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The Control of Language Production and its Neural Substrates in Parkinson's Disease

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Abstract

Individuals with Parkinson's disease (PD) exhibit deficits across a range of language measures. The underlying source of these impairments has yet to be discerned, and this reflects an overarching lack of clarity regarding the participation of the basal ganglia in language production. Current accounts suggest that these nuclei play a secondary role in language processing as a product of involvement in cognitive control. In the language realm, cognitive control encompasses the processes of verbal selection and suppression. This account is consistent with the anatomical connectivity of the basal ganglia, which exchange feedback with regions of the prefrontal cortex subserving cognitive control. What remains to be discerned is the manner in which these networks participate in spoken language production, and the nature of their disruption in PD. This thesis therefore aimed to determine whether the language impairments observed in PD arise as a result of disrupted verbal selection and verbal suppression processes, and to elucidate the associated changes in frontostriatal activity.

A measure that has been widely utilised to study these processes is the Hayling Sentence Completion Task (HSCT). Critical appraisal of this task and consideration of its design in the context of other commonly employed paradigms scaffolded the conceptualisation of this thesis. A number of task limitations were identified: ability to isolate components of cognitive control, variable temporal parameters, minimal consideration of input modality, variation in response requirement, and minimal use of imaging.

Four studies were designed to address the limitations outlined above. The first utilised an object-based negative priming paradigm in which participants were required to name a picture that had previously served as a distractor. It was found that individuals with PD were unimpaired in their ability to suppress an irrelevant representation, recording a negative priming effect equivalent to healthy controls. The second study employed a hybridisation of the HSCT and a competitor priming paradigm to allow for observation of the time-course of verbal suppression. This involved integration of sentence completion trials (in which the prepotent response had to be suppressed in favour of a word unrelated to the sentence) and subsequent naming of a picture representing the suppressed response or its semantic relation. Again, the PD group performed commensurately with the control group, with the exception of error processing. The PD group were found to make significantly more errors in picture naming when the sentence completion trial immediately prior had been executed incorrectly. This effect was postulated to reflect the intermittent failure of frontal

systems responsible for modulating cognitive control, however data analysis was based on a limited number of valid trials and conclusions were thus highