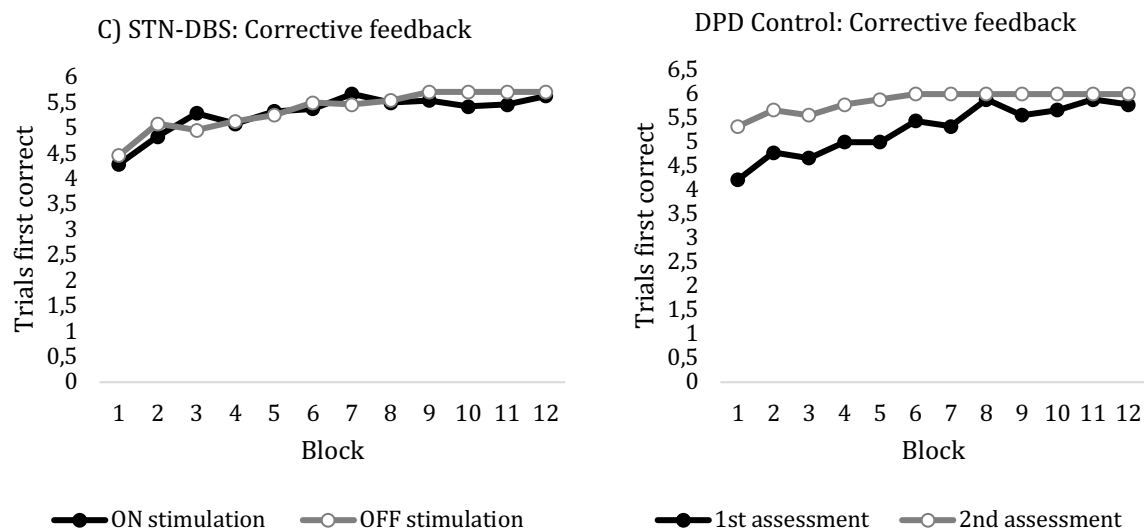
C) STN-DBS: Corrective feedback

DPD Control: Corrective feedback

—●— ON stimulation   —○— OFF stimulation   —●— 1st assessment   —○— 2nd assessment

Figure 4.3 The mean number of trials first correct across 12 blocks on the trial-and-error learning version of the visual conditional associative learning task (VCLT) for (A) the subthalamic nucleus deep brain stimulation (STN-DBS) group with stimulation on and off, and (B) the Parkinsons disease (PD) Control group at the first and second assessment and on the feedback learning version of the VCLT for (C) the STN-DBS group with stimulation on and off, and (D) the PD Control group at the first and second assessment.

For the trial-and-error learning version of the visual conditional associative learning task a series of Wilcoxon signed rank tests revealed significant differences between the on and off stimulation assessments for the patients who were assessed on stimulation first. Therefore, they had fewer trials (Z=-1.97; p=0.049; d=0.82), fewer errors (Z=-2.31; p=0.021; d=0.82) and more 'trials correct first time' (Z=-2.32; p=0.021; d=-0.82) when stimulation was off compared to when it was on. The number of blocks to criterion was also lower off than on stimulation, but this effect only reached borderline significance (Z=-1.79; p=0.072; d=0.71). Overall, these results indicate worse learning on the trial-and-error VCLT on than off stimulation (see Figure 4.3A). There were no significant stimulation effects for the patients who were assessed off stimulation first (all p>0.05).

Figure 4.4 The mean number of trials, errors, trials correct first time and blocks to criterion on the trial-and-error learning version of the visual conditional associative learning task (VCLT), for the patients with deep brain stimulation (DBS) who were assessed (A) on stimulation first and (B) off stimulation first, with stimulation on and off, and on the feedback learning version of the VCLT, for the patients who were assessed (C) on stimulation first and (D) off stimulation first, with stimulation on and off.
Error bars represent standard errors*p<0.05

For the feedback learning version there was an effect of STN stimulation on the number of trials that were correct first time for patients who were assessed on stimulation first (Z=-1.96; p=0.05; d=-0.93). Therefore, they got more trials correct the first time when stimulation was off compared to when it was on (see Figure 4.3C). There were no effects of STN stimulation on any measures in patients who were assessed off first (all p>0.05; see Figure 4.3B and D).

The means and standard deviations for the total number of correct trials for the easy, hard and total items on the Verbal Paired Associate Learning task at the on and off

stimulation sessions for the operated group and at the first and second assessment for the unoperated control group are presented in Table 4.5.

	STN-DBS group		PD Control group	
	ON stimulation	*OFF stimulation*	*Assessment 1*	*Assessment 2*
Correct trials-easy	22.08(2.21)	22.04(2.61)	21.67(1.12)	22.22(2.86)
Correct trials-hard	15.88(6.64)	15.04(6.38)	16.11(5.86)	15.56(6.65)
Correct trials-total	37.96(8.02)	37.08(8.02)	37.78(2.01)	37.78(6.32)

Table 4.5 Comparison of the performance on the trial-error and feedback learning versions of the verbal paired associate learning (PAL) task between the operated and unoperated patients with Parkinson's disease (PD).
Values represent means and standard deviations (in parentheses) for the different measures of the task.
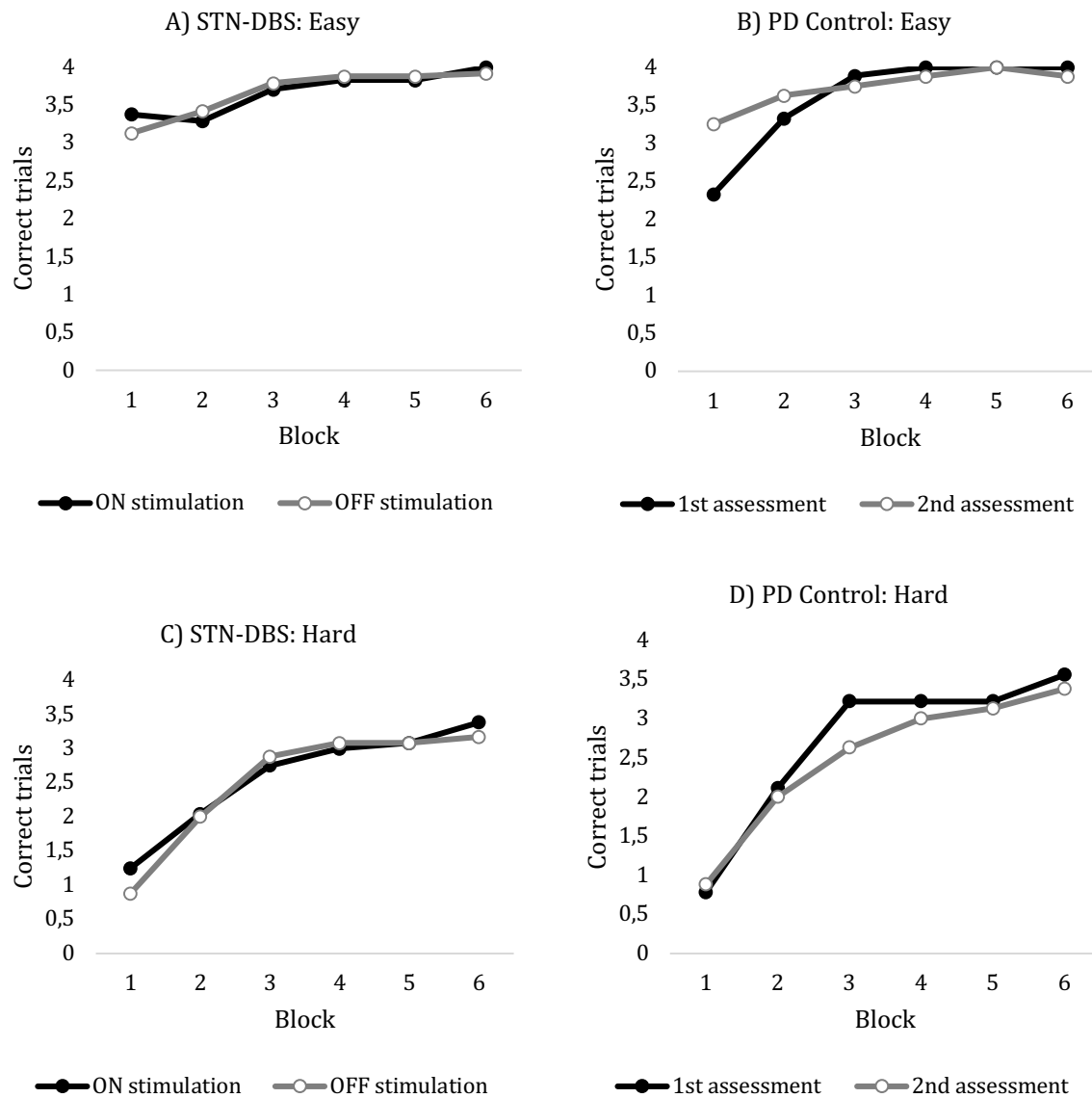
Figure 4.5 The mean number of correct trials first correct across 6 blocks on the easy items of verbal paired associate learning (PAL) task for (A) the subthalamic nucleus deep brain stimulation (STN-DBS) group with stimulation on and off, and (B) the Parkinson's disease (PD) Control group at the first and second assessment and on hard items of the verbal paired associate learning task for (C) the STN-DBS group with stimulation on and off, and (D) the PD Control group at the first and second assessment. The mean number of correct trials across 6 blocks on the easy and hard items of the verbal PAL task for the two study groups.

A series of Wilcoxon signed rank tests did not reveal any changes on the three measures between the on and off stimulation assessments for the operated group or between the first and second assessment for the unoperated control group (all p>0.05). Figure 4.4 presents the mean number of correct trials on the easy and hard items across 6 blocks for the two study groups.

4.3.2 Group differences in the Visual and Verbal Associative Learning tasks

A series of Mann-Whitney U tests did not reveal any differences in any of the measures of the two versions of the visual conditional associative learning task between the stimulation on first, the stimulation off first and the PD control group either at the first or second assessments (p>0.05). Therefore, patients in all three groups did not differ in learning performance independent of the stimulation or assessment order.

A series of Man-Whitney U tests did not reveal any differences between the STN-DBS group and the PD control group in any of the three measures of the verbal paired associative learning task during either assessment (p>0.05). Therefore, patients in the two groups did not differ in learning of the verbal associations.

4.3.3 Effects of learning instructions on the Visual Conditional Associative Learning task

The effects of learning instructions (feedback versus trial-and-error learning) on the learning and performance on the Visual Conditional Associative Learning tasks for the patients in the STN-DBS and PD control groups were analysed separately for each of the two assessments. For the mean and standard deviations of the two groups see Table 4.3. In order to account for any order of stimulation effects, the analyses were repeated for patients who were tested on or off stimulation first.

When patients with STN-DBS were assessed on stimulation a series of Wilcoxon signed rank tests revealed a significant difference in the total number of trials between the two versions of the task (Z=-2.18; p=0.029; d=0.49). The patients required more trials to learn associations on the trial-and-error learning compared to the feedback learning version of the task (see Figure 4.5A). The other measures did not differ between the two tasks (all p>0.05). When the STN-DBS patients were assessed off stimulation a series of Wilcoxon signed rank tests revealed significant differences in all measures between the trial-and-error and feedback learning versions of the task, showing that the patients required more trials (Z=-3.22; p=0.001; d=0.82), produced more errors (Z=-2.38; p=0.017;d=0.29), had fewer trials correct first time (Z=-2.07;p=0.039;d=-0.22) and required more blocks to criterion (Z=-4.29; p<0.001;d=0.62) on the trial-and-error learning compared to the feedback learning version of the task (see Figure 4.5B).
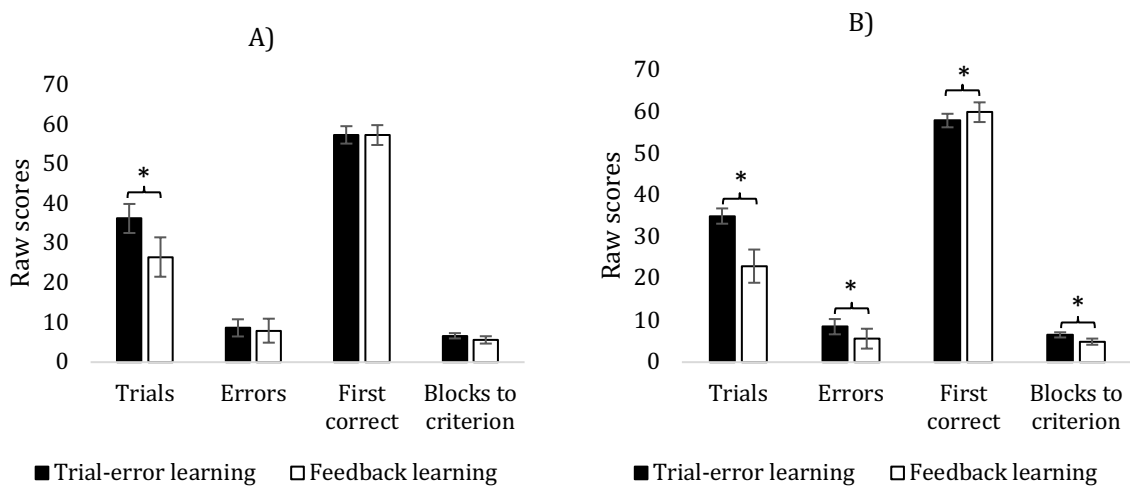
Figure 4.6 The mean number of trials, errors, trials correct first time and blocks to criterion on the two versions of the visual conditional associative learning task for the deep brain stimulation (DBS) group with (A) stimulation on and (B) stimulation off.
Error bars represent standard errors.*p<0.05.

For the patients who were assessed on stimulation first, a series of Wilcoxon signed rank tests revealed significant differences in the measures of the trial-and-error and feedback learning versions of the task for the off stimulation session. The patients had fewer trials (Z=-2.62; p=0.009; d=1.46), fewer errors (Z=-2.61; p=0.009; d=1.31), more trials that were correct the first time (Z=-2.71; p=0.007;d=-1.42) and fewer blocks to criterion (Z=-2.39; p=0.016; d=1.11) on the feedback learning compared to the trial-and-error learning

version (see Figure 4.6A). By contrast, there were no significant differences between any of the measures for the two VCAL learning instructions, feedback versus trial-and-error, when the patients were tested on stimulation (all p>0.05; see Figure 4.6B).
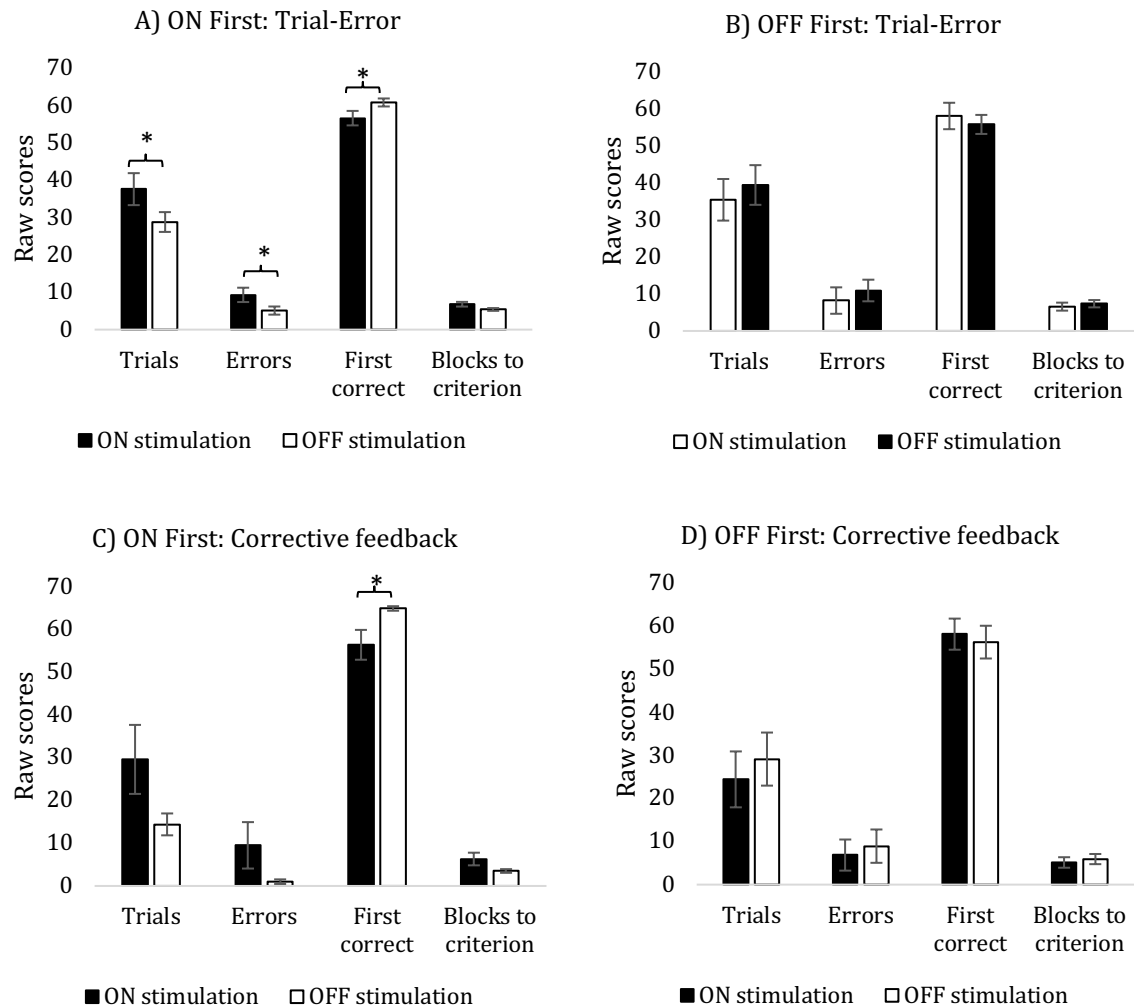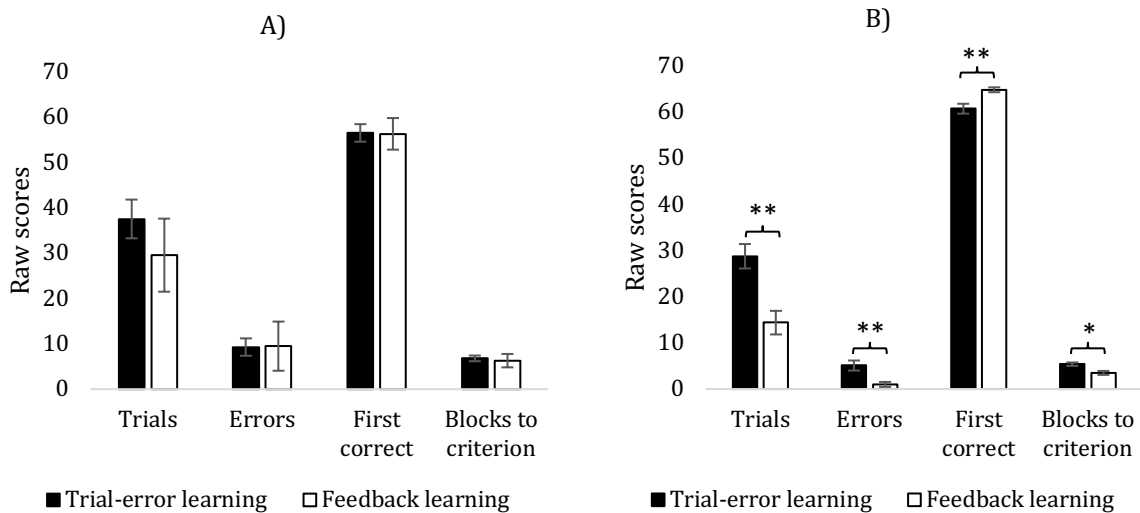

Figure 4.7 The mean number of trials, errors, trials correct first time and blocks to criterion on the two versions of the visual conditional associative learning task for the patients with deep brain stimulation (DBS), who were assessed on stimulation first, with (A) stimulation on and (B) stimulation off. Error bars represent standard errors. *p<0.05,**p<0.001.

For patients who were assessed off stimulation first a series of Wilcoxon signed rank tasks revealed significant differences in the number of trials completed on the two versions of the task both when stimulation was on (Z=-2.01; p=0.044; d=0.52) and when stimulation was off (z=-2.09; p=0.036; d=0.59). Therefore, patients required fewer trials to complete the task for the feedback learning version compared to the trial-and-error learning version (see Figure 4.7A and B). There was also a borderline significant difference in the number of blocks to criterion for the off stimulation first assessment (Z=-1.83; p=0.067; d=0.45). Therefore, patients had fewer blocks to criterion for the feedback compared to the trial-and-error learning version of the task. The remaining comparisons did not reach statistical significance (all p>0.05).
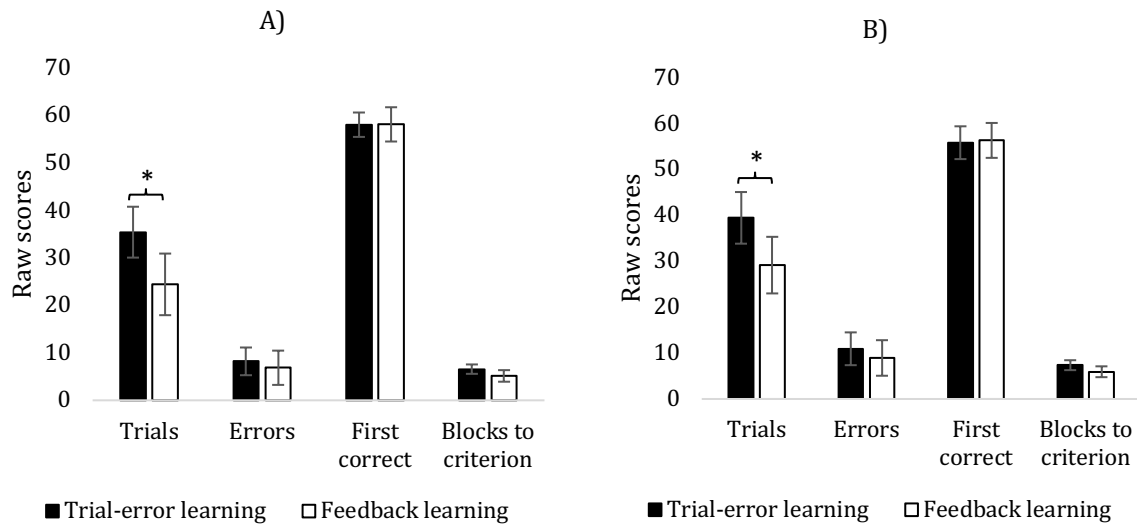
Figure 4.8 The mean number of trials, errors, trials correct first time and blocks to criterion on the two versions of the visual conditional associative learning task for the patients with deep brain stimulation (DBS), who were assessed off stimulation first, with (A) stimulation on and (B) stimulation off. Error bars represent standard errors*p<0.05.

For the PD control patients a series of Wilcoxon signed rank tests revealed differences in the number of trials (Z=-2.410; p=0.016; d=0.922) and number of trials that were correct first time (Z=-1.956; p=0.050; d=-1.027) between the two versions of the task for the first assessment (see Figure 4.8A). The patients required fewer trials to complete and had more correct trials on the feedback compared to the trial-and-error learning version. The difference in the blocks to criterion (Z=-1.85; p=0.064; d=0.72) at the first assessment and the number of trials (Z=-1.87; p=0.062; d=-0.54) at the second assessment both reached borderline significance (see Figure 4.8B). The patients reached criterion with fewer blocks and had fewer total trials for the feedback learning compared to the trial- and error-learning versions of the task, as expected. The remaining comparisons did not reach statistical significance (all p>0.05).
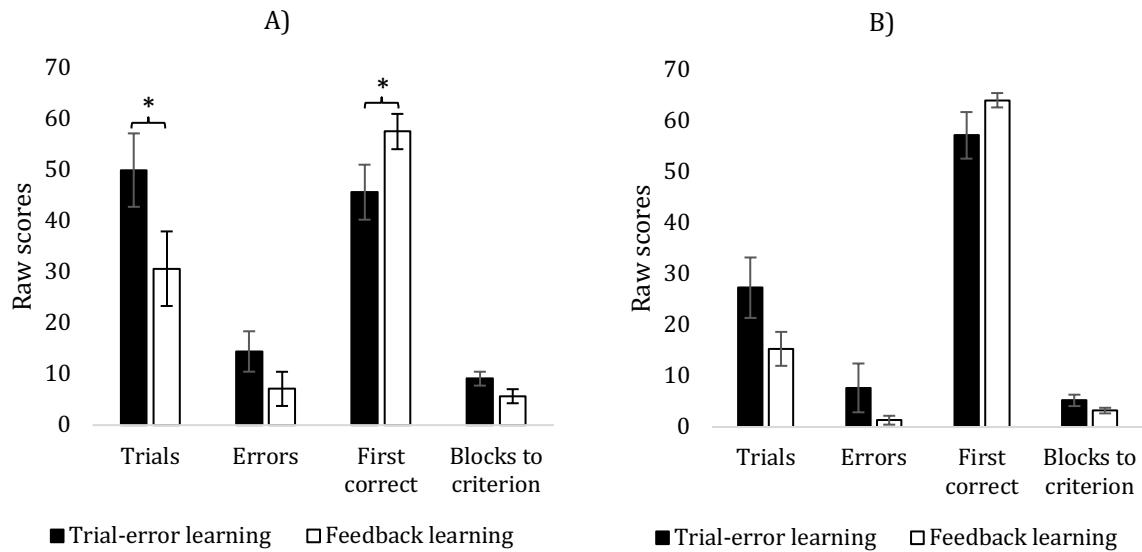
Figure 4.9 The mean number of trials, errors, trials correct first time and blocks to criterion on the two versions of the visual conditional associative learning task for the Parkinson's disease (PD) Control group the (A) first assessment and (B) second assessment.
Error bars represent standard errors*p<0.05.

4.4 Discussion

The general aim of the study was to investigate the effects of acute STN stimulation on CAL. To do so, a total of 33 PD patients were recruited of whom 24 had STN-DBS surgery at least six months before recruitment and 9 were unoperated PD control patients. The patients were matched in age, education and key PD-related variables. Patients in both groups were assessed on the visual conditional associative learning tasks (VCLT) and the verbal paired associate learning (PAL) task twice, the operated group once with their stimulation on and a second time with the stimulation off with order of the on and off assessments being counter-balanced across patients. Furthermore, to investigate how STN stimulation affects different forms of learning in CAL tasks, two learning instructions were used for the VCLT. The classical trial-and-error learning instruction and one feedback learning instruction as suggested by Vriezen and Moscovitch (1990). The hypotheses of the study were: (1) Learning and performance on the trial-and-error learning visual conditional associative learning task would decline with STN stimulation, compared to when stimulation was switched off. (2) Learning and performance on the feedback learning visual conditional associative learning task would remain unchanged with STN stimulation compared to when stimulation was switched off. (3) The total

number of correctly learned associations on the verbal paired associate learning task would decline for the hard items only with STN stimulation, compared to when stimulation was switched off, but would remain stable for the easy items.

4.4.1 The effects of acute STN stimulation on Visual Conditional Associative learning

Analysis of the effects of acute STN stimulation on the trial-and-error learning and feedback learning versions of the VCLT did not reveal any overall significant change in the various measures of the tasks. Previous imaging studies of visual conditional associative learning by trial and error in healthy participants have shown that learning on the task involves the fronto-striatal pathways (Toni et al, 1999; 2001). In the present study based on the results of Jahanshahi et al. (2000a) and the results of the imaging studies (Toni et al, 1999, 2001), it was predicted that STN stimulation would have a negative effect on conditional associative learning by trial and error, based on the assumption that this form of learning would be sensitive to altered output from the striatum to the frontal cortex whereas feedback learning would not be (Vriezen & Moscovitch, 1990). Also, previous research investigating the effects of acute STN stimulation on other tasks sensitive to frontal lobe function which have a learning component, such as the Go no Go reaction time task, indicated a detrimental effect of stimulation (Ballanger et al., 2009; Georgiev et al., 2016; Hershey et al., 2004; Hershey et al., 2010). Despite using four parallel versions of the task, the unoperated PD control group improved on several measures for both versions of the CAL task from the first to the second assessment, indicating a practice effect, an improvement as a result of repeated administration. Therefore, for the trial-and-error learning versions the unoperated PD control patients required fewer trials and fewer blocks to criterion and on the feedback learning version they produced fewer errors during the second compared to the first assessment. The reason for this practice effect may be that the designs used within the parallel versions partially had similar features (e.g. a black-coloured square), making it possible for participants to develop learning strategies during the second assessment.

	PD Control	STN-DBS *on first*	STN-DBS *off first*
Trial-Error CAL	2nd assessment: -Fewer trials -Fewer blocks to criterion	With STN stimulation ON vs. OFF: **-More trials** **-More errors** **-Fewer first trials correct**	No significant differences for DBS on vs. off
Feedback CAL	2nd assessment: - Fewer errors	With STN stimulation ON vs OFF: **-Fewer first trials correct**	No significant differences for DBS on vs. off
Paired associates	No effect of repeated performance	No effect of STN-DBS	No effect of STN-DBS

Table 4.6 Summary of the effects of STN stimulation and repeated performance on the Trial and Error and Feedback versions of the conditional associative learning (CAL) and paired associates tasks. PD=Parkinson's disease; STN=subthalamic nucleus; DBS= deep brain stimulation.

To control for such a potential practice or order of testing effect in the operated group, patients were separated into two subgroups, those who were tested with stimulation 'On First' and those who were tested with stimulation 'Off First'. Interestingly when the effects of stimulation on both versions of the VCLT were analysed for the two stimulation groups separately there were several significant differences between the on and off stimulation assessments for the group that was tested on stimulation first. Therefore, on the trial-and-error learning version of the task patients required more trials to criterion, produced more errors and had fewer first correct trials when stimulation was on compared to when stimulation was switched off, confirming our prediction that STN stimulation would impair learning on this trial-and-error CAL task. On the feedback learning version of the task, patients had fewer first correct trials when they were on stimulation compared to when stimulation was switched off. This suggests that contrary to our second prediction, STN stimulation also impaired learning on the feedback learning version of CAL for a subgroup of the patients tested on stimulation first. For the group assessed off stimulation first, no significant changes on any measure between on and off DBS were found. Table 4.6 presents a summary of the effects of acute STN stimulation and repeated performance on the various VCLT for both learning instructions. It may be suggested that these findings reflect a practice effect for the group of patients who were tested with stimulation on first, whose learning improved on all the measures when assessed on the second occasion off stimulation. Conversely, they may also be the result of changes in proactive interference resolution induced by STN stimulation in the group of patients, who were tested off stimulation first.

Proactive interference occurs when previously learned information interferes with future learning and has been found to be associated with forgetting from long-term memory (McGeoch, 1942) and with age-related cognitive decline (Hasher & Zacks, 1988). Conflict induced by proactive interference results in longer response times (Jonides et al., 1998; D'Esposito et al., 1999; Mecklinger et al. 2003; Nelson et al., 2003). Studies implementing functional imaging to identify brain structures underlying the resolution of proactive interference for tasks, such as the recent-probes task, reported increased activation in the left mid-ventrolateral prefrontal cortex (VLPFC) during negative-recent trials compared to negative-non-recent trials (Jonides et al., 1998, 2000; D'Esposito et al., 1999; Bunge et al., 2001; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). Additional evidence from patients with frontal lobe damage also support the importance of the frontal lobe to occurrence of proactive interference, such that patients with frontal lesions are more susceptible to proactive interference (Gershberg & Shimamura, 1991; Thompson-Schill et al., 2002). One study investigated the brain activity underlying proactive interference during a paired associate learning cued-recall paradigm using fMRI (Henson, Shallice, Josephs & Dolan, 2002). The results indicated increased activation of the left inferior frontal cortex and bilateral frontopolar cortex and the right STN and caudate nucleus in relation to resolution of proactive interference. This imaging finding implicates the STN and caudate as well as the frontal cortex in proactive interference resolution. This would suggest that aside from frontal regions proactive interference resolution may be sensitive to basal ganglia and particularly STN and caudate function. This idea was further supported by research looking at the cognitive effects of pallidotomy that is surgical lesioning of the globus pallidus internus in PD patients (Lombardi et al., 2000; Trepanier, Saint-Cyr, Lozano & Lang, 1998), as increased proactive interference was documented after left-sided surgery compared to patients' pre-operative performance. Similar increase in proactive interference effects have also been documented following STN-DBS surgery in PD (Saint-Cyr et al, 2000). Taking the above findings into account when interpreting the present result, that there was no effect of stimulation on the VCLT in the group that was assessed off stimulation first, it may be proposed that acute STN stimulation interrupted the process of resolving proactive interference or increased the level of proactive interference, which would have confounded the detrimental effect of stimulation on trial-and-error-learning. The result

that the PD control group showed a repeated administration effect may also reflect that unoperated patients without STN-DBS are able to resolve proactive interference normally. This proposal is supported by research that reported normal build up and release of proactive interference in PD patients (Sagar, Sullivan, Cooper & Nigel, 1991).

Analysis of the effect of the different learning instructions for the two versions of the VCLT indicated differences in performance for both the STN-DBS and PD control group. The PD control group performed better on the feedback learning compared to the trial-and-error learning version of the task on both the first and second assessments, with the learning advantage for the feedback task being significant mainly for the first assessment. The former finding was expected considering prior findings in unoperated PD showing a similar advantage for the feedback over trial-and-error learning (Vriezen & Moscovitch, 1990) and the fact that trial-and-error conditional associative learning is more sensitive to fronto-striatal function (Vriezen & Moscovitch, 1990) and requires strategic planning, which becomes impaired early on in PD (Saint-Cyr et al., 1988). Also, it involves working memory, which is also affected by PD (Litvan et al., 2012).

For the STN-DBS group the effect of the learning instruction differed between the on and off stimulation assessments. When stimulation was switched on patients with STN-DBS required fewer trials for completing the feedback learning compared to the trial-and-error learning version of the task with the other measures showing no differences; whereas when stimulation was switched off, learning and performance was superior on all measures for the feedback relative to the trial-and-error version of the task. Thus, they required fewer trials and fewer blocks to criterion, produced fewer errors and had more trials correct first time. These findings suggest that STN-DBS diminishes the previously described effect of learning instruction and the advantage of the feedback over trial-and-error learning (Vriezen & Moscovitch, 1990). Furthermore, it seems that STN stimulation interferes with the patients' ability to use and integrate corrective feedback to guide learning. Table 4.7 presents a summary of the effect of learning instruction.

Summary of the Effect of Learning Instruction – Trial-and-Error vs. Corrective feedback
PD Control Feedback learning advantage over trial-and-error learning at the 1st assessment: fewer trials & more first trials correct.
STN-DBS (whole group) Feedback learning advantage over trial-and-error learning at the off stimulation assessment: **fewer trials, fewer errors, more first trials correct & fewer blocks to criterion.** Feedback learning advantage over trial-and-error learning at the on stimulation assessment: **fewer trials.**
STN-DBS (*on first*) Feedback learning advantage over trial-and-error learning at the off stimulation assessment: **fewer trials, fewer errors, more first trials correct & fewer blocks to criterion.**
STN-DBS (*off first*) Fewer trials on the feedback learning relative to the trial-and-error learning both with STN stimulation on and off.

Table 4.7 Summary of the Effect of Learning Instruction – Trial-and-Error vs. Corrective feedback. PD= Parkinson's disease; ST-DBS= subthalamic nucleus deep brain stimulation.

Again, to control for any effects of repeated administration, analyses were repeated for patients, who were assessed with stimulation 'On First' and 'Off First' separately. Patients who were assessed 'Off First' required fewer trials to complete the feedback learning version relative to the trial-and-error learning version of the task, both with stimulation on and off. Therefore, as expected, they learned the associations faster when learning from corrective feedback than by trial and error. Interestingly, for the group of patients who were assessed 'ON First' there was only a difference in task performance for the two feedback and trial-and-error learning versions when stimulation was off. Therefore, they produced fewer errors, required less trials and blocks to criterion and had more first correct trials during the feedback learning version compared to the trial-and-error learning version only when tested off STN stimulation but not with DBS on. For the subgroup who performed with STN-DBS 'On First', the advantage of feedback over trial-and-error learning was lost when the stimulators were on. This is an interesting finding which suggests that when performed first, unhindered by the potential confounds of practice or proactive interference effects, STN stimulation may interfere with the patients' ability to use corrective feedback to guide their learning. This result has clinical implications, as it suggests that STN-DBS may interfere with the ability to benefit from corrective feedback to guide learning which may influence the extent to which patients may be able to benefit from speech therapy to rectify problems with speech that can occur from STN-DBS surgery.

Figure 4.9 shows how STN-DBS may influence the resolution of proactive interference and in turn the performance on the trial-and-error and feedback learning versions of the VCLT. It is important to mention that the order of the learning instructions was counterbalanced across patients. Therefore, the order of the learning instructions should not have affected the effects of STN stimulation on proactive interference in the case of the VCLT. In order to investigate the effects of acute STN stimulation on proactive interference directly it would be interesting to use tasks such as the California verbal learning test assessing proactive interference more specifically.

These findings for the trial-and-error VCLT are somewhat different from previous studies (Jahanshahi et al., 2000a; Mollion et al., 2011; Ventre-Dominey et al., 2016). Jahanshahi and colleagues (2000a) used the same VCLT in seven patients with STN-DBS and reported that with STN stimulation on patients produced more errors and required more trials to criterion compared to when stimulation was switched off. The current results replicated Jahanshahi et al.'s (2000a) finding only for the subgroup of patients who were tested with STN-DBS first. On the other hand, Mollion and colleagues (2011) and Ventre-Dominey and colleagues (2016) used a task that required patients to learn the associations between colour cues and directions. Both studies reported improved performance when STN stimulation was on compared to when stimulation was switched off. The inconsistency in findings may be explained by differences in properties of the tasks that were administered. Both Jahanshahi et al. (2000a) and the present study used a task that requires participants to learn six different arbitrary associations, whereas Mollion and colleagues (2011) and Ventre-Dominey and colleagues (2016) used a task that requires participants to learn two arbitrary associations. Therefore, the level of cognitive control and load are higher for the former task. Considering that previous research into the effects of acute STN stimulation on different cognitive domains suggests that these depend on the amount of cognitive control and load involved (e.g. Georgiev et al., 2016; Hershey et al., 2004; Williams et al., 2015; Wylie et al., 2010), the different effects of STN stimulation on the different forms of VCLT were to be expected. The effect of acute STN-DBS on VCLT is clearly a topic worthy of further investigation.
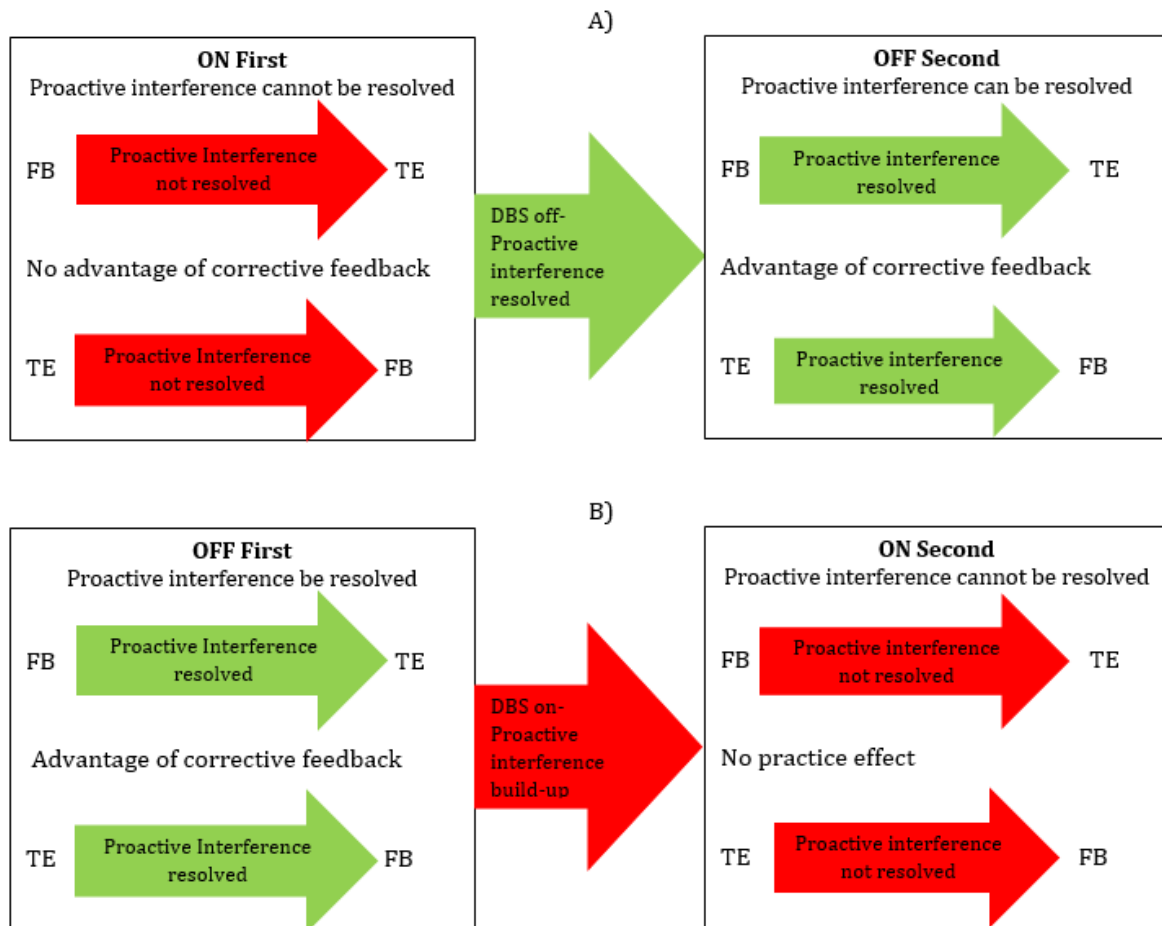
Figure 4.10 Flow chart of how STN stimulation may affect the patients' ability to resolve proactive interference during the two learning instructions of the visual conditional associative learning test. FB=feedback learning; TE=trial-and-error learning; DBS=deep brain stimulation.

4.4.2 The effects of acute STN stimulation on verbal paired associative learning

Analysis of the effects of acute STN stimulation on the PAL task did not reveal any significant changes in the number of correctly recalled associates between the on stimulation and off stimulation assessments for either the hard or the easy items, contrary to our third prediction. There was also no change for the PD control group in the number of correctly named associates between the first and second assessment. This study predicted a negative effect of acute STN stimulation on the number of correctly named hard associates only. This prediction was made based on research into the effects of acute stimulation on several aspects of cognition that found detrimental effects on performance for tasks that require higher levels of cognitive control (Castner et al., 2008a, b; Georgiev et al., 2016; Hershey et al., 2004; Jahanshahi et al., 2000a, b; Thobois et al., 2007; Williams et al., 2015; Wylie et al., 2010b), whereas similar tasks requiring

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less cognitive control remained unchanged or improved with stimulation relative to when stimulation was off (Castner et al., 2008; Georgiev et al., 2016; Hershey et al., 2004; Mollion et al., 2011; Williams et al., 2015; Wylie et al., 2010b; Ventre-Dominey et al., 2016). The reasons for the present results with paired associate learning differing from these previous findings may relate to the nature of the task. Patients' learning was externally driven as paired associates were presented several times. Research into the effects of STN stimulation on both paired associative conditional learning and language function separately reported detrimental effects of STN stimulation only if patients had to generate responses internally (Castner et al., 2008; Jahanshahi et al., 2000a). Additionally, in contrast to the VCLT which involves learning of arbitrary stimulus-stimulus or stimulus-response associations, the PAL uses verbal items that depend on semantic associations and hence require language function, which was unaffected by acute stimulation as in previous studies (Batens et al., 2014; Castner, 2007a, b; Jahanshahi et al., 2000a; Morrison et al., 2004; Pillon et al., 2000; Okun et al., 2009; Silveri et al., 2012; Schulz et al., 2012; Witt et al., 2004). The present findings do not suggest any occurrence of proactive interference during the PAL, as might have been expected from the results on the VCLT mentioned above. This may be explained by the fact that the parallel forms of PAL that were used included associates that were semantically unrelated. Proactive interference usually arises when new information has features overlapping with or similar to previously learned information (Jonides et al., 1998; D'Esposito et al., 1999; Mecklinger et al., 2003; Nelson et al., 2003). One last explanation for the present dissociation of the STN-DBS results for VCLT and PAL may be the patterns of brain activation underlying verbal paired associate learning. Functional imaging studies reported medial temporal lobe activation when participants learned verbal associate pairs (Dolan & Fletcher, 1997; Henkel et al., 1999). Research using single neuron recordings reported activity of neurons in the amygdala, entorhinal cortex and hippocampus during such tasks (Cameron, Yashar, Wilson & Fried, 2001). Considering that acute STN stimulation during performance of verbal cognitive tasks such as verbal fluency or random number generation or the Stroop mainly relates to activity changes in the frontal lobes (Schroeder et al., 2002; 2003; Thobois et al, 2007), this may not lead to changes in word-pair learning.

The present study had a couple of limitations. First, it might have been better to perform the two assessments for each group on different days to avoid fatigue and also control for potential practice and interference effects. However, some of the patients came from outside London and it would have been inconvenient for them to have to travel to the hospital twice. Second, the PD control group was less than half the size of the operated group, making comparisons more difficult. However, the two groups were matched in terms of disease duration. Most patients at that disease stage would also have surgery making it more difficult finding more unoperated patients.

In conclusion, this study was the first to investigate the effects of acute STN stimulation on CAL under different learning instructions: learning by trial and error or through corrective feedback. Furthermore, it investigated the effects on PAL of easy and hard verbal associations. The findings indicated that acute STN stimulation had no overall effect on either trial-and-error learning or feedback learning during a visual CAL task. However, further analysis of order effects showed that this lack of overall impact was due an effect of STN stimulation on the patients' ability to resolve proactive interference. Therefore, patients who were tested off stimulation first did not show any change on learning or performance on the task when they were on stimulation; whereas patients who were tested on stimulation first improved on both versions of the VLCT task when they were subsequently tested off stimulation. Also, patients who were assessed on stimulation first only had a differential learning and performance on the two tasks, with better performance on the feedback version, when they were tested off stimulation but not on stimulation. The benefit of learning with corrective feedback over trial-and-error learning was lost for those tested on STN stimulation first. There was no effect of STN stimulation on the verbal PAL task, suggesting no effect on externally driven associative learning of verbal material. To prevent practice and proactive interference effects, future research should aim to examine the effects of STN-DBS on the trial-and-error and feedback VCLT and the PAL tasks independently on separate samples and conduct the STN-DBS on and off assessment sessions on different days.

Chapter 5. The effects of pedunculopontine nucleus deep brain stimulation in Parkinson's disease and Progressive Supranuclear Palsy on cognition

5.1 Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a highly successful and well-established treatment for the motor symptoms in Parkinson's disease (PD; Deuschl et al., 2006; Follett et al., 2010; Weaver et al., 2012; Williams et al., 2010). However, STN-DBS does not have the desired effect on axial symptoms such as gait abnormalities and postural instability. In PD and atypical Parkinsonism including progressive supranuclear palsy (PSP) cholinergic neurons of the pedunculopontine nucleus (PPN) degenerate (Hirsch et al., 1987; Jellinger, 1988; Schmeichel et al., 2008; Zweig et al., 1987). Proposed motor functions of the PPN include involvement in locomotion (Garcia-Rill, 1991), muscle tone regulation (Garcia-Rill et al., 2004) and voluntary movements (Matsumura, 2005). Therefore, PPN abnormalities seen in PD and PSP may be associated with the postural and gait impairments. This assumption is strengthened by evidence suggesting a correlation between the degree of neuronal loss in the PPN and the severity of motor symptoms (Rinne et al., 2008; Zweig et al., 1989) and PPN lesions produce gait disturbances (Kuo et al., 2008; Masdeu et al., 1994). Based on these findings, the PPN was identified as a new DBS target for treatment of the axial symptoms of PD and PSP. Clinical trials investigating the benefits of low frequency PPN-DBS for motor symptoms have reported mixed results. The greatest improvement of axial symptoms was elicited by a combination of PPN- and STN-DBS (Hamani et al., 2007; Lozano & Snyder, 2008; Lozano et al., 2010; Mazzone et al., 2005; Plaha & Gill, 2005; Stefani et al., 2007), and unilateral PPN-DBS reduced freezing and falls (Ferraye et al., 2008; Moro et al., 2010). Low frequency PPN-DBS improves Unified Parkinson's Disease Rating Scale scores on average by 33% (Stefani et al., 2007).

Since PPN-DBS is a relatively new treatment approach, only a handful or studies have investigated its' effects on cognitive function. These studies are listed and their methods and findings are summarized in Table 5.1. The findings of these studies are diverse. Zanini and colleagues (2009) reported unchanged cognition 6 to 12 months after surgery but reported that acute low frequency PPN stimulation improved grammatical aspects of language in 5 PD patients. Furthermore, it has also been suggested that PPN stimulation improved delayed verbal recall (Ceravolo et al., 2011). On the other hand, Pinto et al.

(2004) found speech degradation in 7 PD patients 12 months after PPN-DBS surgery. Brusa and colleagues (2009) indicated only minor improvements in verbal fluency in a single case of PSP when PPN stimulation was off, but this effect was not observed when stimulation was on. From these mixed findings, it is not possible to conclude what impact PPN-DBS has on language. Across these studies, the other cognitive domains that were altered by PPN-DBS included working memory (Costa et al., 2010), attention (Thevathasan et al., 2010) and executive functions (Ceravolo et al., 2011). These studies implemented the stimulation on versus off methodology and do not provide comparisons to participants' pre-operative performance. Costa and colleagues (2010) reported a decreased/faster response time on an n-back task when patients were on low frequency PPN stimulation compared to when stimulation was switched off. The authors argued that this reflected a modulation of attentional resources. Thevathasan et al. (2010) reported similar results from a reaction time task, indicating improved attention with low frequency PPN stimulation. One study identified beneficial effects of acute low frequency PPN stimulation for executive function as measured by the trail making and phonemic verbal fluency tests (Ceravolo et al., 2011). Recently a case with Parkinson's disease dementia (PD-D) was described and the results indicated that unilateral low frequency PPN stimulation led to improved global cognition compared to when stimulation was switched off (Riccardi et al., 2015).

However, the above findings need careful consideration as they are all based on small samples ranging from 1 to 11 patients and most studies (5 of the 7) included patients who had both STN or zona incerta and PPN-DBS. Furthermore, with exceptions (Costa et al, 2010), most studies only included a limited neuropsychological battery. Also, a large proportion of studies investigated stimulation effects only and failed to examine the effects of PPN-DBS surgery by comparing pre- and post-operative cognitive performance. The few reports of pre- and post-operative data (Brusa et al., 2009; Pinto et al., 2014; Riccardi et al., 2015; Zanini et al., 2009) indicate only minor changes. Therefore, the nature of any cognitive changes that can be solely attributed to PPN-DBS remains unclear.

Investigators	N	DBS Side	Follow-up months	Neuropsychological tests	Findings relating to motor symptoms	Findings relating to Cognition
Zanini et al. (2009)	5 PD	Bilateral PPN Bilateral STN	6,12	Story generation task	UPDRS-III improved	Grammatical aspects of language improved with low frequency stimulation
Brusa et al. (2009)	1 PSP	Unilateral PPN Right	4,6,9	CVLT, phonemic VF, TMT, digit span	UPDRS-III modestly improved	Minimal verbal fluency improvement
Costa et al. (2010)	5 PD	Bilateral PPN Bilateral STN	3	Modified card sorting test, phonemic VF, RPM, RAVLT, Rey's complex figure test, digit span, Corsi's block tapping, TMT	UPDRS-III improved	Significant working memory improvement
Thevathasan et al. (2010)	11 PD	Bilateral PPN Unilateral PPN Bilateral ZI	2-38	Simple reaction time task, digit vigilance task, choice reaction time task	Gait and balance improved	In attention test speed but not accuracy of reaction improved
Ceravolo et al. (2011)	6 PD	Bilateral PPN Bilateral STN	12	CVLT, digit span, TMT, phonemic VF, BNT	UPDRS-III improved	Executive functions and delayed verbal recall improved
Pinto et al. (2014)	7 PD	Bilateral PPN Bilateral STN	12	Speech task	Not assessed	Speech degradation
Ricciardi et al. (2015)	1 PD-D	Unilateral PPN	6, 48	MMSE, RPM47, RAVLT, digit span, VF, nouns naming, copying, MFTC, Stroop	UPDRS-III improved slightly	Improvement of global cognition.

Table 5.1 Effects of pedunculopontine nucleus deep brain stimulation (PPN-DBS) on cognitive function.
PD= Parkinson's disease; PD-D= Parkinson's disease dementia; PSP= Progressive supranuclear palsy; PPN = Pedunculopontine nucleus; STN= Subthalamic nucleus; ZI= Zona incerta; UPDRS= Unified Parkinson's disease rating scale; CVLT= California verbal learning test; VF= Verbal fluency; TMT= Trial making test; RPM= Rey's

progressive matrices; RAVLT= Rey auditory verbal learning test; BNT= Boston naming test; MMSE= mini mental status examination; MFTC= Multiple features target cancellation.

The aim of this study was twofold. First, to identify the 'pure' or 'direct' effects of PPN-DBS on cognition, we examined the performance of 7 patients with PD or PSP who had solely PPN-DBS on a large neuropsychological battery before and one year after surgery. Second, in light of suggestions from a previous single case study (Riccardi et al, 2015) of the beneficial effects of acute PPN stimulation on global aspects of cognition in PD-D, we investigated the effects of six weeks of PPN stimulation on cognition by assessing two cases, one with PD and one with PSP, who developed dementia following surgery.

5.2 Methods

5.2.1 Participants

For the first part of the study five patients (5 males) with the clinical diagnosis of Parkinson's disease based on the UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) and two patients with the clinical diagnosis of Progressive supranuclear palsy (1 male) based on the National Institute of Neurological Disorders and Society for PSP (NINDS-SPSP) criteria (Litvan et al., 1996) were assessed. Before surgery, the PD patients were assessed on the Unified Parkinson's Disease Rating Scale (UPDRS: Fahn & Elton, 1987) and the PSP patients were assessed on the Progressive Supranuclear Palsy Rating Scale (PSPRS: Golbe & Ohman-Strickland, 2007). The mean age was 68.0 years (SD=5.54; range 59-74). All patients had PPN-DBS surgery, which was unilateral in 6 and bilateral in one case. The demographic and clinical information for the sample at baseline are presented in Table 5.2. At the one-year follow-up assessment, low-frequency PPN stimulation was switched on in the patients with PD only.

Patient	Age	Gender	Years of Education	Disease Duration years	UPDRS/ PSPRS	Operation side	MMSE	BDI	SAS
PD 1	71	M	17	21	20	R	30	2	7
PD 2	74	M	13	9	39	L	29	16	23
PD 3	70	M	19	17	23	L	29	12	6
PD 4	66	M	10	3	31	L	28	3	2
PD 5	73	M	10	11	16	B	27	19	21
PSP 1	59	F	16	2	30	L	30	33	18
PSP 2	63	M	10	8	44	L	27	2	8

Table 5.2 Demographic and clinical information for the seven patients with Parkinson's disease (PD) or Progressive supranuclear palsy (PSP).

M=Male; F=Female; PD=Parkinson's disease; PSP=Progressive Supranuclear Palsy; UPDRs=Unified Parkinson's disease rating scale; PSPRS=Progressive supranuclear palsy rating scale; R=Right; L=Left; B=Bilateral; MMSE=Mini Mental State Examination; BDI Beck Depression Inventory; SAS= Starkstein Apathy Scale.

For the second part of the study one female patient with the clinical diagnosis of PSP and one male patient with the clinical diagnosis of PD were assessed. Both patients had left-sided PPN-DBS and developed dementia following surgery. The demographic and clinical information for both patients at baseline is presented in Table 5.3.

Patient	Age years	Gender	Years of Education	Disease Duration years	MMSE	DRS-2 Scaled score
PSP 1	63	F	16	6	28	3
PD 1	76	M	17	26	21	4

Table 5.3 Demographic and clinical information for the two patients who developed dementia after surgery. F=Female: M=Male; PSP=Progressive Supranuclear Palsy; PD-D=Parkinson's disease with Dementia; MMSE=Mini Mental State Examination; DRS-2=Dementia rating scale version 2.

5.2.2 Design

For the first part of the study a within subject repeated measures design was used. Each participant completed the neuropsychological assessment two times. Patients were assessed shortly (within one month prior) before having PPN-DBS surgery and a second time one year after the surgery.

For the second part of the study a within subject repeated measures design was used. Each of the two patients completed the neuropsychological assessment two times. The patients were assessed after having been chronically off stimulation at the first session, and following re-introduction of low frequency PPN stimulation for six weeks at the second session conducted six weeks after the first.

5.2.3 Neuropsychological assessment

An extensive neuropsychological test battery was compiled to assess all major cognitive domains with the major focus on executive function, which is particularly impaired in PD. Selected tasks had little motor and timed elements to reduce interfering effects of motor slowness in PD on cognitive task performance. The Mini Mental State Examination (MMSE, Folstein, Folstein & McHugh, 1975) and the Dementia rating scale, second edition

(DRS-II, Jurica, Leitten & Mattis, 2004) were administered to evaluate global cognitive function.

Mini Mental State Examination (MMSE, Folstein et al., 1995) is a short questionnaire that assesses several aspects of cognition, including orientation in time and place, registration, attention and working memory, recall, language, repetition and the execution of complex demands. The maximum score is 30 points and scores of 24 points and above indicate normal cognition, whereas scores below that indicate mild (19-23 points), moderate (10-18 points) or severe (9 points or below) cognitive impairments. For PD patients, it was proposed that scores above 26 points reflect normal cognition and scores below 26 points reflect impaired cognition (Dubois et al., 2007)

Dementia Rating Scale-2 (DRS-2, Jurica et al., 2004) is a more extensive measurement of global cognition assessing attention, initiation and perseveration, construction, conceptualization and memory. The maximum score on the DRS-2 is 144 and raw scores on the separate subscales were transformed into age-corrected scaled scores ranging from 2 to 18 (Lucas et al., 1998). Scaled scores of 14 to 18 indicate intact performance above average, scaled scores of 11 to 13 indicate intact performance in the average range, scaled scores of 9 and 10 indicate intact performance below average and any scaled score below that indicates mildly (6 to 8), moderately (4 and 5) or severely (3 and 2) impaired performance.

National Adult Reading Test (NART, Nelson & Willison, 1991) provides estimates of premorbid Full scale IQ. The NART involves reading 50 words with increasing levels of difficulty. Average premorbid Full scale IQ of 100 requires the correct pronunciation of at least half of the words.

Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999): The vocabulary and matrix reasoning subtests of the WASI were administered to evaluate current Full Scale IQ. The vocabulary subtest was used to measure expressive vocabulary, verbal knowledge and information resources with a maximum score of 80 points. The Matrix reasoning subtest was used to measure nonverbal fluid reasoning and general intellectual

ability with a maximum score of 32. Raw scores of the WASI subtests were transformed into age-corrected T-scores, from which a Full Scale IQ was obtained relative to normative data.

Wechsler Adult Intelligence Scale–III (WAIS-III) Working Memory Index (WMI) and Processing Speed Index (PSI) (Wechsler, 1997): To assess the participants' working memory, the digit span, number-letter sequencing and arithmetic subtests from the WAIS-III were completed. The digit span subtest involves the recall of a sequence of numbers between 1 and 9 of increasing length either in the same (Digit Span Forward) or reverse (digit Spam Backward) order. The letter-number sequencing subtest involves the orientation of a sequence of intermixed letters and numbers of increasing length, which the patient has to hold in working memory and recall in the following order: first the numbers in increasing order followed by the letters in alphabetical order. The arithmetic subtest involves solving a series of mental arithmetic problems of increasing difficulty and complexity. For each subtest, raw scores were transformed into age-corrected scaled scores ranging from 1 to 19 with a scaled score of 10 reflecting average performance. From the sum of the scaled scores, a WMI was obtained relative to the normative data.

The symbol search and digit symbol subtests from the WAIS-III were administered to obtain the Processing Speed Index (PSI). During the symbol search subtest participants are provided with two symbol groups, one target and one search group and are asked to indicate whether either of the two target symbols is in the search group within the limit of 120 seconds. During the digit-symbol subtest participants are provided with individual symbols associated with each of the numbers 1 to 9 and requested to draw for as many random numbers as possible the corresponding symbols within a 120 seconds time limit. Both these subtests measure visually guided processing speed and the digit symbol subscale has an additional visuospatial component. Similar to the previously described WAIS-III subtests scaled scores were calculated from raw scores and then the PSI was obtained relative to normative data.

California Verbal Learning test (CVLT, Delis, Kramer & Kaplan, 1987) was administered to assess immediate and delayed verbal memory. The test requires participants to listen to a list of 16 words (List A) in 5 consecutive trials and recall as many words as possible from that list after each trial. There are four more recall trials of List A (short-delay free and cued recall; long-delay free and cued recall), followed by yes/no and forced choice recognition tests. In addition to the number of words correctly recalled, the number of intrusion and repetition errors were also recorded for the free recall trials and the number of false positives for the yes/no recognition test. The raw scores on the total amount of words recalled on trials 1 to 5 were transformed into t-scores.

Visual Conditional Associative Learning Task (VCLT; Petrides, 1985; Gotham et al., 1988) was also completed in order to assess associative learning of non-verbal information. During the task participants are required to learn arbitrary associations between 6 abstract geometric designs and 6 colours (red, black, yellow, green, blue and brown) by trial and error within maximal 12 blocks. The test material consists of six cards each showing one colour and six cards each showing all six designs in random order. During every block of trials the participants are presented with each colour in a predetermined order and asked to indicate, which design they thought was associated with that colour. For each selection, participants are told if they were correct or not. If the selection was wrong the participants continue to choose other designs until they find the correct association. The task is discontinued if two consecutive blocks of trials were correct. The number of errors, the number of trials that were correct first time, the total number of trials and the number of blocks till criterion was reached were recorded.

Delis-Kaplan Executive Function Scale (DKEFS, Delis, Kaplan & Kramer, 2001a, b) was used for the assessment of executive function, specifically 3 of the subtests: the Stroop colour-word interference, the Trail making and the verbal fluency were used.

Stroop Colour-Word interference task has four conditions each consisting of 100 items. Each time the participants are instructed to perform the task as quickly as possible and to correct themselves if they make any errors and then carry one. During the 'colour-

naming' condition participants are requested to name the ink colours of rectangles, during the 'word-reading' condition they are requested to read colour-words (red, blue, green) that are printed in black ink, during the 'interference' condition participants are requested to name the ink colour of colour-words that are printed in incongruent ink colour (e.g. the word red printed in blue ink) and during the 'switching-interference' condition patients have to switch between naming the ink colour of colour-words that are printed in incongruent colour or to read the word if framed by a black rectangle. Each condition is discontinued after a certain amount of time is exceeded. For condition 1 and 2 the time limit is 90 seconds and for condition 3 and 4 the time limit is 180 seconds. The time (seconds) taken to complete each condition and total number of errors were recorded. The colour-word interference test measures processing speed, inhibition of habitual reading responses and switching between automatic and controlled responses.

Trail Making Test has five conditions. For 4 of them participants are presented with an A3 sheet showing letters and numbers that are randomly spread across the sheet. During the 'visual scanning' condition participant are requested to cross out all the 3s they can find, during the 'number sequencing' condition participants are asked to connect the numbers 1 to 16 in increasing order (e.g. 1-2-3-4), during the 'letter sequencing' condition participants are instructed to connect the letters A to P in alphabetical order (e.g. A-B-C-D), during the 'number-letter sequencing' condition participants are instructed to connect numbers and letters 1 to P in alternating order (e.g. 1-A-2-B-3-C), and during the 'motor speed' condition participants are instructed to follow dotted lines between empty circles. Each condition is discontinued after 150 seconds, except for condition 4, which is discontinued after 240 seconds. The time (seconds) taken to complete each condition was recorded. The Trail making test measures behavioural regulation, visuospatial function, processing speed and response switching.

Verbal Fluency test has three conditions. During the 'letter' fluency condition participants are given three letters (F-A-S), one at a time and are asked to produce as many words as they could think of starting with that letter in in 1 minute, during the 'category' fluency condition participants are given two categories (animals or items of clothing), one at a time and are asked to produce as many words belonging to that

category as they could think of in 1 minute. During the 'category switching' condition, patients are given two categories (Furniture and Boy's names) and asked to produce as many words as they could think of and alternate between words belonging to one or the other category. The number of correct words produced was recorded for all three conditions and for the third condition the number of correct switches was also recorded. This test measures the ability to fluently generate words according to a phonemic criterion or belonging to a semantic category or switching between two semantic categories. The raw scores on the three DKEFS subtests (time in seconds for colour-word interference and trail making tests and number of correct words/switches for the verbal fluency test) were transformed into age-corrected scaled scores.

To screen for depression and apathy the Beck Depression Inventory (BDI, Beck et al., 1961) and the Starkstein apathy Scale (SAS, Starkstein et al., 1992) were administered respectively. The BDI has 21 items and scores can range between 0 and 63 points, with 0 to 13 points indicating no depression, 14 to 19 points indicating mild depression, 20 to 28 points indicating moderate depression and 29 to 63 points indicating severe depression. The SAS has 14 items and scores range from 0 to 42 with higher scores indicating higher levels of apathy. The cut-off score is 14.

For the assessment of the short-term acute PPN stimulation effects in the two patients who developed dementia after surgery, a shorter test battery was used. This included the MMSE, the DRS-2, the three DKEFS subtests letter and category verbal fluency, the interference and switching interference conditions on the Colour-word interference test, the letter- and letter-number sequencing conditions of the Trail-making subtest; the WAIS-III digit span; and CVLT. Language was assessed using two spontaneous speech tests – one providing a picture for the participant to describe (cued speech) and the other asking the participant to describe their last holiday (free speech) – and a sentence construction task. Additionally, a simple and a five-choice reaction time task were respectively used to assess processing speed and sustained attention and alertness. During the simple reaction time task, participants were instructed to continuously press a button and respond as quickly as possible to a stimulus that appeared on a computer screen by releasing the button. The number of errors and correct responses, reaction time

and movement time in milliseconds were recorded. During the five-choice reaction time task participants were firstly shown with 1 of 5 stimuli followed by presentation of all 5 stimuli and were instructed to touch the stimulus they had just seen as quickly as possible. For this task the same measures as for the simple reaction time task were recorded. Depression and apathy were also assessed with the BDI, SAS and the Hospital Anxiety and Depression scales (HADS, Zigmond & Snaith, 1983). The HADS scales have 7 items each for anxiety and depression and the scores range between 0 to 21 points for both subscales with a cut-off of 8 points. Higher scores indicate higher anxiety and depression levels.

5.2.4 Statistical analysis

To analyse the effects of PPN-DBS surgery on different cognitive domains a series of paired t-tests was performed, with 'assessment time' (pre-operative versus post-operative) as the independent variable and the various cognitive tests as the dependent variables. For variables where the normality assumptions for a t-test were not met, a non-parametric Wilcoxon signed rank test was performed. For changes that reached statistical significance Cohen's d was calculated to evaluate the robustness of the change. An effect size of 0.2 is considered a small effect, of 0.5 a moderate effect and of 0.8 a large effect (Cohen, 1992). To determine effects for the PD group, Wilcoxon signed rank tests were also performed for the 5 PD patients only. Reliable change indices (RCI) were computed to assess for statistically reliable decline increase or no change in a neuropsychological score from the pre- to post-operative assessments, while taking into account the reliability of the test, indicating a significant change in score not attributable to measurement variability (Jacobson & Turax, 1991). The formula for calculating the RCI is: RCI = x_1-x_2/S_{diff} (baseline score – follow-up score/ standard error of the difference. The S_{diff} is calculated $\sqrt{2}(S_E)$, with S_E being the standard error of the measurement. RCIs of -1.96 or lower were considered as reliable decline, RCIs of 1.96 or above were considered as reliable increase and RCIs in-between were considered as no change. The 95% RCI criterion is calculated S_{diff} x 1.96. For tests on which at least 50% of patients declined reliably, z-scores were calculated based on suitable sample means and standard deviations and plotted for each participant. As mentioned in the introduction chapter Bonferroni correction was not applied. Despite it overcoming the risk of giving too much

weight to what may be differences obtained by chance due to multiple comparisons, it may also increase the risk of a type two error that is accepting the null hypothesis when it is in fact false. From a clinical point of view, this would be problematic when considering changes in cognition with DBS of the PPN, as it would result in important changes to be overlooked.

To assess the effects of acute low frequency PPN stimulation in the two patients who developed dementia following surgery, descriptive analysis was done in order to identify any change in cognition between off stimulation and after 6 weeks of continuous PPN stimulation.

5.3 Results

5.3.1 Effects of PPN-DBS surgery on cognition

The means and standard deviations of the scores on the tests of cognitive function before and 12 months after surgery are presented in Table 5.4. Values represent scaled scores, unless indicated otherwise. Comparisons of the patients' performance on the neuropsychological tests between the pre- and post-operative assessments revealed decline in performance in several cognitive domains.

The effect of surgery on the total DRS-2 score was large (d=0.81) but failed to reach statistical significance (t(6)=1.99; 0.094). This indicates a moderate decline in overall performance on the DRS-2 from before to after surgery. Paired t-tests evaluating the effects of surgery on the different subscales of the DRS-2 revealed a significant decline on the Initiation/Perseveration subscale only (t(5)=1.78; p=0.038; d=1.28), from before to after surgery. There was no effect of surgery for the other DRS-2 subscales. Figure 5.1 shows the scaled score on the total DRS-2 and the different subscales before and after surgery.
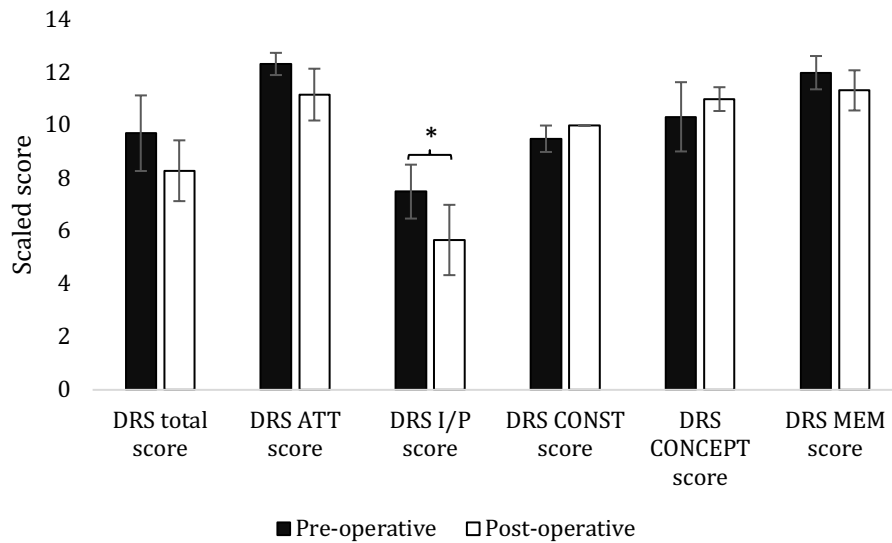
Figure 5.1 Mean age-corrected scaled scores on the total Dementia Rating Scale (DRS-II) and the five DRS-II subscales before and after surgery.
Error bars represent standard errors.*p<0.05. ATT=Attention; I/P=Initiation/Perseveration; CONST= Construction; CONCEPT=Conceptualization; MEM=Memory.

On the CVLT, the total number of words that were recalled on trials 1 to 5 were significantly lower after than before surgery (t(5)=3.09; p=0.027; d=1.34). Figure 5.2 shows the T-scores for the total number of words recalled on trials 1 to 5 before and after surgery. There was no effect of surgery on the free and cued short and long delay recall trials, on the yes or no and forced recognition trials and on the number of intrusion and repetition errors (all p>0.05).
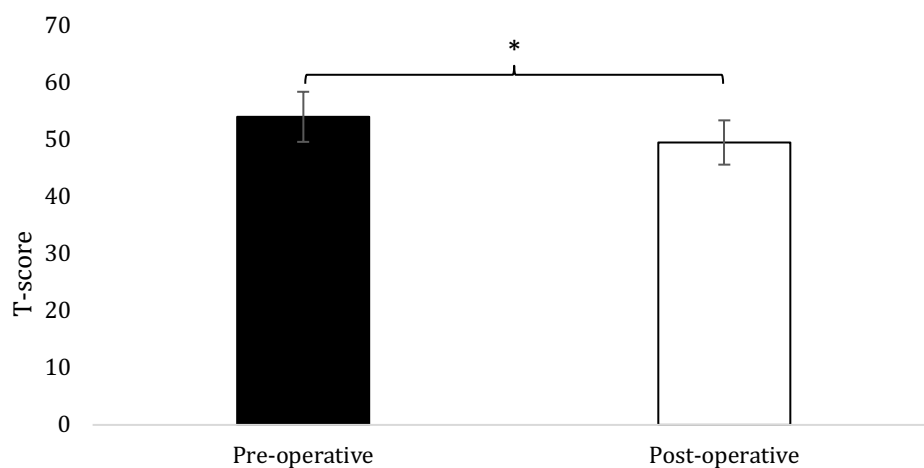
Figure 5.2 Mean T-scores for trials 1 to 5 of the California Verbal Learning Test before and after surgery.
Error bars represent standard errors.*p<0.05

A series of paired t-tests revealed worse performance on the colour naming condition of the DKEFS colour word interference task (t(5)=3.51; p=0.017; d=2.05) from before to after surgery. The effects of surgery on the word reading (t(5)=2.45; p=0.058; d=1.04) and switching/interference (t(5)=2.45; p=0.058; d=1) conditions approached significance, also suggestive of slowing of performance after surgery. There was no significant effect of surgery on the interference condition (t(6)=1.6; p=0.16) Figure 5.3 shows the mean scaled scores for the different colour-word interference subtests before and after surgery. A series of Wilcoxon signed rank tests did not show any significant effects of PPN-DBS surgery on the number of errors made on the four conditions, however the effect on total errors made on the switching/interference condition reached borderline significance (z=-1.83; p=0.068), indicating that patients made more errors post-operatively compared to before surgery.

The category switching verbal fluency task of the DKEFS was worse after compared to before surgery both in terms of the number of correct words generated (t(6)=3.8; p=0.009; d=1.5) and the number of correct switches (t(6)=3.74; p=0.01; d=1.43). The effect of surgery on category verbal fluency was large but the decline failed to reach statistical significance (t(6)=2.12; p=0.078; d=0.9). The effect of surgery on letter verbal fluency was not significant (t(6)=1.54; p=0.17). Figure 5.4 shows mean scaled scores for the different verbal fluency subtests before and after surgery.

Neuropsychological test	N	Pre-operative assessment	N	Post-operative assessment	P-value
DRS-2					
Attention	6	12.33 (1.03)	6	11.17 (2.4)	0.135
Initiation/Perseveration[1]	6	7.5 (2.5)	6	5.67 (3.27)	0.038
Construction	6	9.5 (1.22)	6	10 (0)	0.363
Conceptualization	6	10.33 (3.2)	6	11 (1.1)	0.699
Memory	6	12 (1.55)	6	11.33 (1.86)	0.501
Total Score	7	9.71 (3.77)	7	8.29 (3.04)	0.093
NART					
Premorbid Estimated Full scale IQ	7	107.29 (12.57)	7	109.86 (12.9)	0.179
WASI					
Vocabulary[1]	6	48.5 (17.48)	6	42.5 (16.07)	0.410
Matrix reasoning[1]	6	54.33 (8.69)	6	51.83 (10.19)	0.120
Full scale IQ	6	103.5 (18.51)	6	97 (16.53)	0.316
CVLT					
Total recall trials 1 to 5[1]	6	54 (10.75)	6	49.5 (9.5)	0.027
Free short-delay recall[2]	6	9.17 (3.31)	6	8.67(3.2)	0.737

Cued short-delay recall[2]	6	10.33 (2.5)	6	10.83 (3.06)	0.415
Free long-delay recall[2]	6	9.67 (1.97)	6	9.83 (2.99)	0.842
Cued long-delay recall[2]	6	10.67 (2.94)	6	10.33 (2.8)	0.611
Total intrusions[2]	6	4 (3.58)	6	5.5 (5.39)	0.537
Total repetitions[2]	6	5.17 (3.82)	6	6.17 (4.26)	0.562
Yes/No Recognition Total correct[2]	6	15 (1.1)	6	15.5 (0.84)	0.203
Recognition false positives[2]	6	5.5 (5.92)	6	3.83 (3.87)	0.489
Forced choice recognition percentage correct	6	98.96 (2.55)	6	100 (0)	0.363
WAIS-III					
Digit Span	7	9.86 (1.86)	7	10.43 (2.07)	0.386
Letter-number sequencing	6	8.83 (3.06)	6	8.67 (3.27)	0.907
Arithmetic	7	9.71 (2.87)	7	10.29 (2.87)	0.172
Working Memory Index	6	98 (10.73)	6	98.5 (9.33)	0.276
Digit symbol	7	5.86 (1.77)	7	5.14 (2.34)	0.499
Symbol search	7	8.29 (2.29)	7	6.43 (2.51)	0.081
Processing Speed Index	7	78.57 (12.27)	7	73.43 (8.73)	0.411
Visual Conditional Associative Learning task					
Total trials[2]	6	71.8 (67.16)	4	82.5 (49.11)	Not applicable
Total errors[2]	6	33.83 (45.01)	4	33.25 (30.92)	Not applicable
Blocks to criterion[2]	6	7.5 (4.64)	4	9.75 (3.77)	Not applicable
First trial correct[2]	6	50.83 (17.16)	4	49.25 (14.24)	Not applicable
DKEFS					
Word interference-colour naming	6	5.5 (3.21)	6	2.83 (1.83)	0.017
Total errors[2]		0 (0)		0.17 (0.41)	0.317
Word interference-word reading	6	6.5 (3.62)	6	4.5 (4.18)	0.058
Total errors[2]		0 (0)		0 (0)	1
Word interference-interference	7	6.29 (3.09)	7	4.0 (3.65)	0.160
Total errors[2]		3.57 (3.41)		3.57 (2.94)	0.799
Word interference-switching interference	6	5.5 (3.51)	6	3.67 (3.44)	0.058
Total errors[2]		2.17 (3.54)		5.33 (3.67)	0.068
Trail making-visual scanning	6	5.5 (4.18)	6	3.83 (4.26)	0.195
Trail making-number sequencing	7	7.71 (4.82)	7	5.57 (3.46)	0.073
Trail making-letter sequencing	6	6.5 (4.42)	6	4.67 (3.72)	0.459
Trail making-number-letter sequencing	7	8.0 (4.83)	7	5.29 (5.38)	0.153
Trail-making-processing speed	6	7.5 (4.04)	6	5.17 (5.08)	0.252
Verbal fluency-letter	7	8.57 (3.78)	7	7.0 (3.0)	0.174
Verbal fluency-category	7	6.29 (2.87)	7	5.43 (2.37)	0.078
Verbal fluency-switching category (correct)	7	8.57 (3.78)	7	5.86 (3.18)	0.009
Verbal fluency switching category (accuracy)	7	8.57 (3.51)	7	6.14 (3.08)	0.01

Table 5.4 Means and standard deviations (in parentheses) for the neuropsychological tests before and 12 months after surgery for the whole sample of 5 patients with Parkinson's disease and 2 with progressive supranuclear palsy.
DRS-II=Dementia Rating Scale-2; NART=National Adult Reading Test; WASI=Wechsler Abbreviated Scale of Intelligence; CVLT=California Verbal Learning Test; WAIS-III=Wechsler Adult intelligence Scale; DKEFS=Delis-Kaplan Executive Function Scale. [1]t-scores, [2]raw scores.

PPN-DBS surgery produced a large slowing on the number sequencing condition of the Trail making test of the DKEFS (d=0.95), although this failed to reach statistical

significance (t(6)=2.12; p=0.073). There was no effect of surgery on the remaining Trail making subtests (all p>.05). Figure 5.5 shows the mean scaled scores for the different Trail making subtests before and after PPN-DBS.
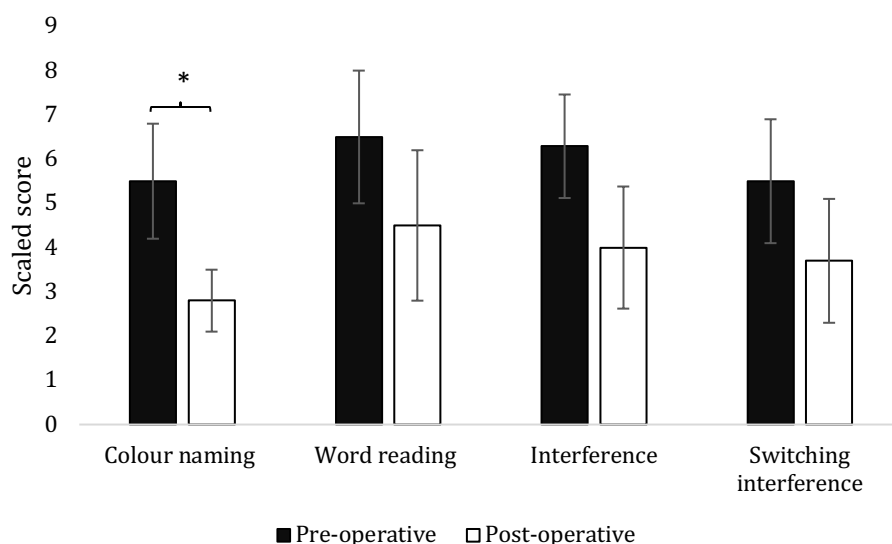
Figure 5.3 Mean scaled scores for the subtests of the Delis-Kaplan Executive Function Scale (DKEFS) Colour-word Interference task before and after surgery.
Error bars represent standard errors.*p<0.05

For the remaining neuropsychological tests, namely, current IQ on the WASI, the Working Memory Index and the Processing Speed Index of the WAIS-III, the Trail Making Test of the DKEFS, the VCLT, the BDI and the SAS, surgery did not produce any significant change, as there was no difference in performance between the pre- and post-operative assessments (all p>0.05).
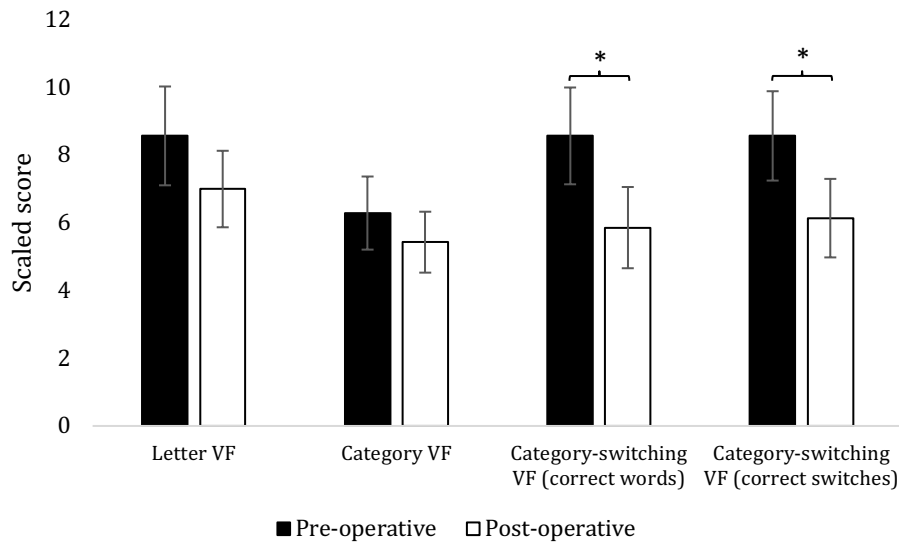
Figure 5.4 Mean scaled scores for the verbal fluency subtests of the Delis-Kaplan Executive Function Scale (DKEFS) verbal fluency task before and after surgery.
Error bars represent standard errors.*p<0.01
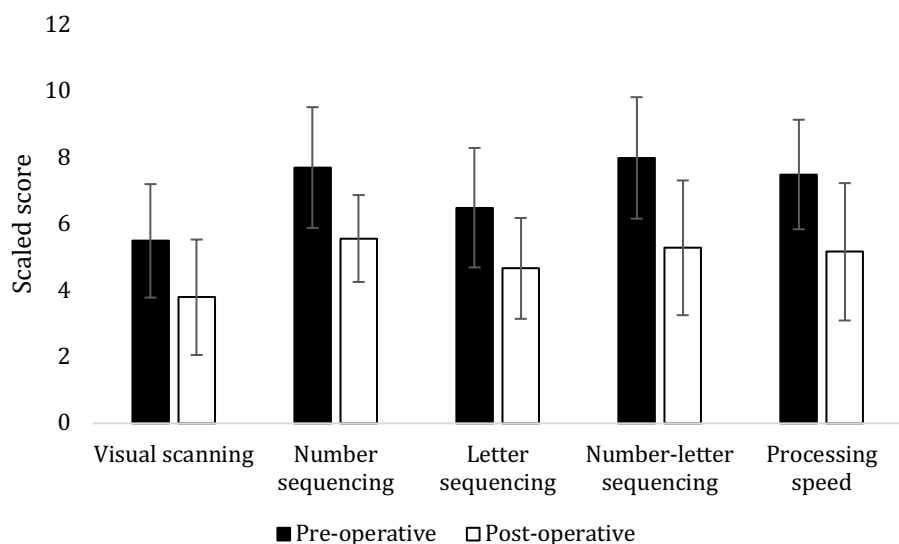
Figure 5.5 Mean scaled scores for the subtests of the Delis-Kaplan Executive Function Scale (DKEFS) trail making task (TMT) before and after surgery.
Error bars represent standard errors.

The means and standard deviations of the scores on the tests of cognitive function for the PD patients before and 12 months after surgery are presented in Table 5.5. Wilcoxon signed rank tests, only including the PD patients, were performed to compare the pre- versus post-operative scores of these patients for all neuropsychological tests. The results revealed a significant change from before to after PPN-DBS surgery for both the total number of correct words (z= -2.04; p=0.041) and the total number of correct

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switches (z= -2.03; 0.042) on the switching-category fluency test. Therefore, the PD patients produced significantly fewer correct words and switches after surgery compared to before surgery. The changes for the remaining tests were not significant (all p<0.05).

Neuropsychological test	N	Pre-operative assessment	N	Post-operative assessment
DRS-2				
Attention	4	12.5 (1)	4	11 (2.83)
Initiation/Perseveration[1]	4	7.25 (2.06)	4	5 (2.31)
Construction	4	10 (0)	4	10 (0)
Conceptualization	4	10.5 (3.79)	4	11.25 (1.26)
Memory	4	12.25 (1.5)	4	11.5 (1.73)
Total Score	5	9.4 (3.29)	5	7.8 (1.64)
NART				
Premorbid Estimated Full scale IQ	5	104.2 (13.52)	5	107.6 (14.12)
WASI				
Vocabulary[1]	4	54 (15.75)	4	44 (12.96)
Matrix reasoning[1]	4	58 (5.42)	4	55.5 (6.77)
Full scale IQ	4	110.5 (13.92)	4	99.75 (4.99)
CVLT				
Total recall trials 1 to 5[1]	4	57 (10.68)	4	51.25 (10.69)
Free short-delay recall[2]	4	9 (3.16)	4	9.25(3.4)
Cued short-delay recall[2]	4	10.25 (2.5)	4	11.25 (2.99)
Free long-delay recall[2]	4	9.75 (2.22)	4	9.75 (2.06)
Cued long-delay recall[2]	4	10.5 (3.42)	4	10.25 (2.99)
Total intrusions[2]	4	4.5 (4.2)	4	6 (6.88)
Total repetitions[2]	4	6.75 (3.77)	4	7.75 (4.5)
Yes/No Recognition Total correct[2]	4	14.75 (1.26)	4	15.25 (0.96)
Recognition false positives[2]	4	4 (3.46)	4	4.5 (4.65)
Forced choice recognition percentage correct	4	98.44 (3.13)	4	100 (0)
WAIS-III				
Digit Span	5	9.4 (1.52)	5	9.6 (1.82)
Letter-number sequencing	4	9.25 (2.06)	4	9 (2.58)
Arithmetic	5	10.4 (3.13)	5	11.2 (2.59)
Working Memory Index	4	100 (6.73)	4	99.75 (6.55)
Digit symbol	5	6.4 (1.52)	5	5.8 (2.49)
Symbol search	5	9.4 (1.52)	5	6.8 (2.77)
Processing Speed Index	5	84.4 (7.7)	5	76.4 (5.08)
Visual Conditional Associative Learning task				
Total trials[2]	4	59 (44.56)	2	82 (57.98)
Total errors[2]	4	21.5 (22.07)	2	32 (38.18)
Blocks to criterion[2]	4	7.25 (4.35)	2	10 (4.24)
First trial correct[2]	4	54.25 (11.03)	2	50.5 (16.26)
DKEFS				
Word interference-colour naming	4	4.75 (2.99)	4	2.5 (1)
Total errors[2]		0.5 (1)		0 (0)
Word interference-word reading	4	5.5 (3.7)	4	4 (3.83)
Total errors[2]		0.25 (0.5)		0.25 (0.5)
Word interference-interference	5	7 (2.45)	5	4.6 (4.16)
Total errors[2]		9.2(5.07)		8.2 (4.97)

Word interference-switching interference	4	4.5 (3.51)	4	3.25 (3.3)
Total errors[2]		7 (7.44)		9 (6.63)
Trail making-visual scanning	4	7 (4.32)	4	4.5 (5.2)
Trail making-number sequencing	5	8.8 (4.66)	5	5.8 (3.11)
Trail making-letter sequencing	4	7.5 (4.51)	4	6.25 (3.59)
Trail making-number-letter sequencing	5	8.8 (4.44)	5	5 (5.52)
Trail-making-processing speed	4	10 (1.41)	4	6.75 (5.68)
Verbal fluency-letter	5	8.8 (3.11)	5	7.2 (2.68)
Verbal fluency-category	5	6.4 (2.07)	5	5.4 (1.52)
Verbal fluency-switching category (correct)	5	9.8 (2.95)	5	6.2 (2.59)
Verbal fluency switching category (accuracy)	5	9.8 (2.39)	5	6.6 (2.3)

Table 5.5 Means and standard deviations (in parentheses) for the neuropsychological tests before and 12 months after surgery for the PD patients only.
DRS-II=Dementia Rating Scale-2; NART=National Adult Reading Test; WASI=Wechsler Abbreviated Scale of Intelligence; CVLT=California Verbal Learning Test; WAIS-III=Wechsler Adult Intelligence Scale; DKEFS=Delis-Kaplan Executive Function Scale. [1]t-scores, [2]raw scores.

The RCIs on the neuropsychological tests are presented in table 5.6. The RCIs for the Initiation/Perseveration subscale of the DRS-2 are supportive of the significant post-operative decline reported above, as a reliable decline at the post-operative assessment was present in 66.67% of the patients (see Figure 5.6A). The RCIs for the total number of words recalled across 5 trials on the CVLT are not consistent with the significant results reported above, as only 33.33% of the patients showed a reliable decline at the post-operative assessment. For the colour naming condition of the Stroop colour-word interference test, RCIs support the above results, as 66.67% of the patients showed a reliable decline (see Figure 5.6B). For the total number of correct words on the alternating category fluency test, RCIs are supportive of the above results as a large proportion, 57.14% (see Figure 5.6C), of the patients showed a reliable decline at the post-operative assessment. Also, when looking at the RCIs for only the PD patients, 4 out of 5 patients or 80% showed a reliable decline at the post-operative assessment. On the other hand, RCIs for the accuracy score on the alternating category fluency test, suggest that 42.86% of the patients had a reliable decline at the post-operative assessment, which is not in support of the significant results above.

A: DRS Initiation / Perseveration

PD1   PD2   PD3   PD4   PSP1   PSP2

B: Stroop Colour Naming

PD1   PD2   PD3   PD4   PSP1   PSP2

C: Switching Category Fluency (correct)

PD1   PD2   PD3   PD4   PD5   PSP1   PSP2

D: WASI Full Scale IQ

E: CVLT Total Intrusions

F: WAIS Digit Symbol
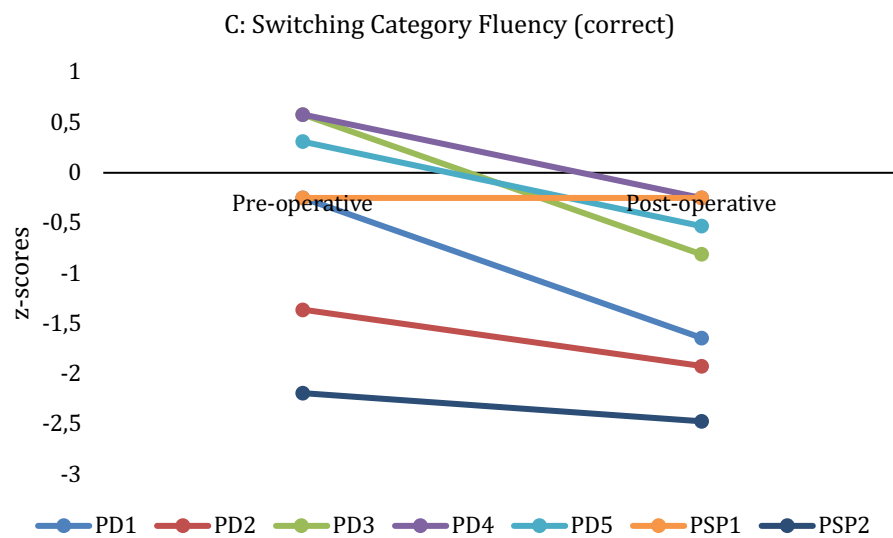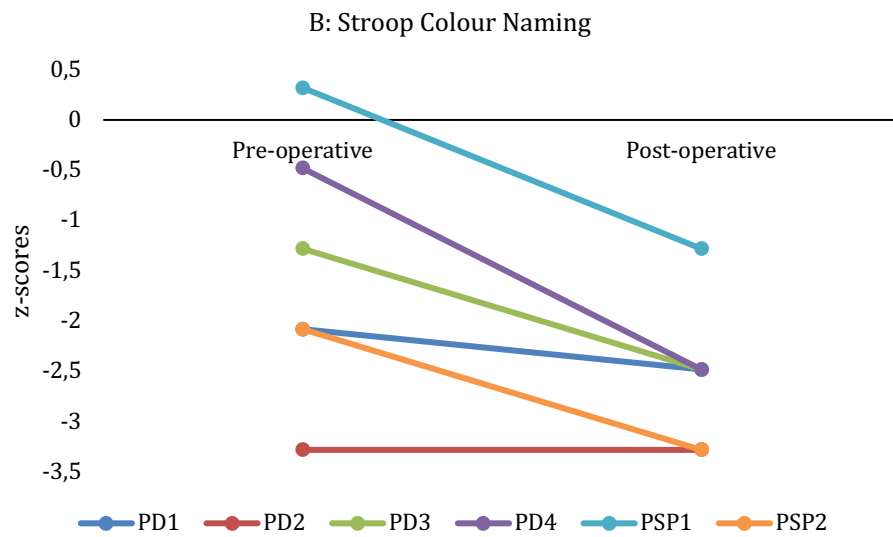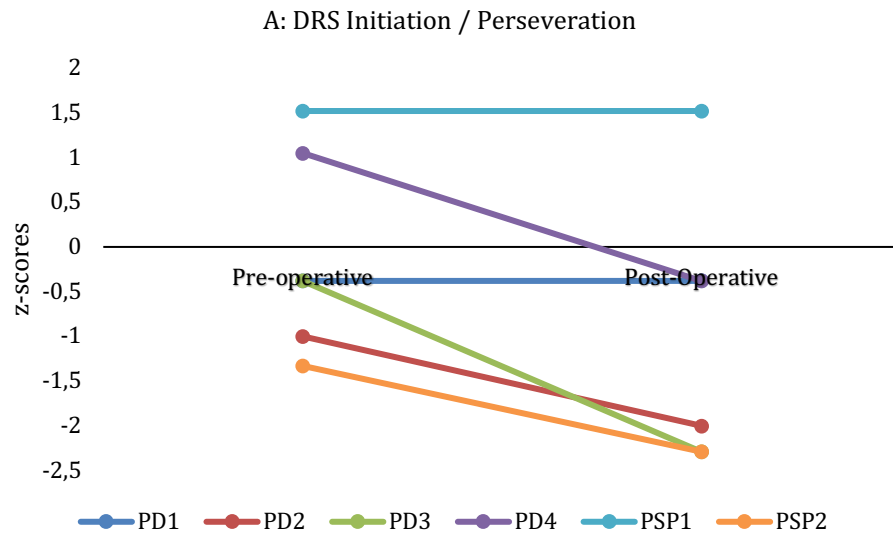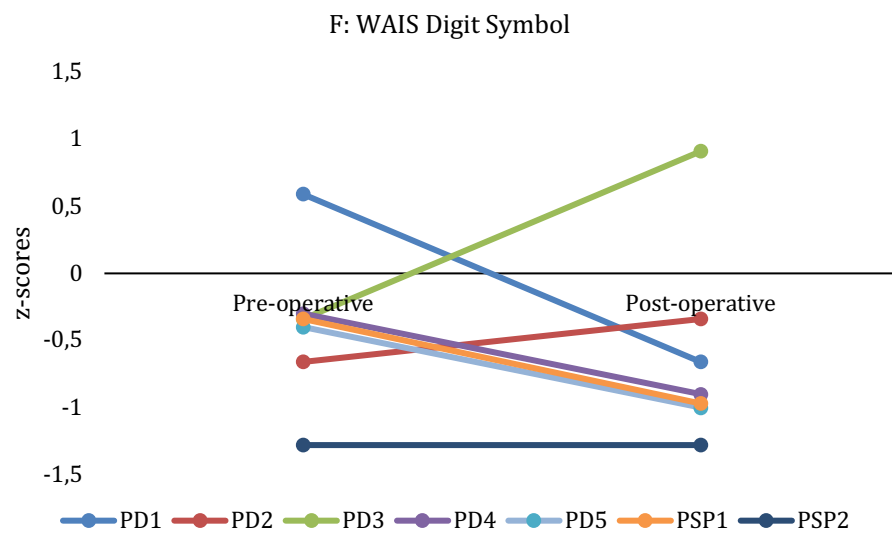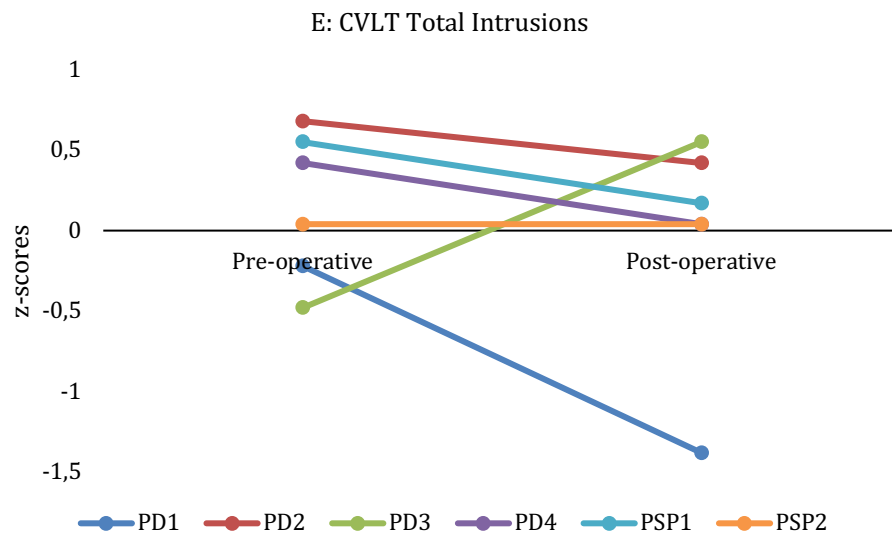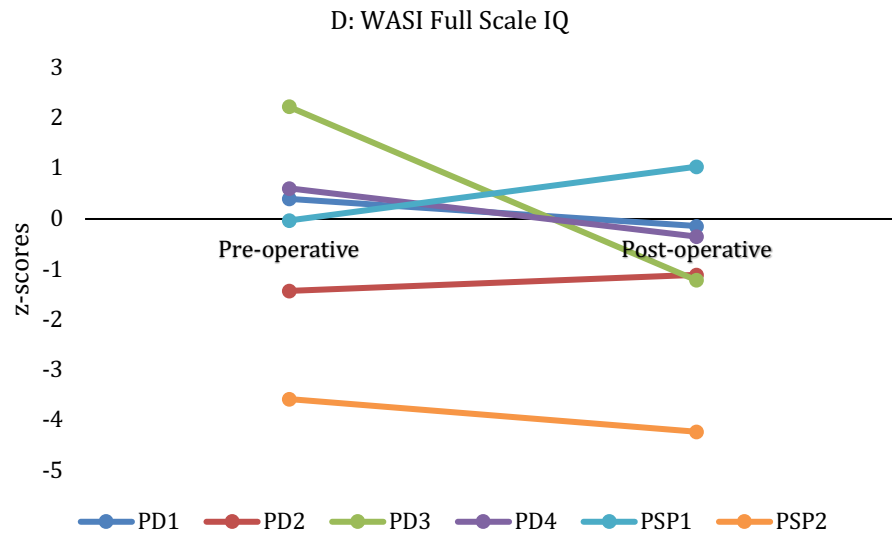
Figure 5.6 z-scores for each patient on tests for which at least 50% of the patients declined reliably, namely (A) the Initiation/Perseveration subscale of the Dementia Rating Scale; (B) the Stroop Colour naming subtest; (C) the number of correct words on the switching category fluency test; (D) the WASI Full scale IQ; (E) the CVLT total number of intrusions; and (F) the WAIS digit symbol subtest.
DRS=Dementia rating scale; WASI=Wechsler Abbreviated Scale of Intelligence; CVLT= California Verbal Learning Test; WAIS=Wechsler Adult Intelligence Scale.

For the remaining tests that were found to not change significantly from the pre- to post-operative assessments the RCIs revealed that on some of the measures at least half of the patients declined reliably. Therefore, 50% of the patients had a reliable decline on the WASI full-scale IQ (see Figure 5.6D) and the total number of intrusions on the CVLT (see Figure 5.6E) and 57.14% of the patients had a reliable decline on the digit symbol test of the WAIS-III (see Figure 5.6F).

Neuropsychological test	Decline %	No Change %	Improve %	95% Criterion
DRS-2				
Attention	33.33	*66.67*	0	1.33
Initiation/Perseveration[1]	*66.67*	33.33	0	1.88
Construction	0	*83.33*	16.67	1.45
Conceptualization	16.67	*66.67*	16.67	2.34
Memory	33.33	*50*	16.67	1.62
Total Score	33.33	*66.67*	0	2.55
NART				
Premorbid Estimated Full scale IQ	0	*71.43*	28.57	4.65
WASI				
Vocabulary[1]	33.33	*50*	16.67	5.59
Matrix reasoning[1]	33.33	*66.67*	0	3.87
Full scale IQ	*50*	33.33	16.67	5.64
CVLT				
Total recall trials 1 to 5[1]	33.33	*66.67*	0	4.29
Free short-delay recall[2]	33.33	33.33	33.33	2.38
Cued short-delay recall[2]	0	*100*	0	2.07
Free long-delay recall[2]	33.33	*50*	16.67	1.84
Cued long-delay recall[2]	0	*100*	0	2.24
Total intrusions[2]	*50*	33.33	16.67	2.48
Total repetitions[2]	33.33	*50*	16.67	2.56
Yes/No Recognition Total correct[2]	0	*100*	0	1.37
Recognition false positives[2]	0	*83.33*	16.67	3.19
Forced choice recognition percentage correct	0	*83.33*	16.67	2.09
WAIS-III				
Digit Span	14.29	*50*	28.57	1.79
Letter-number sequencing	16.67	*50*	33.33	2.29

Arithmetic	0	*100*	0	2.13
Working Memory Index	16.67	*66.67*	16.67	4.29
Digit symbol	*57.14*	28.57	14.29	1.74
Symbol search	42.86	*57.14*	0	1.98
Processing Speed Index	*42.86*	28.57	28.57	4.59
DKEFS				
Word interference-colour naming	*66.67*	33.33	0	2.35
Total errors[2]	0	*100*	0	1.22
Word interference-word reading	16.67	*83.33*	0	3.37
Total errors[2]	0	*100*	0	1.11
Word interference-interference	42.86	*57.14*	0	2.3
Total errors[2]	28.57	*57.14*	14.29	2.42
Word interference-switching interference	33.33	*66.67*	0	2.46
Total errors[2]	33.33	*66.67*	0	2.46
Trail making-visual scanning	33.33	*66.67*	0	2.68
Trail making-number sequencing	28.57	*71.43*	0	2.88
Trail making-letter sequencing	33.33	*50*	16.67	2.76
Trail making-number-letter sequencing	28.57	*71.43*	0	2.88
Trail-making-processing speed	33.33	*66.67*	0	2.64
Verbal fluency-letter	42.86	*57.14*	0	2.55
Verbal fluency-category	0	*100*	0	2.22
Verbal fluency-switching category (correct)	*57.14*	42.86	0	2.25
Verbal fluency switching category (accuracy)	42.86	*57.14*	0	2.03

Table 5.6 Percentage of patients with PPN-DBS meeting 95% RCI criterion for reliable decline or increase or no change from pre- to post-operative assessment on the neuropsychological measures.
DRS-II=Dementia Rating Scale-2; NART=National Adult Reading Test; WASI=Wechsler Abbreviated Scale of Intelligence; CVLT=California Verbal Learning Test; WAIS-III=Wechsler Adult Intelligence Scale; DKEFS=Delis-Kaplan Executive Function Scale. [1]t-scores, [2]raw scores.

5.3.2 Effects of chronic PPN stimulation on cognition in two cases with dementia

The two patients who developed dementia, did so after the one year follow-up cognitive assessment. At these further post-operative assessments, they were unable to perform the complete neuropsychological test battery.

Patient 1 was a 63-year-old woman with a 6-years history of PSP and was assessed 3 years after surgery. She received 16 years of academic education and worked as a civil servant. The first cognitive assessment was after a prolonged period of stimulation

having been off and the second after 6 weeks of continuous PPN-DBS with the stimulation parameters 2 V; 60 µs; 20Hz. Patient 1 could not speak but could write, and consequently, where possible tests that required speech were completed in a written format. Table 5.7 presents the scores on the tests that could be done during the 'on' and 'off' stimulation assessments. At the first assessment patient 1 performed in the severely impaired range on the DRS-2 indicating a global cognitive deficit. Particularly the Construction and Initiation/Perseveration subscales were in the severely impaired range. The patient was also in the impaired range of both the verbal fluency and trail making subtests of the DKEFS, suggesting executive dysfunction. On the other hand, patient 1 performed in the average to above average range for both the CVLT and digit span indicating intact verbal learning and working memory respectively. When stimulation was switched on the patient improved slightly on the digit span test indicating a mild improvement of working memory. The patient showed decreased verbal learning as shown by the total number of words recalled on trials 1-5 of the CVLT during the PPN-DBS on assessment.

Neuropsychological test	OFF stimulation	ON simulation
MMSE[1]	28	28
DRS-2		
Attention	13	13
Initiation/Perseveration	2	2
Construction	3	3
Conceptualization	11	11
Memory	13	13
Total Score	3	3
DKEFS		
Verbal fluency -letter	4	3
Verbal fluency -category	1	1
Trail making-letter sequencing	1	1
Trail making-number-letter sequencing	1	1
WAIS-III		
Digit span forward[1]	12	11
Digit span backward[1]	10	9
Digit span total	13	14
CVLT		
Total recall trials 1 to 5[2]	61	54
Free short-delay recall[1]	14	13
Cued short-delay recall[1]	13	14
Free long-delay recall[1]	15	14
Cued long-delay recall[1]	15	14
Total intrusions[1]	0	0
Total repetitions[1]	0	0
Recognition correct[1]	15	16
Recognition false positives[1]	0	0

Table 5.7 Scaled scores (unless indicated otherwise) on the cognitive tests that patient 1 could perform 3 years after surgery with no stimulation' and after 6 weeks of low frequency PPN stimulation. MMSE=Mini Mental State Examination; DRS-II=Dementia Rating Scale; DKEFS=Delis-Kaplan Executive Function Scale; WAIS-III=Wechsler Adult Intelligence Scale; CVLT=California Verbal Learning test. [1]raw scores; [2]t-scores.

Patient 2 was a 76-year-old man with a 26-year history of PD and was assessed 4 years after surgery. He received 17 years of education and worked as a design engineer. The first cognitive assessment was after a prolonged period of stimulation having been off and the second after 6 weeks of continuous PPN-DBS with the stimulation parameters 2 V; 60 µs; 20Hz. Table 5.8 presents the scores on the tests that could be performed at the 'off' and 'on' stimulation assessments. At the first assessment patient 2 performed in the moderately impaired range on the DRS-2 indicating a global cognitive deficit. In particular, his score on the Initiation/Perseveration subscale was in the severely impaired range. The scores on the verbal fluency and trail making tests were also in the impaired range indicating executive dysfunction. The digit span of patient 2 was also below average implying attention and working memory deficits. His scores on the CVLT were in the severely impaired range and he produced a large number of intrusion errors indicating both a verbal learning and monitoring deficit. The patient's reaction and movement times on the simple reaction time task were in the severely impaired range and he produced a large number of errors. Also, he was unable to perform the five-choice reaction time task, indicating an inability to comprehend and hold instructions 'on line' in working memory.

When PPN stimulation was switched on the global cognitive performance worsened. Both the total scores on the MMSE and the DRS-2 and in particular the score on the initiation/perseveration subscale of the DRS-2 declined. The patient produced less words on both verbal fluency tests when stimulation was switched on compared to when stimulation was off. By contrast, the patient had an increased digit span with PPN stimulation on and also produced less intrusion and repetition errors on the CVLT when stimulation was on compared to when stimulation was switched off. Also, the patient produced less errors on the simple reaction time task and was able to complete the five-choice reaction time task, which he was not able to with stimulation off. These changes

indicate that low-frequency PPN stimulation led to an improvement of the patient's attention and working memory.

Neuropsychological test	OFF simulation	ON stimulation
MMSE[1]	21	17
DRS-II		
Attention	10	8
Initiation/Perseveration	3	2
Construction	10	7
Conceptualization	7	10
Memory	8	2
Total Score	4	2
DKEFS		
Verbal fluency-letter	5	3
Verbal fluency-category	1	1
Trial making-letter sequencing	1	1
Trial making-number-letter sequencing	1	1
WAIS-III		
Digit span forward[1]	5	7
Digit span backward[1]	3	5
Digit span total	5	8
CVLT		
Total recall trials 1 to 5[2]	12	14
Free short-delay recall[1]	0	0
Cued short-delay recall[1]	3	3
Free long-delay recall[1]	0	1
Cued long-delay recall[1]	1	1
Total intrusions[1]	39	13
Total repetitions[1]	3	0
Recognition correct[1]	7	10
Recognition false positives[1]	18	17
Simple reaction time task[1]		
Accuracy	6	5
Error	6	0
Movement time	2,508.83	2,328.60
Reaction time	580.5	581.2
Five choice reaction time task[1]		
Accuracy	NA	8
Error	NA	0
Movement time	NA	1,892.62
Reaction time	NA	637.75

Table 5.8 Scaled scores (unless indicated otherwise) on the cognitive tests that patient 2 could perform 4 years after surgery with low frequency PPN stimulation off for a prolonged period or after 6 weeks of continuous stimulation.
MMSE=Mini Mental State Examination; DRS-II=Dementia Rating Scale; DKEFS=Delis-Kaplan Executive Function Scale; WAIS-III=Wechsler Adult Intelligence Scale; CVLT=California Verbal Learning Test. NA=not able to complete. [1]raw scores; [2]t-scores.

5.4 Discussion

The aim of this study was to investigate the effects of PPN-DBS on cognitive function in depth, by firstly examining cognitive performance of patients before and after surgery and secondly assessing the effects of acute PPN stimulation on cognition in patients with PSP and PD, who developed dementia after surgery. To do so, the study was split into two parts. For the first part of the study, 5 PD and 2 PSP patients undergoing PPN-DBS surgery were recruited to perform a large neuropsychological test battery covering all major cognitive domains shortly before having surgery and a second time one year or more after surgery. For the second part of the study, one PD and one PSP patient, who underwent PPN-DBS surgery and developed dementia at some point after the surgery were recruited. Both patients were assessed on a shorter neuropsychological test battery twice, once after a period of being chronically off PPN stimulation and a second time 6 weeks after being switched on low frequency PPN stimulation. This was done to follow up the findings of Ricciardi and colleagues (2015), who described a PD-D patient whose cognition improved with low frequency PPN stimulation. Due to the limited literature in this field, this study was exploratory and not hypotheses-driven.

5.4.1 Effects of PPN-DBS surgery

The results of this study are suggestive that PPN-DBS surgery leaves most aspects of cognitive function unaffected, but results in a decline of certain cognitive aspects in a proportion of the patients. Therefore, initial statistical analysis indicated a significant post-operative decline of the Initiation/ Perseveration subscale of the DRS-2, the total number of words recalled on 5 trials of the CVLT, the colour naming condition of the Stroop colour-word interference test and the number of both correct words and switches on the switching category fluency test, relative to the pre-operative assessment. Reliable Change indices (RCIs) where calculated to estimate the proportion of patients, who had a reliable decline improvement or no change on the different cognitive tests. For the significant results, RCIs only supported the findings for the Initiation/Perseveration subscale of the DRS-2 and the colour naming condition of the Stroop colour-word interference test, with 66.67% of the patients showing a reliable decline on both these tests, and the total number of correct words on the switching category verbal fluency test,

with 57.14% of the whole group and even 80% of the PD patients showing a reliable decline. Interestingly, RCIs also revealed reliable decline in a percent of the sample on some of the tests that did not change significantly. Thus, 50% of the patients showed a reliable decline on the WASI full scale IQ and the total number of intrusions of the CVLT, and 57.14% of the patients showed a reliable decline on the WAIS-III digit symbol test. When analysis was performed including only the PD patients merely the decline on the total number of correct words and switches for the switching category fluency test remained significant. The results of this study need to be considered carefully, as they are based on a small number of patients, and a mixed sample of PD and PSP patients. Nevertheless, inspection of Table 5.6 clearly shows that the majority of tests of cognitive function do not show any reliable change after PPN-DBS surgery.

Other studies investigating the effects of PPN-DBS surgery on cognition assessed specific domains rather than global cognition and their results suggested improvements in some aspects of cognition, including grammatical errors, attention, working memory and executive function (Brusa et al., 2009; Ceravolo et al., 2011; Costa et al., 2010; Riccardi et al., 2015; Thevathasan et al., 2010; Zanini et al., 2009). The only paper that assessed cognitive function more thoroughly and reported improvements on several aspects, looked at a single case of PD-D (Riccardi, et al., 2015). The present findings are not consistent with these previous results, as none of the tests used in this study improved after PPN-DBS, and performance on a minority of the tests declined at the post-operative relative to the pre-operative assessment. In particular tests that are sensitive to frontal lobe executive function, such as the Initiation/Perseveration subscale of the DRS-2 and the switching category verbal fluency test declined after surgery. Additionally, 50% of the patients produced reliably more intrusions on the CVLT after surgery compared to the pre-operative assessment, suggestive of failure of monitoring. These results are not consistent with the results of Ceravolo and colleagues (2011), who reported improved executive function in 6 patients with PD 12 months after surgery with acute low frequency PPN stimulation compared to when stimulation was off. The authors did not look at changes from before to after surgery, leaving it unclear whether the reported findings reflected a surgery-induced improvement. Additionally, Ceravolo and colleagues (2011) included patients with bilateral PPN- and STN-DBS and reported increased

glucose utilization in the dorsal prefrontal, orbitofrontal, and anterior cingulate cortices, which was associated with the improvement of executive function. The majority of patients included in the present study had left-sided rather than right-sided or bilateral PPN-DBS and no STN-DBS, which may relate to the differences in findings.

The significant decline on the switching category fluency test may also suggest that PPN-DBS surgery has an effect on language function. Previous research on the effects of PPN-DBS on language has produced diverse results. Zanini and colleagues (2009) reported improved grammatical aspects of language, and Brusa et al. (2009) found minor verbal fluency improvements in one patient with PSP. On the other hand, Pinto and colleagues (2014) suggested speech degeneration after PPN-DBS surgery. Two of these studies included patients with simultaneous bilateral PPN- and STN-DBS (Pinto et al., 2014; Zanini et al., 2009), therefore the effects are not purely attributable to PPN-DBS. However, Pinto's group did suggest that the speech degradation was related to low frequency PPN stimulation only. Combined with the results of the present study it appears that PPN-DBS surgery may result in verbal fluency deficits but language function in general remains unaffected.

The analysis of California verbal learning test data indicated a significant decline on the total number of words recalled on trials 1 to 5. However, the results were not statistically significant anymore when analysis was done including the PD patients only. In addition, RCIs indicated that only 1 of the 6 patients (16.67%), who performed the task showed a reliable decline. There was no change for the short and long delay recall. That there was no change contradicts the findings of Ceravolo et al. (2011) that suggested better verbal long-term memory with low frequency PPN stimulation. Again, the reason for these differences may be that previous results indicate changes with low frequency PPN stimulation, rather than surgery-induced changes.

Performance on the colour naming condition of the Stroop colour-word interference task declined significantly and the decline on the word reading condition reached borderline significance. Also, for the colour naming condition, 66.67% of the patients had a reliable decline and 50% of the patients had a reliable decline on the digit symbol test of the WAIS-

III, suggesting that a large proportion of the patients declined on these measures of processing speed. Research implementing an n-back task or a reaction time task indicated better processing speed with low frequency PPN stimulation (Costa et al., 2010; Thevathasan et al., 2010). As mentioned previously these studies did not provide any pre-operative comparisons and therefore the positive effects may be due to acute stimulation effects rather than surgery.

The PPN is highly interconnected with the basal ganglia and the cerebral cortex. Consequently, it receives inputs from several cortical regions including the supplementary motor area (SMA), the preSMA, the dorsal and ventral premotor cortex, the frontal eye fields and the medial prefrontal cortex (Matsumura et al., 2000). Also, the basal ganglia output nuclei, the deep cerebellar nuclei and the STN project to the PPN (Kang & Kitai, 1990; Saper & Loewy, 1982). On the other hand, projections from the PPN target the GPi, SNc, the associative and intralaminar nuclei of the thalamus (Martinez-Gonzalez et al., 2011) and the STN (Lavoie & Parent, 1994). Considering this interconnectivity of the PPN with the basal ganglia and the prefrontal cortex and that tasks for which performance was worse after PPN-DBS surgery relative to before surgery are sensitive to frontal lobe function, it could be suggested that PPN-DBS surgery interrupts functioning of the fronto-striatal circuits resulting in the cognitive deficits described above. Further support for this idea is the finding that low frequency PPN stimulation induced increased glucose utilization in prefrontal regions, indicating that it has an impact on prefrontal neuronal activity (Costa et al., 2010; Ceravolo et al., 2011). The fact that this change in activity was previously associated with improved cognition (Costa et al., 2010; Ceravolo et al., 2011) may reflect different effects of PPN-DBS surgery and acute low frequency PPN stimulation. Also, previous studies included patients, who also had STN-DBS, and research suggests that STN-DBS surgery leads to decreased prefrontal activity during performance of cognitive tasks such as the Stroop, verbal fluency and random number generation (Schroeder et al., 2003, 2002; Thobois et al, 2007). Recently, on the basis of electrophysiological studies in animals performing a stop signal ask, it was proposed that the PPN may serve as an accelerating mechanism for the indirect 'stop' basal ganglia pathway and may decrease striatal activity (Schmidt et al., 2013). Thus, it is possible that in the present study PPN-DBS surgery had an impact on

the patients' ability to inhibit habitual responses in order to produce controlled responses during performance of tasks such as the switching category verbal fluency test.

5.4.2 Effects of low frequency PPN stimulation on cognition in two patients with dementia

The effects of low frequency PPN stimulation on cognitive function in two patients (1 PD and 1 PSP), who developed dementia following PPN-DBS surgery were evaluated using the stimulation on versus off methodology. Both patients were assessed 3 to 4 years after surgery with stimulation off and 6 weeks later with chronic low frequency PPN stimulation on. The cognitive profile of the first patient remained mostly unchanged, apart from slight improvements on the digit span. Also, there was a mild worsening of the patient's verbal learning when stimulation was switched on. For patient 2 the cognitive profile changed between the two sessions. The patient had a decline in global cognition when stimulation was on compared to the off session as shown by lower scores on the mini mental status examination and the dementia rating scale. In particular the score on the initiation/perseveration subscale of the dementia rating scale declined. Additionally, the patient produced fewer words during the verbal fluency test with stimulation on. On the other hand, the patient's digit span increased and he produced less intrusion and repetition errors during the California verbal learning test. Furthermore, during the on session the patient produced less errors on a simple reaction time task and was able to perform a five-choice reaction time task which he was not able to do when stimulation was off. These findings indicate that chronic low frequency PPN stimulation may have differential effects on cognition and also it may produce different cognitive profiles in patients with PD-D and PSP with dementia. According to the present results chronic low frequency PPN stimulation may be associated with a mild improvement of attention and working memory. This supports the findings of Riccardi and colleagues (2015) about the role of the PPN in alertness and may also strengthen the hypothesis of increased glucose utilization in the frontal cortex with low frequency stimulation (Ceravolo et al., 2011). However, the present study also suggests a detrimental effect of chronic PPN stimulation on initiation and perseveration and verbal fluency in the patient with PD-D. Riccardi and colleagues (2015) reported improved global cognition, verbal fluency and memory with chronic stimulation. Reasons for these differences are unclear but they may relate to

differences in patient profiles. First at all the present study looked at one PSP and PD-D patient who presented with different cognitive profiles at the two sessions. When comparing the patient with PD-D in this study to the one described by Riccardi et al. (2015), it should be mentioned that there was a large gap in terms of age and disease progression. The man in Riccardi et al.'s study was much younger and had a shorter history of PD. These could be factors influencing cognitive outcome. Longer disease duration and older age were reported as risk factors for cognitive outcome after STN-DBS surgery (Smeding et al., 2011; York et al., 2009), which might also be the case for PPN-DBS.

This study had a couple of limitations. Firstly, the sample size is rather small making it difficult to generalize from the results. However, this is due to the fact that PPN-DBS is a relatively new approach to treating PD and related disorders and only a few patients have been treated with it. Secondly, this study included PD and PSP patients and therefore the treatment could have produced different effects on cognition for the two patient groups. However, this inclusion of both PD and PSP patients was done to increase the sample size for this rare treatment approach.

The present study was the first to use an extensive neuropsychological test battery to assess cognitive function in a sample of PD and PSP patients who had PPN-DBS only before and after surgery. Additionally, the study investigated the effects of chronic low frequency PPN stimulation on the cognitive profiles of one PD and one PSP patient who developed dementia following PPN-DBS surgery. Our data are limited to very few patients and a conclusion to a general PD population could not be reliably drawn, but they suggest that while some patients can have little post-operative effect on executive function and processing speed, in others executive dysfunction and processing speed may decline. It remains an important clinical challenge to identify those in whom a decline could be predicted pre-operatively, and further in whom such a decline could lead to clinically meaningful consequences for that individual. Additionally, chronic low frequency PPN stimulation left cognitive function in one patient with PD-D and one patient with PSP and dementia mostly unaffected. However, the patients showed minor improvements in measures of working memory and attention and minor declines in measures of executive

function and verbal learning. These results are in contrast to previous research reporting beneficial effects of PPN-DBS on specific aspects of cognition, but further support the cognitive safety of this procedure. These results suggest that a thorough cognitive assessment should be included before and after PPN-DBS surgery.

Chapter 6. General Discussion

The general aim of my PhD thesis was to investigate the effects of Deep Brain Stimulation (DBS) in Parkinson's disease (PD) on cognitive function. To do so I conducted four studies looking at different aspects of cognitive function with the focus being on executive function. The aim of my first study was to investigate the effects of acute STN stimulation on probabilistic decision-making. The aim of my second study was investigate the effects of STN-DBS as a whole and also of acute STN stimulation on verbal fluency and its' different functional aspects. The aim of my third study was to investigate the effects of acute STN stimulation on conditional associative learning. The aim of my fourth and final study was to investigate the effects of DBS of the pedunculopontine nucleus (PPN), as a relatively new DBS target, in PD and progressive supranuclear palsy (PSP) on various aspects of cognition. In the following sections the main findings of each study will be discussed, followed by the theoretical and clinical implications of the results of my thesis.

6.1 The subthalamic nucleus and integration of probabilistic information during decision-making: evidence from the effect of STN-DBS for PD

The aim of my first study was to investigate the effects of acute STN stimulation on probabilistic decision-making. This was done, by assessing PD patients with STN-DBS and two healthy control groups on a probabilistic decision-making task designed to assess situations where decision-making does not depend on previously learned information and does not involve a conflict or reward component. Based on decision-making models suggesting that the STN is involved in computing conflict and modulating the decision threshold accordingly (Bogacz & Gurney, 2007; Frank, 2006) the following hypotheses were tested: (1) PD patients with STN stimulation on would make more impulsive decisions compared to when stimulation is switched off and compared to healthy control participants; (2) when STN stimulation is switched on PD patients who receive high frequency stimulation would make more impulsive decisions, compared to patients who receive low frequency stimulation.

The results of my study indicated that acute STN stimulation did not have an effect on the patients' reaction times and accuracy scores. The results of the study are relevant to the theoretical framework for the role of the basal ganglia in decision-making (Bogacz &

Gurney, 2007; Frank, 2006; Mink, 1996), predicting that tonic inhibition from the basal ganglia output nuclei puts a brake on cortical and brain stem activity in order to accumulate and integrate enough evidence before an alternative is chosen (Mink, 1996). Furthermore, it has been suggested that the STN would compute the conflict between competing alternatives and modulate the decision threshold accordingly (Bogacz & Gurney, 2007; Frank, 2006). The results from my study suggest that these predictions are valid only when tasks involve conflict, time pressure or reward and not when probabilistic decision-making is engaged in the absence of these key factors.

Previous research investigating the effects of acute STN stimulation on decision-making is inconsistent. While some authors reported that acute STN stimulation led to impaired decision-making performance (Antoniades et al., 2014; Canvanagh et al., 2011; Coulthard et al., 2012; Evens et al., 2015; Green et al., 2013; Florin et al., 2013; Frank et al., 2007; Oyama et al., 2011; Pote et al., 2016; Rogers et al., 2011; Seinstra et al., 2016; Seymour et al., 2016; Zaehle et al., 2017), others reported that decision-making remained unchanged or even improved with STN stimulation (Boller et al., 2014; Brandt et al., 2015; Castrioto et al., 2015; Djamshidian et al., 2013; Evens et al., 2015; Fumagalli et al., 2015; Seinstra et al., 2016; Torta et al., 2012; Seymour et al., 2016; Zaehle et al., 2017). These inconsistencies across studies may reflect the specific processes involved in the various decision-making tasks used and the particular forms of impulsivity involved.

The task I used for my study measured reflection impulsivity. Reflection impulsivity refers to an inability to slow down the decision-making process in order to collect a sufficient amount of information before making a choice. This aspect of impulsivity can be assessed using the beads task (Djamshidian et al., 2013) or probabilistic decision-making tasks (Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007). The majority of research using probabilistic decision-making tasks reported increased reflection impulsivity leading patients to have faster reaction times when stimulation was on, compared to when stimulation was off (Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007). These inconsistencies between previous research and my findings may be a function of differences in the task properties. Frank and colleagues (2007) investigated the effects of STN stimulation when patients were making decisions between

alternatives that were previously associated with different reward probabilities and suggested that STN stimulation resulted in impulsive decision-making. Behaviourally this was reflected by PD patients failing to slow down when facing high conflict when they were on stimulation compared to when stimulation was off. However, this stimulation effect was only present for high conflict situations where both alternatives were associated with high reward probabilities, whereas the effect was not present in situations where both alternatives had low reward probabilities (Frank et al., 2007). Research implementing the same task supported these findings and further provided evidence for the underlying brain mechanisms using EEG (Cavanagh et al., 2011). The authors reported that acute STN stimulation resulted in decreased theta band activity over the medial prefrontal cortex, which was thought to be associated with raising the decision threshold for high conflict trials, supporting the involvement of the STN in decision-making. Coulthard and colleagues (2012) used a slightly different task. Stimuli associated with certain responses were presented consecutively requiring participants to constantly update probabilistic information over time. Their results indicated that STN stimulation led to reduced accuracy and faster reaction times compared to when stimulation was off.

By contrast to the tasks used in these three studies, the task in my study did not involve a learning phase. Therefore, participants did not initially learn the associations between stimuli and response outcomes. Instead, participants had to constantly update information and recalculate the probability of either outcome. Additionally, the other studies implemented reward-based learning, whereas for the task I used there was no reward involved. Therefore, it may be suggested that the STN is only involved in computing conflict and resetting the threshold for situations where the probability of an alternative to result in the desired outcome is already known. This idea may also be supported by research using the beads task (Djamshidian et al., 2013). Similar to the task I used the beads task does not involve an initial learning phase and does not provide participants with a reward. Djamshidian and colleagues (2013) also reported that STN stimulation did not lead to patients making more impulsive decisions. Thus, the findings of my study may reflect a lack of previously learned stimulus-action-reward associations in the task that appear to be critical for engagement of the STN in threshold adjustments

during decision-making. This proposal is also supported by recent evidence from our group (Kojovic et al, 2016), that STN stimulation enhances responsiveness to high reward value in patients with PD. In a reaction time and reward study, it was demonstrated that not only motivational modulation of movement speed in PD is maintained with STN-DBS, but that STN stimulation has a further energizing effect on movement initiation in response to greater incentive value. These results suggested that the STN plays a role in integrating motivational influences into motor action, which may explain some previous reports of STN-DBS induced impulsivity with increased motivational salience of stimuli (Frank et al, 2007; Cavanagh et al, 2011; Coulthard et al, 2012). Study 1 of my thesis established that not all forms of probabilistic decision-making are impaired after STN-DBS but that such impairments are only seen in tasks with conflict, time pressure, or reward at stake.

6.2 Dissociable effects of subthalamic nucleus deep brain stimulation surgery and acute stimulation on verbal fluency in Parkinson's disease

The aim of my second study was to investigate the effects of STN-DBS on verbal fluency in more detail, and to differentiate between the effects of surgery and acute stimulation and the potential mechanisms of any change. To do so, two separate studies were designed investigating the effects of STN-DBS surgery as a whole and acute STN stimulation separately. For the first study PD patients undergoing STN-DBS surgery were assessed shortly before surgery and one year after surgery. Three verbal fluency tests were administered and aside from the total number of correct words I recorded the number of sematic and phonemic switches and semantic and phonemic cluster sizes. These additional measures were obtained as they were predicted to reflect executive and semantic functions involved in verbal fluency respectively (Troyer et al., 1997). For the second study two patient samples were recruited. One group consisted of patients who had STN-DBS for at least six months and the second group consisted of matched unoperated PD control patients. All patients were assessed two times, patients with STN-DBS once on stimulation and a second time off stimulation. The same verbal fluency tasks and outcome measures as for the first study were used. The following hypotheses were investigated: (1) The total number of words on all three verbal fluency tasks would be

lower after surgery compared to before surgery; (2) the total number of semantic and phonemic switches would be lower for the category and letter fluency respectively, after surgery compared to before surgery; (3) the average phonemic and semantic cluster size on the category and letter fluency tasks would remain unchanged after surgery compared to before surgery; (4) acute STN stimulation would have no effect on verbal fluency performance and the total number of words on all three verbal fluency tasks would remain unchanged with STN stimulation on compared to when stimulation was switched off; (5) the total number of semantic and phonemic switches and the average semantic and phonemic cluster size would remain unchanged with STN stimulation on compared to when stimulation was switched off.

The results of the first verbal fluency study indicated that, as predicted, STN-DBS surgery resulted in decreased verbal fluency performance, as PD patients produced less words on all three verbal fluency tasks after STN-DBS surgery compared to their pre-operative assessment. These findings support previous research suggesting that STN-DBS induces a verbal fluency impairment. (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). In addition, the largest effect was found for category fluency, indicating that the largest deficit is seen for words requiring retrieval from semantic memory. This may be explained by research using PET in PD patients with STN-DBS during verbal fluency and suggesting decreased blood flow in cortical areas including the left inferior temporal gyrus (Schroeder et al., 2003). Further analysis of semantic and phonemic switches and clusters indicated that, as predicted, patients made fewer phonemic switches on both the letter and category fluency tasks after STN-DBS surgery compared to the pre-operative assessment, suggesting that patients became impaired in the ability to switch and shift attention between phonemic subcategories. This impairment could be explained by decreased activation of different frontal regions, including the orbitofrontal cortex, inferior frontal cortex and the dorsolateral prefrontal cortex, during verbal fluency following STN-DBS surgery (Cilia et al., 2007; Kalbe et al., 2009; Schroeder et al., 2003). Empirical evidence suggests that fronto-striatal circuits are involved in switching and set shifting (Cools et al., 2001; Owens et al., 1993). These results are also supportive of previous research reporting fewer switches after surgery compared to before surgery (De Gaspari et al., 2006; Saint-Cyr et al., 2000). My results also indicated that contrary to

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prediction, patients produced smaller semantic clusters on the category fluency task after surgery compared to the pre-operative assessment. This may reflect a deficit in retrieval from semantic memory relating to decreased activity in the inferior temporal lobe after STN-DBS surgery (Hershey et al., 2003; Schroeder et al., 2003) and could also be the reason for the greater impairment in category fluency which is more reliant on the temporal lobes than phonemic verbal fluency (Mummery et al, 1996, Perret, 1974).

The results from the second verbal fluency study indicated that acute STN stimulation did not have an effect on the total number of words produced on either of the verbal fluency tasks, as predicted. This is in agreement with the majority of the previous literature (Jahanshahi et al., 2000; Morrison et al., 2004; Okun et al., 2009; Pillon et al., 2000; Tremblay et al., 2015; Schulz et al., 2012; Witt et al., 2004), with the exception of two studies who reported stimulation-induced impairments (Schroeder et al., 2003; Wojtecki et al., 2006). However, Schroeder and colleagues (2003) only investigated the effects of STN stimulation on letter fluency and Wojtecki and colleagues (2006) found stimulation frequency dependent impairments, without finding a change between the on and off stimulation assessments. Taking my findings together with previous research it can be suggested that acute STN stimulation does not have an effect on verbal fluency performance. Further analysis of semantic and phonemic switches and clusters revealed that when stimulation was on patients made fewer semantic switches on the category fluency task compared to when stimulation was off. Previous research on the effects on switching reported patients produced more switches when on stimulation compared to when they were off stimulation, but they did not differentiate between semantic and phonemic switches (Vonberg et al., 2016). My results on clustering indicated that patients produced larger semantic clusters on the category fluency task when STN stimulation was on compared to when it was off, whereas others reported clustering to remain stable with acute STN stimulation (Vonberg et al, 2016). As discussed in the relevant chapter, the changes in cluster size together with the changes in the number of switches may reflect a stimulation-induced modulation of strategies and in the way patients retrieve information from semantic memory. This idea is supported by PET findings of acute STN stimulation induced decreased blood flow in frontotemporal regions during performance of a verbal fluency task (Schroeder et al., 2003).

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Considering the findings for STN-DBS surgery and acute STN stimulation effects together it can be stated that verbal fluency impairments associated with STN-DBS only result from and relate to the combined effects of surgery and stimulation. Furthermore, these detrimental effects on verbal fluency are the result of an executive dysfunction. An impairment of information retrieval from semantic memory seems to additionally magnify the category fluency deficit, relative to letter fluency. Despite the fact that acute STN stimulation does not have an effect on verbal fluency itself, it may modulate the strategies that patients use to retrieve information from semantic memory.

6.3 The effects of subthalamic nucleus deep brain stimulation on associative learning of verbal and visual information

The aim of my third study was to investigate the effects of acute STN stimulation on associative learning. To do so two groups of PD patients were recruited. One group consisted of PD patients, who have had STN-DBS for at least six months and the other group consisted of unoperated PD control patients. All patients were tested twice, the STN-DBS group once with stimulation on and a second time with their stimulation switched off, with order of the stimulation conditions being counterbalanced across patients. The main task was a visual conditional associative learning task. Based on previous research suggesting that PD affects two distinctive learning strategies differently (Moscovitch & Vriezen, 1990), I used two versions of the task, one requiring participants to learn the arbitrary visual associations by trial and error and the other requiring them to use feedback in order to learn arbitrary visual associations. The secondary task was a verbal paired associate learning task, with easy and hard associations to be learnt. Based on previous findings of the effects of STN-DBS on cognition in PD, the following hypotheses were tested: (1) the performance on the trial-and-error learning visual conditional associative learning task would decline with STN stimulation on compared to when stimulation was switched off; (2) the performance on the feedback learning visual conditional associative learning task would remain unchanged with stimulation on compared to when stimulation was switched off; (3) the total number of correctly learned associates on the verbal paired associate learning task

would decline for 'hard' unrelated pairs with STN stimulation on compared to when stimulation was switched off, but would remain unchanged for 'easy' related pairs.

My findings indicated that overall acute STN stimulation did not have an effect on the performance on either versions of the visual conditional associative learning task or the verbal paired associative learning task. The finding that there was no effect on the trial-and-error learning version contradicts the predictions of this study and the results of previous research, implementing the same or similar tasks, that reported that STN stimulation impaired (Jahanshahi et al., 2000a) or improved (Ventre-Dominey et al., 2016) the patients' performance. However, when I controlled for order effects and analysed patients, who were assessed on and off stimulation first separately, the results suggested that patients who were assessed on stimulation first performed worse on the two versions of the visual conditional associative learning task when they were on stimulation compared to when stimulation was switched off, whereas there was no change in performance between the stimulation conditions for patients who were assessed off stimulation first. This suggests that, in the group of patients who were assessed off stimulation first, STN stimulation affected the patients' ability to resolve proactive interference, diminishing the effects of acute STN stimulation on the trial-and-error learning version of the VCLT. Proactive interference refers to previously learned information that interferes with the process of learning new information. Imaging studies indicated activity in the left mid-ventrolateral prefrontal cortex to be related to resolving proactive interference (Jonides et al., 1998, 2000; D'Esposito et al., 1999; Bunge et al., 2001; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). Research with fMRI reported increased activation not only in frontal regions but also in the right STN and caudate nucleus in association with proactive interference resolution (Henson et al., 2002). Empirical evidence from PD patients who received surgical lesioning of the globus pallidus internus (GPi) indicated that patients with left GPi lesions had increased proactive interference after surgery compared to their pre-operative levels (Lombardi et al., 2000). The idea of STN stimulation-induced impairments in resolving proactive interference may also account for the differences in performance on the two versions of the visual conditional learning task between the on and off stimulation condition for the group of patients, who were assessed on stimulation first. While both the PD control

group and the operated group of patients who were assessed off stimulation first performed significantly better on the feedback learning relative to the trial-and-error learning version of the task at both assessments, patients who were assessed on stimulation first only showed this differentially better performance on the feedback relative to the trial-and-error version of the task when they were off stimulation. The former finding was expected based on the assumption that trial-and-error learning is related to fronto-striatal activity (Vriezen & Moscovitch, 1990). The lack of effect of the type of learning involved in the on stimulation first group also suggests that with STN stimulation on first, patients were unable to use the feedback provided to improve their learning, so they did not benefit from feedback.

In terms of the verbal paired associative learning, the analysis did not reveal any effects of acute STN stimulation on learning of either easy or hard item pairs. I expected/predicted impaired performance for the hard items only when patients were on stimulation relative to when stimulation was switched off, based on previous findings that cognitive tasks requiring higher levels of cognitive control would become impaired by acute STN stimulation (Castner et al., 2008a, b; Georgiev et al., 2016; Hershey et al., 2004; Jahanshahi et al., 2000; Thobois et al., 2007; Williams et al., 2015; Wylie et al., 2010b), whereas tasks requiring less cognitive control would not (Castner et al., 2008; Georgiev et al., 2016; Hershey et al., 2004; Mollion et al., 2011; Williams et al., 2015;Wylie et al., 2010b; Ventre-Dominey et al., 2016). My results may be a function of the nature of the task I used. During the verbal paired associative learning task learning was externally guided as with the feedback learning version of the visual conditional associative learning task. Therefore, the level of cognitive control required was relatively low. STN stimulation-induced impairments in both language and associative learning were only reported for tasks where patients had to generate responses internally (Castner et al., 2008a, b; Jahanshahi et al., 2000a).

6.4 The effects of pedunculopontine nucleus deep brain stimulation in Parkinson's disease and Progressive Supranuclear Palsy on cognition

The aim of my fourth study related to DBS of a different target, the pedunculopontine nucleus (PPN). Therefore, I aimed to investigate the effects of PPN-DBS in PD and Progressive Supranuclear Palsy (PSP) on various domains of cognitive function. To do so, the study was separated into two parts. For the first part PD and PSP patients undergoing PPN-DBS surgery were recruited and assessed on a large neuropsychological test battery covering all major cognitive domains once shortly before the surgery and a second time one year or more after the study. This was done to explore the cognitive effects in a detailed manner, because the number of previous studies on this is limited and most studies did not investigate all cognitive domains in detail and included patients who received both STN- and PPN-DBS. For the second part of the study I assessed one PD patient and one PSP patient, who developed dementia at some point after surgery, on a less extensive neuropsychological test battery once after chronically being off PPN stimulation and a second time six weeks after being switched on low frequency PPN stimulation. This was done to follow up on the findings of an independent research group who reported improved cognitive function in a PD-Dementia patient with low frequency PPN stimulation relative to when stimulation was switched off (Riccardi et al., 2015). On the basis of limited prior empirical evidence, this study was not hypothesis-driven but exploratory in nature.

The results for the first part of this study indicated that PPN-DBS surgery did not have an impact on cognitive function in general. However, there was some evidence suggesting that PPN-DBS surgery may result in impaired executive function, as the switching category fluency test and the initiation/perseveration subscale of the dementia rating scale were the most consistently declined tests, with a majority of the patients showing reliable decline. Also, 50% of the patients produced reliably more intrusions on the California verbal learning test at the post-operative relative to the pre-operative assessment suggesting deficits in monitoring. Previous research on the effects of PPN-DBS on cognition mostly reported improvements in executive function (Ceravolo et al., 2011), language (Brusa et al., 2009; Zanini et al., 2009), verbal long-term memory

(Ceravolo et al., 2011), processing speed, attention and working memory (Costa et al., 2010; Thevasthasan et al., 2010). However, these results need to be considered carefully, because some studies did not report comparisons between pre-and post-operative performance, but looked at the effects of acute low frequency PPN stimulation only (Ceravolo et al., 2011; Costa et al., 2010; Thevathasan et al., 2010). Also, the majority of the studies assessed patients, who were treated with STN- or zona incerta (ZI) - and PPN-DBS simultaneously (Ceravolo et al., 2010; Costa et al., 10; Pinto et al., 2014; Thevathasan et al., 2010; Zanini et al., 2009) and therefore findings may relate to changes induced by DBS of the other targets rather than by PPN-DBS.

The results of my study may be explained by the connectivity of the PPN. Empirical evidence from primates suggests that the PPN receives the main GABAergic input from the GPi and the substantia nigra pars reticulata (SNr) (Granata & Kitai, 1991; Noda & Oka, 1986; Shink et al., 1997). Research with rats reported glutamatergic input from the STN (Hammond et al., 1983; Jackson & Crossman, 1983; Kita & Kitai, 1987; Granata & Kitai, 1989, Steininger et al., 1992), but this was not the case in primates. The PPN also receives glutamatergic input from several cortical areas including the premotor cortex, the supplementary motor area, medial prefrontal cortex and frontal eyefields (Matsumura et al., 2000). Furthermore, animal studies reported several basal ganglia nuclei to receive excitatory input from the PPN, including, the SN (Charara, Smith & Parent, 1996; Takakusaki, Shiroyama, Yamamoto & Kitai., 1996), the STN (Edley & Graybel, 1983; Woolf & Butcher, 1986), GP (Lavoie & Parent, 1994b) and the striatum, as well as the thalamus (Hallanger et al., 1987; Lavoie & Parent, 1994a; Rye et al., 1987; Steriade et al., 1988). Taking these connections between the PPN and the basal ganglia and frontal cortex into account, it could be argued that PPN-DBS surgery interferes with frontal lobe activity and produces impairments on tests that are sensitive to frontal lobe function, such as the switching category verbal fluency task.

The findings for the second part of the study indicated that low frequency PPN stimulation might have minor beneficial effects for certain cognitive domains. The cognitive profile of the PSP patient, who developed dementia remained mostly unchanged, apart from slight improvements on the digit span, indicating that working

memory became improved with acute low frequency PPN stimulation relative to when stimulation was switched off. The patient's verbal learning became slightly impaired with PPN stimulation compared to when stimulation was off. For the second patient few aspects of cognition changed between the on and off PPN stimulation sessions. The patient declined globally and also had domain specific impairments in executive function on low frequency PPN stimulation relative to when stimulation was off. On the other hand, the patient improved on measures of working memory and attention when he was on PPN stimulation compared to the off stimulation assessment. My finding that the PPN stimulation induced improvements in working memory and attention support the findings of Riccardi and colleagues (2015) and may be explained by the elevated glucose utilization in the frontal cortex with low frequency PPN stimulation (Ceravolo et al., 2011). However, the findings of my study also indicate a detrimental effect of PPN stimulation on executive function, verbal learning and verbal fluency, which contradicts Riccardi et al. (2015), who reported these aspects to become improved with PPN stimulation. These inconsistencies may relate to the differences in profiles of the patients assessed in the two studies.

Taking the results of the first and second part of my study together it may be suggested that PPN-DBS surgery is generally safe from a cognitive perspective but produces isolated impairments in executive function. Low frequency PPN stimulation may lead to impairments in executive function and verbal learning on one hand, but also improve working memory and attention.

6.5 Theoretical and clinical implications

The findings of the first three studies of my thesis provide further knowledge about the functions of the STN. The results of the first study were relevant to theoretical works predicting that during the decision-making process the STN would be involved in accumulating and integrating evidence for alternative choices in order to compute conflict and adjust the decision threshold accordingly (Bogacz & Gurney, 2007; Frank, 2006; Mink, 1996), and previous research reporting increased reflection impulsivity with

STN stimulation during decision-making under high conflict. (Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007).

The negative findings of my study may also indicate that the STN is involved in outcome value estimation rather than computing decision conflict. Further support for this idea comes from research investigating the effects of acute STN stimulation on movement initiation speed on a simple reaction time task during rewarded and unrewarded trials (Kojovic et al., 2016). They reported that speeding of movement initiation was greater for high reward value trials only when patients were on STN stimulation relative to when stimulation was off, indicating increased responsivity to higher reward value. Another recent study, looking at the local field potential of STN neurons in PD patients during an effort based decision-task found that neuronal activity was related to both subjective cost of effort and subjective reward value and that this information was predictive of patients' decisions (Zénon et al., 2016). Additionally, they reported that neural responses of the STN did not reflect conflict. Therefore, it is possible that the STN is involved in computing cost-benefit rather than decision conflict. My first study established that not all forms of probabilistic decision-making are impaired after STN-DBS but that such impairments are only seen in tasks with conflict, time pressure or reward at stake.

Findings on the effects of STN-DBS on pathological gambling and other impulsive control disorders (ICDs) are inconsistent. While some indicated that STN-DBS would reduce pathological gambling in PD patients (Ardouin et al., 2006; Bandini et al., 2006), one case was described suggesting increased gambling with STN-DBS (Smeding et al., 2007). Smeding and colleagues (2007) reported that alteration of the stimulation parameters combined with the significant reduction of dopaminergic medication resolved pathological gambling in a man, who covered up the problem for three years. One study reported hypersexuality in 5 out of 30 patients treated with STN-DBS, however this state was largely transient (Romito et al., 2002). Similarly, Witt, Krack and Deuschl (2006) reported the case of an artist, who changed his painting imagery after STN-DBS surgery, which included sexual content. Again this form of impulsivity was resolved after a while (Witt et al., 2006). Reviews of the STN-DBS literature which has shown that STN surgery can either resolve pre-existing cases of impulse control disorders or give rise to de novo

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new cases of ICDs after surgery (Broen, Duita, Visser-Vanderwalle, Temel & Winogrodzka, 2011; Lim et al. 2010). STN-DBS outcome in relation to improvement or emergence of ICDs probably depends on the fine tuning of dopaminergic medication and STN stimulation in each individual case.

Research implementing various tasks of decision-making is also inconsistent, with some reporting increased impulsivity with acute STN stimulation (Antoniades et al., 2014; Evens et al., 2015; Green et al., 2013; Florin et al., 2013; Oyama et al., 2011; Pote et al., 2016; Rogers et al., 2011; Seinstra et al., 2016; Seymour et al., 2016), and others reporting no change or lower levels of impulsivity with stimulation on relative to when stimulation was off (Boller et al., 2014; Brandt et al., 2015; Castrioto et al., 2015; Djamshidian et al., 2013; Evens et al., 2015; Fumagalli et al., 2015; Seinstra et al., 2016; Torta et al., 2012; Seymour et al., 2016). The results of my first study have clarified that the inhibitory deficits and impulsivity associated with STN-DBS are situation and task specific which makes it clear why new cases of post-operative impulse control disorders are only reported in some patients.

The findings of my second study supported the proposal that STN-DBS leads to impaired verbal fluency and that this impairment is greater for category fluency relative to letter fluency (Combs et al., 2015; Parsons et al., 2006; Xie et al., 2016). The results indicating a decreased number of phonemic switches for both category and letter fluency following STN-DBS surgery compared to the pre-operative assessment may reflect decreased post-operative frontal lobe activity during performance of verbal fluency tasks (Cilia et al., 2007; Kalbe et al., 2009; Schroeder et al., 2003) and are consistent with the theoretical framework and empirical evidence suggesting that the basal ganglia and more specifically the STN are interconnected with various regions of the frontal lobes including the SMA, inferior frontal cortex, dorsolateral prefrontal cortex, the orbitofrontal cortex, and the anterior cingulate that may be important for performance of verbal fluency tasks (Alexander et al., 1986; Aron et al., 2007; Baunez & Gubellini, 2010; Chudasama, Baunez, & Robbins, 2003; Dias, Robbins, & Roberts, 1996; Eagle & Baunez, 2010; Eagle et al., 2008). On the other hand, the results that patients produced smaller semantic clusters on the category fluency task after STN-DBS surgery relative to pre-operative performance is

consistent with research that reported decreased blood flow in the inferior temporal lobe in PD patients with STN-DBS during verbal fluency task performance (Schroeder et al., 2003) and functional imaging research that reported activity in different areas of the inferior temporal cortex to be associated with verbal semantic processing (Vandenberghe et al., 1996). Acute STN stimulation modulated the number of semantic switches and semantic cluster size on the category fluency task between the on and off stimulation assessments, whereas the total number of correct words remained unchanged. This is consistent with Schroeder and colleagues' (2003) reports of decreased blood flow in a fronto-temporal network when patients performed a letter fluency task on STN stimulation relative to when stimulation was off, which may explain the modulation of semantic processing and switching processes during verbal fluency.

My results suggested that STN-DBS surgery induced verbal fluency impairments in PD and that these are strongly associated with an executive dysfunction. A recent study reported that higher verbal fluency scores were predictive of better quality of life and decreased caregiver burden in PD patients (Rosenthal et al., 2017), suggesting that decline in verbal fluency has an impact on the quality of life and so is relevant for the clinical management of PD. Additionally, Rosenthal and colleagues (2017) investigated factors that were related to verbal fluency impairments and reported that higher Hoehn & Yahr stage, higher age at baseline, longer disease duration at baseline, cardiovascular disease, and psychiatric symptoms were associated with impaired verbal fluency performance. In order to decrease the risk of verbal fluency impairments and subsequently worsened quality of life following STN-DBS surgery, these factors should perhaps be considered before selecting patients for treatment with STN-DBS. Research into factors that increase the risk of executive dysfunction after STN-DBS surgery indicated that age, levodopa-equivalent dosage and the axial subscore of the UPDRS in the off-medication state at baseline were indicative of an executive dysfunction post-operatively (Daniels et al., 2010; for review Hojlund et al., 2017). Yaguez and colleagues (2013) investigated the cognitive predictors for post-operative immediate story recall deficits and reported that mild impairments in intellectual status and list learning pre-operatively increased the risk of post-operative verbal memory decline. Furthermore, some empirical evidence suggested that certain surgical parameters were related to

cognitive outcome (Hershey et al., 2011; Le Goff et al., 2015; Witt et al., 2013; York et al., 2009). For example, Hershey and colleagues (2011) reported that DBS of the ventral STN is more likely to induce cognitive deficits as opposed to DBS of the dorsal STN. York and colleagues (2009) indicated that decline in verbal learning was associated with electrodes that were closer to the approximated STN and more superiorly located in the left hemisphere, verbal short-term memory decline was associated with electrodes that were located more laterally in the right hemisphere, whereas decline of verbal long-term memory was more associated with electrodes that were located posterior-laterally within the left hemisphere, decline in verbal fluency was associated with electrodes located more laterally and superiorly in the left hemisphere and those that were closer to the approximated STN and more posteriorly and superiorly located in the right hemisphere. Le Goff and colleagues (2015) suggested decline in semantic verbal fluency was associated with a more anterior cortical entry point of the left trajectory passing through the thalamus less frequently. Finally, Witt and colleagues (2013) reported that electrode trajectories intersecting with the caudate nuclei were also associated with declines in global cognition, working memory, verbal fluency and response inhibition (Witt et al., 2013). Consequently, the exact electrode position within the STN and the electrode trajectories should be considered to ensure that STN-DBS is safe from a cognitive point of view (for review see Hojlund et al., 2017).

The results of my third study indicated that acute STN stimulation impaired the patients' ability to resolve proactive interference and hence influenced the pattern of results on visual conditional associative learning tasks (VCLT). This was reflected by differences in performance on the error-and-trial and feedback learning versions of the VCLT between the groups of STN-DBS patients who were assessed on or off stimulation first and the PD control group. Patients who performed the VCLT tasks on stimulation first showed an impairment of learning with STN stimulation relative to DBS off, whereas patients who were tested off stimulation first did not show a similar deficit in VCLT learning when the stimulators were switched on. Furthermore, the results of Study 3 indicated that the patients who performed the VCLT tasks on stimulation first, failed to benefit from corrective feedback and to show the usual advantage of learning by corrective feedback over trial and error learning. These results may have clinical implications for the patients'

ability to benefit from speech therapy or physiotherapy which require a fair degree of associative learning and feedback learning after DBS surgery.

Functional imaging studies, investigating brain areas underlying proactive interference reported that activity in the VLPFC to be associated with proactive interference resolution (Jonides et al., 1998, 2000; D'Esposito et al., 1999; Bunge et al., 2001; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). Also, patients with frontal lobe lesions were more susceptible to proactive interference. Evidence for basal ganglia involvement for proactive interference comes from a study using fMRI during a paired associate learning cued-recall paradigm, that reported increased activation not only in frontal regions but also the right caudate and STN (Henson et al., 2002). These results indicate the frontal cortex as well as basal ganglia, and particularly the STN and caudate to be involved in proactive interference resolution, which is also supported by empirical evidence from PD patients with pallidotomy (Lombardi et al., 2000; Trepanier e al, 1998) and STN-DBS (Saint-Cyr et al., 2000), both leading to elevated levels of proactive interference. The findings of my study further support the involvement of the STN in proactive interference resolution during conditional associative learning.

The results of my fourth study established that PPN-DBS was generally cognitively safe but also produced some cognitive deficits especially those that relate to frontal executive function. This could be explained by PPN connections with the basal ganglia and frontal lobe regions. The PPN receives projections from the medial prefrontal cortex (Matsumura et al., 2000), the basal ganglia output nuclei, the deep cerebellar nuclei and the STN (Kang & Kitai, 1990; Saper & Loewy, 1982). Projections from the PPN target the GPi, SNc, the associative and intralaminar nuclei of the thalamus (Martinez-Gonzalez et al., 2011) and the STN (Lavoie & Parent, 1994a). More recently, it was hypothesized that the PPN may serve as an accelerating mechanism for the indirect stop pathway of the basal ganglia, by sending excitatory projections to the STN and inhibitory projections to the striatum in order to inhibit cortical targets of the basal ganglia to prevent impulsive responding (Schmidt et al., 2013). If this hypothesis is true, the present results may reflect a PPN-DBS induced dysfunction of this accelerating mechanism, resulting in patients' inability to inhibit automatic responding. In my study, this was behaviourally reflected by for

example a decreased performance on the switching category fluency task, where patients produced fewer correct words and switches post-operatively compared to their pre-operative performance.

The results concerning the two PD or PSP patients, who developed dementia at some point after PPN-DBS surgery, indicated that low frequency PPN stimulation had detrimental effects on executive function and verbal learning on the one hand and led to improved attention and working memory on the other hand. These inconsistent effects of PPN-DBS are difficult to interpret. In PD and PSP the cholinergic neurons within the PPN degenerate (Hirsch et al., 1987; Jellinger et al., 1988), and it is possible that low frequency PPN stimulation has an impact on the remaining PPN neurons and also activates the fronto-striatal network to which the PPN is intimately connected which may mediate the improvement of working memory and attention observed in these cases.

In contrast to previous findings mostly indicating improvement of specific aspects of cognitive function, such as grammatical errors or attention with low frequency PPN stimulation (Brusa et al., 2009; Ceravolo et al., 2011; Costa et al., 2010; Ricciardi et al., 2015; Thevastan et al., 2015), the results of my study suggested that PPN-DBS surgery had no overall effect on the majority of the tests of cognitive function or a detrimental effect on specific tests. Thus, patients showed a decline in performance for 4 tests requiring executive function and processing speed. The number of previous studies is limited and most of them reported improved cognition with PPN-DBS. However, it is important to mention that the majority of these studies used the stimulation on versus off methodology and do not provide a comparison between the pre- and post-operative assessments (Ceravolo et al., 2011; Costa et al., 2010; Thevastan et al., 2010). Additionally, most patients who were included in previous research had PPN-DBS in combination with STN-DBS or ZI-DBS, making it impossible to say whether cognitive effects were purely related to PPN-DBS. In my sample of 5 PD and 2 PSP patients, PPN-DBS by itself did not have a major impact on most cognitive domains and was associated with specific deficits on tests of executive function and processing speed. These results need replication in a larger and more homogenous sample.

In general, the four studies of my thesis are suggestive that from a surgical point of view both STN-DBS and PPN-DBS as surgical procedures are reasonably safe. However, it is important to mention that the overall clinical safety outcomes on an individual patient do not only depend on this but may also be influenced by how an individual could be affected by even a small change in verbal fluency or working memory. For example, a patient with a pre-existing speech impairment may be less likely to accept the same risk of verbal fluency decline as a patient without a pre-existing speech impairment.

6.6 Limitations

The studies completed as part of my PhD thesis had several limitations. The first limitation concerns the sample size. Most studies included relatively small groups of patients, reducing the statistical power. However, PD patients are vulnerable and, in many cases, unable to take part in research that requires them to stay focused for a longer period, especially if they have to do parts of the assessment off STN stimulation resulting in worsening of the motor symptoms and discomfort. Therefore, it is relatively common for behavioural studies that study PD patients to work with small sample sizes.

The second limitation concerns the time period between on and off stimulation assessments for studies investigating acute STN stimulation effects. For the convenience of the participants, the on and off stimulation sessions as well as the two assessment sessions for PD and healthy control participants took part during the same day, with a 30 minute gap between the sessions. This might have resulted in participants becoming fatigued, being less focused and feeling less comfortable especially when being off STN stimulation. This might also make it difficult to draw conclusions from my findings of acute stimulation in relation to the clinical treatment protocols, which use chronic high frequency DBS. However, previous research used similar time gaps and did not test patients on two separate occasions (eg Jahanshahi et al, 2000; Pote et al, 2017; Georgiev et al, 2017; Kojovic et al, 2016). Additionally, many participants live outside London and have to travel from far in order to participate and doing the assessment on one day is more convenient for them. It is also important to mention that in this study for STN-DBS high frequency stimulation and for PPN-DBS low frequency stimulation was used and

that the physiological mechanisms by which the cognitive changes were brought about may not be similar.

A third limitation was that I did not control for medication effects. For all studies PD patients were on their normal dopaminergic medication, and therefore it cannot be stated for certain what impact medication had for the effects that I found. Nevertheless, most research looking at the effects of DBS surgery or acute stimulation effects assessed patients on medication and it is unlikely to find a sufficient number of patients that are willing to participate in research that requires them to be off stimulation and off medication at the same time, as it would result in significant worsening of the motor symptoms and discomfort. In my experience, it was impractical to assess patients off medication and off stimulation, as this would have limited my sample sizes of willing participants even further.

A fourth limitation was that some of the tests used as part of my research (e.g. the Stroop colour-word interference task or the Trial making task) may not have been as suitable to identify the clinical impact of the described changes in cognition, as they do not necessarily measure these in a situation applicable to real life. From a clinical point of view, it is difficult to extract a translatable clinical meaning, for example explaining to a patient how semantic and phonemic verbal fluency can respond differently after surgery does not provide the patient with the appropriate information, which would be the percentage of likelihood of the patient becoming impaired in their speech and noticing this impairment on a daily basis. Other tests such as the Hayling test or a storytelling test would have been more suitable to investigate the clinical relevance of changes in executive function or language respectively. However, in this research the main focus was to further investigate the involvement of the STN and the PPN in different aspects of cognitive function, and the chosen tests were previously found sensitive to effects of DBS of these targets. Additionally, most of the tests that were used in my research are an inherent part of the test battery used for the neuropsychological assessment of PD patients undergoing DBS surgery at the functional neurosurgery unit of the National hospital for Neurology and Neurosurgery.

One final limitation has to do with the repeated administration of the cognitive tests. Considering that for the on and off stimulation studies, assessment was repeated on the same day, it is likely that participants would have experienced some 'learning to learn' and practice effects. However, where possible, parallel versions of a task were used and also inclusion of control groups as well as counterbalancing the order of the stimulation conditions helped to minimize the potential confounding effects of such practice effects.

Another factor that should be pointed out is that previous studies investigating the cognitive effects of DBS of the ventral or dorsal subregions of the STN have to be considered carefully as it cannot be stated for certain that cognitive changes are merely the result of dorsal or ventral stimulation but may be also related to activity changes in surrounding white matter tracts. In addition, MRI artefacts have only limited suitability for precisely localizing the dorsal and ventral STN.

6.7 Future directions

In future, research looking at the cognitive effects of STN-DBS should aim to conduct larger scale multicentre trials comparing PD patients with STN-DBS to matched healthy control and unoperated PD participants in order to strengthen the findings concerning the role of the STN in different aspects of cognition. Moreover, it would be interesting to investigate the impact of different surgical and stimulation parameters on the specific aspects of cognition that were considered in this thesis. In terms of STN involvement for decision-making it would be interesting to investigate and compare the dissociable effects of acute STN stimulation on reward-based and non-reward based decision-making tasks directly and also investigate the associated brain activity using fMRI or PET, in order to test the hypothesis suggested from some of my findings that the STN is involved in outcome-value estimation rather than evaluating decision conflict. Further work to firmly establish that STN-DBS induced deficits in decision-making are situation and task-specific to tasks that involve high reward stake, conflict or time pressure would be informative both from a theoretical and clinical perspective as it would clarify the role of the STN as well as outline situations that may lead to impulsivity and ICD development.

To follow up the present findings concerning switching and clustering performance during verbal fluency, it would be interesting to investigate the brain activity underlying the changes in semantic clustering post-operatively as well as the modulation of information retrieval from semantic memory with acute STN stimulation to further the knowledge about the connectivity of the basal ganglia with other cortical regions such as areas of the temporal lobes during performance of semantic verbal fluency tasks. Additionally, it would be very interesting to further investigate the effects of acute STN stimulation on proactive interference by using tasks, such as the California verbal learning task that assess the build-up and resolution of proactive interference more directly, and how changes in proactive interference may affect different aspects of cognition with STN-DBS on versus off. Finally, it would be interesting to investigate the effects of PPN-DBS surgery and low frequency PPN stimulation in a larger sample and use imaging techniques such as fMRI, PET and PPN electrode recordings to understand the exact brain mechanisms that result in the cognitive changes induced by PPN-DBS. However, given that evidence suggests that the impact of PPN-DBS on the motor symptoms of PD, particularly mobility and axial symptoms is not as impressive as expected (Stefani et al., 2007)., this form of surgery seems to be largely 'on hold' at most centres.

Finally, I have enjoyed the process of completing a PhD and have acquired a series of useful research skills. I hope my contributions to the existing literature will form the foundation for future research.

7. **Bibliography**

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8. Appendices

A. Study 1. Patient and Control Participant Information Sheet and Consent Form

<u>Patient Information Sheet</u>

UCLH Project ID number: ▮▮▮▮▮▮

Version number: 2, March 2007

Study Title: The effect of deep brain stimulation of the subthalamic nucleus on cognitive function, mood, motivation, personality, quality of life and speed of movement in Parkinson's disease

You are invited to participate in a research study conducted at the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery.

<u>What is the purpose of the study?</u>

The aim of the study that you are asked to participate in is to find out what effect deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease has on tests of cognitive function and on decision-making.

We know that DBS of the STN significantly improves the symptoms of Parkinson's disease and speeds up movement in most people who have the surgery. Relatively less information is available on the effects that DBS of the STN may have on different aspects of cognitive functioning such as decision-making. The aim of this study is to investigate the effect of DBS of the STN on decision-making in people with Parkinson's disease who have had surgery.

<u>Why have I been chosen?</u>

This investigation aims to study people with Parkinson's disease who have had deep brain stimulation of the subthalamic nucleus more than 6 months ago.. You have been chosen either because you have Parkinson's disease and have had DBS of STN..

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?

a.   What will happen to me if I take part?

Should you agree to take part, you would be asked to attend the Functional Neurosurgery Unit, at 33 Queen Square on one occasion for approximately 2 hours. You will complete the following tests twice, with your stimulation on and then off.

We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do

1. *Tests of cognitive function:* These are simple tests that assess different aspects of cognitive functioning, such as attention, planning, and generating words starting with particular letters.

2. *Measures of mood, motivation, and quality of life:* You will be asked to complete a number of questionnaires to show us if you are experiencing any anxiety or depression or feelings of apathy.

3. *Computerized decision-making task:* On the computer screen you will see a picture of a mouse, with the nose pointing to the left or right of the screen. On the basis of the sequence of presentations, you have to decide if you think the mouse is likely to run to the right or to the left and press either a right or left button.

b.   What will I be required to do?

For this assessment, you will be asked to take your medication as normal on the day of assessment. You will perform the tests twice, with the DBS STN on and off. The study will not restrict you in any other way. For example, there are no dietary restrictions or activities that we would ask you not to do.

What are known risks of the study or the side effects of the investigations?

No risks are involved during the completion of the tasks. You may become a bit tired and experience some discomfort as a result of having your stimulators switched off for about 45 minutes.

What are the possible disadvantages of taking part?

Apart from the time commitment, there are no disadvantages of taking part in the study.

What are the possible benefits of taking part?

Participation in this study will not directly give you any benefit. The study will lead to a better understanding of the role of the subthalamic nucleus in decision-making. This may in return help researchers and clinicians refine the treatment for Parkinson's disease in the future.

What would happen to the information about me that is collected? Who would have access to it?

All information, which is collected about you during the course of the research, will be kept strictly confidential. Any information about you, which leaves the Institute will have your name and address, date of birth and all identifiable information removed so that you cannot be recognized from it. The information held would include a brief medical history, if there is any, and the results of the assessment outlined above.

The 'data controller' (i.e. the organisation collecting, storing, handling and processing the information) would be the Institute of Neurology. As principal investigator, Professor Marjan Jahanshahi would be responsible by law for the safety and security of this information. No other organisations would have access to the data without his permission and if this were allowed it would be in a coded form (so that the identity of the normal subjects involved would remain anonymous).

What happens if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence,

then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns regarding this study, then these should be directed to the Director of the Institute of Neurology, Professor Mike Hanna, at the above address.

What will happen to the results of the research study?
Once we have included a sufficient number of participants in the study we would analyse all the data and would attempt to draw conclusions about the role of the STN in inhibition. We would hope to publish our findings in a scientific journal – should this be the case we would inform you of the publication and send you a copy should you wish it. The identities of individual people who participated would not be included in any such publication.

Who is organising and funding the research?
This project is being organised by the UCL Institute of Neurology. The costs of research (including researchers' salaries and equipment) are being paid by the UCL Institute of Neurology.

Withdrawal from the project
Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. All information regarding your medical history will be treated as strictly confidential and will only be used for research purposes. Your medical history and results of our investigations may be inspected by regulatory authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

Who has reviewed the study?
This study has been reviewed by the Joint NHNN / Institute of Neurology and Neurosurgery Research Ethics Committee.

Contact for further information
Please feel free to contact us for any further information.

Ms Friedrike Leimbach
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Participant Information Sheet

UCLH Project ID number: ███████

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Why have I been chosen?

This investigation aims to study people with Parkinson's disease who have had deep brain stimulation of the subthalamic nucleus more than 6 months ago. You have been chosen as a healthy control participant.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent

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form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?

c. What will happen to me if I take part?

Should you agree to take part, you would be asked to attend the Functional Neurosurgery Unit, at 33 Queen Square on one occasion for approximately 2 hours. You will complete the following tests twice, with your stimulation on and then off.

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d. What will I be required to do?

The study will not restrict you in any way. For example, there are no dietary restrictions or activities that we would ask you not to do.

What are known risks of the study or the side effects of the investigations?

No risks are involved during the completion of the tasks. You may become a bit tired.

What are the possible disadvantages of taking part?

Apart from the time commitment, there are no disadvantages of taking part in the study.

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Participation in this study will not directly give you any benefit. The study will lead to a better understanding of the role of the subthalamic nucleus in decision-making. This may in return help researchers and clinicians refine the treatment for Parkinson's disease in the future.

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Withdrawal from the project

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. All information regarding your medical history will be treated as strictly confidential and will only be used for research purposes. Your medical history and results of our investigations may be inspected by regulatory authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

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This study has been reviewed by the Joint NHNN / Institute of Neurology and Neurosurgery Research Ethics Committee.

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UCLH Project ID number: ▉▉▉▉▉

Version number: 2, March 2007

CONSENT FORM

Study title: **The effect of deep brain stimulation of the subthalamic nucleus on cognitive function, mood, motivation, personality, quality of life and speed of movement in Parkinson's disease**

Name of Principal Investigator: Prof. Marjan Jahanshahi

Please **initial** box

1 I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions

2 I confirm that I have had enough time to consider whether or not I want to be included in the study.

3 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

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4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Institute of Neurology, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

☐

5. I agree to take part in the above study.

☐

Would you like to be contacted to take part in subsequent phases of this research project to help better understand habit formation and maintenance in Parkinson's disease?

Please note that for each phase, you will be given detailed information about the study and you are free to withdraw at any time without giving any reason.

YES ☐   NO ☐

_____   _____

_____
Name of participant   Date   Signature

_____   _____

_____
Name of Person taking consent   Date   Signature
(if different from researcher)

Name of the researcher to be contacted if there are any problems:

Professor Marjan Jahanshahi,
phone: ████████████
email: ████████████████

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, University College Hospitals. Please quote the **UCLH** project number at the top of this consent form.

1 form for participant
1 to be kept as part of the study documentation
1 to be kept with hospital notes

Patient Information Sheet

UCLH Project ID number: ▮▮▮▮▮

Version number: 2, March 2007

Study Title: The effect of deep brain stimulation of the subthalamic nucleus on cognitive function, mood, motivation, personality, quality of life and speed of movement in Parkinson's disease

You are invited to participate in a research study conducted at the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery.

What is the purpose of the study?

The aim of the study that you are asked to participate in is to find out what effect deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease has on tests of cognitive function and on decision-making.

We know that DBS of the STN significantly improves the symptoms of Parkinson's disease and speeds up movement in most people who have the surgery. Relatively less information is available on the effects that DBS of the STN may have on different aspects of cognitive functioning such as decision-making. The aim of this study is to investigate the effect of DBS of the STN on decision-making in people with Parkinson's disease who have had surgery.

Why have I been chosen?

This investigation aims to study people with Parkinson's disease who have had deep brain stimulation of the subhthalamic nucleus more than 6 months ago. You have been chosen either because you have Parkinson's disease and have had DBS of STN.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?

e.   What will happen to me if I take part?

Should you agree to take part, you would be asked to attend the Functional Neurosurgery Unit, at 33 Queen Square on one occasion for approximately 2 hours. You will complete the following tests twice, with your stimulation on and then off.

We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do

7. *Tests of cognitive function:* These are simple tests that assess different aspects of cognitive functioning, such as attention, planning, and generating words starting with particular letters.

8. *Measures of mood, motivation, quality of life:* You will be asked to complete a number of questionnaires to show us if you are experiencing any anxiety or depression or feelings of apathy.

9. *Computerized test of speed of reactions:* On the computer screen you will see a stimulus to which you have to respond quickly.

f. What will I be required to do?

For this assessment, you will be asked to take your medication as normal on the day of assessment. You will perform the tests twice, with the DBS STN on and off. The study will not restrict you in any other way. For example, there are no dietary restrictions or activities that we would ask you not to do.

What are known risks of the study or the side effects of the investigations?

No risks are involved during the completion of the tasks. You may become a bit tired and experience some discomfort as a result of having your stimulators switched off for about 45 minutes.

What are the possible disadvantages of taking part?

Apart from the time commitment, there are no disadvantages of taking part in the study.

What are the possible benefits of taking part?

Participation in this study will not directly give you any benefit. The study will lead to a better understanding of the role of the subthalamic nucleus in cognition. This may in return help researchers and clinicians refine the treatment for Parkinson's disease in the future.

What would happen to the information about me that is collected? Who would have access to it?

All information which is collected about you during the course of the research will be kept strictly confidential.   Any information about you which leaves the Institute will have your name and address, date of birth and all identifiable information removed so that you cannot be recognized from it. The information held would include a brief medical history, if there is any, and the results of the assessment outlined above.

The 'data controller' (i.e. the organisation collecting, storing, handling and processing the information) would be the Institute of Neurology. As principal investigator, Professor Marjan Jahanshahi would be responsible by law for the safety and security of this information. No other organisations would have access to the data without his permission and if this were allowed it would be in a coded form (so that the identity of the normal subjects involved would remain anonymous).

What happens if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence,

then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns regarding this study, then these should be directed to the Director of the Institute of Neurology, Professor Mike Hanna, at the above address.

What will happen to the results of the research study?
Once we have included a sufficient number of participants in the study we would analyse all the data and would attempt to draw conclusions about the role of the STN in inhibition. We would hope to publish our findings in a scientific journal – should this be the case we would inform you of the publication and send you a copy should you wish it. The identities of individual people who participated would not be included in any such publication.

Who is organising and funding the research?
This project is being organised by the UCL Institute of Neurology. The costs of research (including researchers' salaries and equipment) are being paid by the UCL Institute of Neurology.

Withdrawal from the project
Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. All information regarding your medical history will be treated as strictly confidential and will only be used for research purposes. Your medical history and results of our investigations may be inspected by regulatory authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

Who has reviewed the study?
This study has been reviewed by the Joint NHNN / Institute of Neurology and Neurosurgery Research Ethics Committee.

Contact for further information
Please feel free to contact us for any further information.

Ms Friedrike Leimbach
PhD student,
Sobell Department of Motor Neurosciences
Institute of Neurology,
33 Queen Square, London WC1N 6BT.

Tel: ███████████████████
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Professor Tom Foltynie
Consultant Neurologist
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Professor Patricia Limousin
Consultant Neurologist
Functional Neurosurgery Unit
Sobell Department of Motor Neurosciences
Institute of Neurology,
33 Queen Square, London WC1 3BG

CONSENT FORM

Study title: **The effect of deep brain stimulation of the subthalamic nucleus on cognitive function, mood, motivation, personality, quality of life and speed of movement in Parkinson's disease**

Name of Principal Investigator: Prof. Marjan Jahanshahi

Please **initial** box

1   I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions

2   I confirm that I have had enough time to consider whether or not I want to be included in the study.

3   I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Institute of Neurology, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

5. I agree to take part in the above study.

Would you like to be contacted to take part in subsequent phases of this research project to help better understand habit formation and maintenance in Parkinson's disease?

Please note that for each phase, you will be given detailed information about the study and you are free to withdraw at any time without giving any reason.

YES ☐   NO ☐

_____   _____

_____
Name of participant   Date   Signature

_____   _____

_____
Name of Person taking consent   Date   Signature
(if different from researcher)

Name of the researcher to be contacted if there are any problems:

Professor Marjan Jahanshahi,
phone: ███████████
email: ███████████████████

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, University College Hospitals. Please quote the **UCLH** project number at the top of this consent form.

1 form for participant
1 to be kept as part of the study documentation
1 to be kept with hospital notes

C. Study 4 Patient Information Sheet and Consent Form

Patient Information Sheet

UCLH Project ID number: ███████
Version number: 2, March 2007

Study Title:

The effect of deep brain stimulation of the Pedunculopontine nucleus (PPN) on cognitive function in Parkinson's disease.

You are invited to participate in a research study conducted at the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery.

What is the purpose of the study?

The aim of the study that you are asked to participate in is to find out what effect deep brain stimulation (DBS) of the Pedunculopontine nucleus (PPN) in Parkinson's disease has on tests of cognitive function. There is a report from a single person with Parkinson's disease who had developed dementia that DBS of the PPN was helpful in improving cognitive function when it was switched on. Our aim is to find out if DBS of the PPN can improve cognitive function.

Why have I been chosen?

This investigation aims to study people with Parkinson's disease who have had deep brain stimulation of the Pedunculopontine nucleus. You have been chosen because you have Parkinson's disease and have had DBS of PPN.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?
   a.   **What will happen to me if I take part?**
Should you agree to take part, you would be asked to attend the Functional Neurosurgery Unit, at 33 Queen Square on two occasions for approximately 3 hours each time. You will complete a neuropsychological test battery, during the first visit with your PPN stimulators off and during your second visit 6 weeks

later, with the PPN stimulators switched on. At the end of the first visit your PPN stimulators will be switched on and left on for a period of 6 weeks.

b.   What will I be required to do?

For this assessment, you will be asked to take your medication as normal on the day of assessment. You will perform the tests twice, with the PNN DBS on and off, on two different occasions, with an interval of 6 weeks during which your PPN stimulators will be sqirched on. The study will not restrict you in any other way. For example, there are no dietary restrictions or activities that we would ask you not to do.

What are known risks of the study or the side effects of the investigations?

No risks are involved during the completion of the tasks. You may become a bit tired during the neuropsychological assessments.

What are the possible disadvantages of taking part?

Apart from the time commitment, there are no disadvantages of taking part in the study.

What are the possible benefits of taking part?

There is a report from a single person with Parkinson's disease who had developed dementia that DBS of the PPN was helpful in improving cognitive function when it was switched on. You may derive such a cognitive benefit from the PPN DBS when it is switched on. The study will lead to a better understanding of the role of the PPN in cognitive function. This may in return help researchers and clinicians refine the treatment for Parkinson's disease in the future.

What would happen to the information about me that is collected? Who would have access to it?

All information, which is collected about you during the course of the research, will be kept strictly confidential. Any information about you, which leaves the Institute will have your name and address, date of birth and all identifiable information removed so that you cannot be recognized from it. The information held would include a brief medical history, if there is any, and the results of the assessment outlined above.

The 'data controller' (i.e. the organisation collecting, storing, handling and processing the information) would be the Institute of Neurology. As principal investigator, Professor Marjan Jahanshahi would be responsible by law for the safety and security of this information. No other organisations would have access

to the data without his permission and if this were allowed it would be in a coded form (so that the identity of the normal subjects involved would remain anonymous).

What happens if something goes wrong?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns regarding this study, then these should be directed to the Director of the Institute of Neurology, Professor Mike Hanna, at the above address.

What will happen to the results of the research study?
We will analyse all the data and attempt to draw conclusions about the role of the PPN in cognition. We would hope to publish our findings in a scientific journal – should this be the case we would inform you of the publication and send you a copy should you wish it. The identities of individual people who participated would not be included in any such publication.

Who is organising and funding the research?
This project is being organised by the UCL Institute of Neurology. The costs of research (including researchers' salaries and equipment) are being paid by the UCL Institute of Neurology.

Withdrawal from the project
Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. All information regarding your medical history will be treated as strictly confidential and will only be used for research purposes. Your medical history and results of our investigations may be inspected by regulatory authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

Who has reviewed the study?
This study has been reviewed by the Joint NHNN / Institute of Neurology and Neurosurgery Research Ethics Committee.

Contact for further information
Please feel free to contact us for any further information.

Ms Friederike Leimbach

Phd student,
Sobell Department of Motor Neuroscience & Movement Disorders
Institute of Neurology,
33 Queen Square, London WC1N 6BT.
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Professor Patricia Limousin
Consultant Neurologist
Functional Neurosurgery Unit
Sobell Department of Motor Neuroscience & Movement Disorders

Institute of Neurology,
33 Queen Square, London WC1 3BG

CONSENT FORM

Title of project: **Pedunculopontine nucleus Deep Brain Stimulation
for thinking & memory problems**

Name of Principal Investigator : Pr. Marjan Jahanshahi

Please initial
box

1. I confirm that I have read and understood the information sheet (DATE) for the above study and have had the opportunity to ask questions.

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study.

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the sponsor of the trial (University College London), from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

5   I agree to my GP being informed of my participation in the study.

6. I agree to take part in the above study.

1 form for Patient;
1 (original) to be kept as part of the study documentation,
1 to be kept with hospital notes   Continued on next

page

UCLH Project ID number:
Patient Identification Number for this study: Form version: 1

<u>**CONSENT FORM**</u>

Title of project: **Pedunculopontine nucleus Deep Brain Stimulation**
for thinking & memory problems

Name of Principal Investigator : Pr. Marjan Jahanshahi

_____ _____
_____
Name of patient   Date   Signature

_____ _____
_____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____ _____
_____
Researcher (to be contacted   Date   Signature
if there are any problems)

Comments or concerns during the study

If you have any comments or concerns you may discuss these with
the investigator.   If you wish to go further and complain about any
aspect of the way you have been approached or treated during the
course of the study, you should write or get in touch with the
Complaints Manager, UCL hospitals.

1 form for Patient;
1 (original) to be kept as part of the study documentation,

336

1 to be kept with hospital notes

D. Study 2. Scoring Instructions and Sheets for Clustering and Switching

Analysis of Word Fluency data:

All word fluency tasks will be scored as follows:
  (i)   Number of repetitions (same item repeated during the 60 s)
  (ii)   Number of intrusions (production of inappropriate words)
  (iii)   number of phonemic clusters ((two successive words with the same first two words (eg arm and art), with the same second phoneme (eg barn bark or barn lark), two words which differed only in a vowel sound (eg foot, fat) or two successive words which rhymed (eg bank, blank or blast, last, flight and fright) or two words which were homonyms (eg sail, sale))
  (iv)   number of semantic clusters ((any two consecutive words sharing the same semantic category (boar, bear, or banana, lemon), or the same semantic subcategory (eg farm animals, jungle animals, pets, aquatic animals, insects or that were semantic derivatives (eg bring, brought))
  (v)   number of switches (number of transitions between clusters including single words for the phonemic and semantic tests)
  (vi)   From the tape recordings, the number of words generated in each of the 6 successive 10 s periods are calculated and plotted to show the cummulative words recalled as a function of recall time to examine whether the rate of reaching asymptote changes with stimulation on vs off.

D. Study 2 Scoring and clustering instructions and sheets for the verbal fluency tasks

<u>Scoring of clustering and switching in verbal fluency tasks</u>

Key words (taken from (Troster, et al., 1997).

- cluster - burst of words over time that are related in semantically or phonemically
- cluster size - a measure of the ability to access words within phonemic and semantic subcategories.
- switching - a measure of the ability to shift efficiently from one category to another.

NB: Errors and repetitions are included in calculations of cluster size and switching because any word that is produced provides information about the underlying cognitive processes regardless of whether or not it contributes to the total correct number of words generated (Troyer et al, 1998).

I. Phonemic Fluency/Letter Task

A phonemic cluster is defined as a group of successively generated words that:

1. begin with the same first two letters
   e.g. bat, ban, bad
2. differ only in a single vowel sound
   e.g. bit, bat/foot, fat
3. rhyme
   e.g. chip, ship
4. are homonyms
   e.g. sea, see/pane, pain
   * scored only if the subject indicates that the two words are different exemplars during the word generation task.

A semantic cluster is scored if two or more successively generated words that

1. share a semantic category
   e.g. peach, pineapple

2. are two forms of a word
   e.g. sing, sang/finance, financial

Scoring

- Count beginning with the second word. A single word is given a cluster size of 0, two words - 1, three words – 2, and so forth.

- Calculate the mean cluster size by counting the cluster size divided by the number of clusters.
- **Switches are counted as the number of transitions between clusters, including single words. A simple algorithm for calculating the number of switches is: Total switches = Total number of words (including Repetitions and Errors) – 1 – Cluster size. If there are no clusters, then the total switches is the total number of words (including repetitions and errors) –1.**
- Repetitions and rule violation errors are included in the calculation of cluster size and switches.

II. Semantic Fluency/Semantic Task (Animals)

A semantic cluster consists of successively generated words belonging to the same category.

Troyer, Moscovitch and Winocur, 1997 provide definition and categories:

"Clusters on semantic fluency trials consisted of successively generated words belonging to the same subcategories, as specified here. Sub categories are organised by living environment, human use, and zoological categories. Commonly generated examples are listed for each category, although listings are not exhaustive." (Troyer, Moscovitch and Winocur, 1997.)

"**Living Environment**:

Africa; aardvark, antelope, buffalo, camel, chameleon, cheetah, chimpanzee, cobra, eland, elephant, gazelle, giraffe, gnu, gorilla, hippopotamus, hyena, impala, jackal, lemur, leopard, lion, manatee, mongoose, monkey, ostrich, panther, rhinoceros, tiger, wildebeest, warthog, zebra.

Australia; emu, kangaroo, kiwi, opossum, platypus, Tasmanian devil, wallaby, wombat

Arctic/Far North; auk, caribou, musk, ox, penguin, polar bear, reindeer, seal

Farm; chicken cow, donkey ferret, goat, horse, mule, pig, sheep, turkey

North America; badger, bear, beaver, bobcat, caribou, chipmunk, cougar, deer, elk, fox, moose, mountain, lion, puma, rabbit, racoon, skunk, squirrel, wolf.

Water; alligator, auk, beaver, crocodile, dolphin, fish, frog, lobster, manatee, muskrat, newt, octopus, otter, oyster, penguin, platypus, salamander, sea lion, seal, shark, toad, turtle, whale.

Human Use:

Beasts of Burden; camel, donkey, horse, llama, ox

Fur; beaver, chinchilla, fox, mink, rabbit

Pets; budgie, canary, cat, dog, gerbil, golden retriever, guinea pig, hamster, parrot, rabbit

Zoological Categories:

Bird; budgie, condor, eagle, finch, kiwi, macaw, parrot, parakeet, pelican, penguin, robin, toucan, woodpecker

Bovine; bison, buffalo, cow, musk, ox, yak

Canine; coyote, dog, fox, hyena, jackal, wolf

Deer; antelope, caribou, eland, elk, gazelle, gnu, impala, moose, reindeer, wildebeest

Feline; bobcat, cat, cheetah, cougar, jaguar, leopard, lion, lynx, mountain lion, ocelot, panther, puma, tiger

Fish; bass, guppy, salmon, trout

Insect; ant beetle, cockroach, flea, fly, praying mantis

Insectivores; aardvark, anteater, hedgehog, mole, shrew

Primates; ape, baboon, chimpanzee, gibbon, gorilla, human, lemur, marmoset, monkey, orang-utan, shrew

Rabbit; Coney, hare, pika, rabbit

Reptile/Amphibian; alligator, chameleon, crocodile, frog, gecko, iguana, lizard, newt, salamander, snake, toad, tortoise, turtle,

Rodent; beaver, chinchilla, chipmunk, gerbil, gopher, groundhog, guinea pig, hamster, hedgehog, marmot, mole, mouse, musk rat, porcupine, rat, squirrel, woodchuck

Weasel; badger, ferret, marten, mink, mongoose, otter, polecat, skunk

General scoring Rules:
In the case in which two categories overlapped, with some items belonging to both categories, some items belonging exclusively to the first category, some items belonging exclusively to the second category, the overlapping items were assigned to both categories. For example, for dog cat tiger lion, the first two items were scored as pets, and the last three items were scored as feline. Cat was included in both the pet category and the feline category.

In the case where smaller clusters were embedded within larger ones, or two categories overlapped, but all items could correctly be assigned to a single category, only the larger, common category was used. For example for, sly slit slim slam, all begin with sl but an additional cluster was not scored for the last two words, which differ only by a vowel sound.

A phonemic cluster is scored when two or more successive words generated 1) begin with the same phoneme e.g. cat, cow or 2) rhyme e.g. cat, bat, & teacher, preacher.

III. Mixed Alternating Tasks

Only phonemic clusters are scored and these consisted of two successive words beginning with the same phoneme (e.g. cat, cow, or potato, pink) or which rhymed (e.g. bat, cat or bean, green) from Downes et al., 1993.

**** In a study by Raskin et al., switches were not scored for semantic clusters in a letter task and phonemic clusters in a semantic task.

**** All protocols must be scored by two independent raters and calculated using Pearson r to establish interrater reliability.

Letter F or V	**Letter A or I**	**Letter S or P**
Tot. N = ____	Tot. N = ____	Tot. N = ____
Intr/Rep = ____/____	Intr/Rep = ____/____	Intr/Rep = ____/____
Net N = ____	Net N = ____	Net N = ____
#ph.cl. = ____/____	#ph.cl. = ____/____	#ph.cl. = ____/____
×ph.cl. = ____	×ph.cl. = ____	×ph.cl. = ____
#PSw. = ____	#PSw. = ____	#PSw. = ____
#sem.cl.= ____/____	#sem.cl.= ____/____	#sem.cl.= ____/____
×sem.cl.= ____	×sem.cl.= ____	×sem.cl.= ____
#SSw. = ____	#SSw. = ____	#SSw. = ____
#10s = ____	#10s = ____	#10s = ____
#20s = ____	#20s = ____	#20s = ____
#30s = ____	#30s = ____	#30s = ____
#40s = ____	#40s = ____	#40s = ____

#50s = ____   #50s = ____   #50s = ____

#60s = ____   #60s = ____   #60s = ____

Category—Animal or Occupation

Tot. N = ____

Intr/Rep = ____/____

Net N = ____

#ph.cl. = ____/____

×ph.cl. = ____

#PSw. = ____

#sem.cl. = ____/____

×sem.cl.= ____

#SSw. = ____

Minute 1   Minute 2   Minute 3   Minute 4   Minute 5

#10s = ____   #10s = ____   #10s = ____   #10s = ____   #10s = ____

344

#20s = ____   #20s = ____   #20s = ____   #20s = ____   #20s = ____

#30s = ____   #30s = ____   #30s = ____   #30s = ____   #30s = ____

#40s = ____   #40s = ____   #40s = ____   #40s = ____   #40s = ____

#50s = ____   #50s = ____   #50s = ____   #50s = ____   #50s = ____

#60s = ____   #60s = ____   #60s = ____   #60s = ____   #60s = ____

Alternating Item—Name   **Alternating Letter—Letter**   **Alternating Letter—Item**

Tot. N   = ____   Tot. N   = ____   Tot. N   = ____

Intr/Rep   = ____/____   Intr/Rep   = ____/____   Intr/Rep   = ____/____

Net N   = ____   Net N   = ____   Net N   = ____

#ph.cl. = ____/____   #ph.cl. = ____/____   #ph.cl. = ____/____

×ph.cl. = ____   ×ph.cl. = ____   ×ph.cl. = ____

#sem.cl.= ____/____   #sem.cl.= ____/____   #sem.cl.= ____/____

×sem.cl.= ____   ×sem.cl.= ____   ×sem.cl.= ____

#10s   = ____   #10s   = ____   #10s   = ____

#20s = ____	#20s = ____	#20s = ____
#30s = ____	#30s = ____	#30s = ____
#40s = ____	#40s = ____	#40s = ____
#50s = ____	#50s = ____	#50s = ____
#60s = ____	#60s = ____	#60s = ____

Cued Alternating Categories Item	**Cued Alternating Letters**	**Cued Alternating Letter—**
Tot. N = ____	Tot. N = ____	Tot. N = ____
Intr/Rep = ____/____	Intr/Rep = ____/____	Intr/Rep = ____/____
Net N = ____	Net N = ____	Net N = ____
#ph.cl. = ____/____	#ph.cl. = ____/____	#ph.cl. = ____/____
×ph.cl. = ____	×ph.cl. = ____	×ph.cl. = ____
#sem.cl.= ____/____	#sem.cl.= ____/____	#sem.cl.= ____/____
×sem.cl.= ____	×sem.cl.= ____	×sem.cl.= ____

#10s   = ____   #10s   = ____   #10s   = ____

#20s   = ____   #20s   = ____   #20s   = ____

#30s   = ____   #30s   = ____   #30s   = ____

#40s   = ____   #40s   = ____   #40s   = ____

#50s   = ____   #50s   = ____   #50s   = ____

#60s   = ____   #60s   = ____   #60s   = ____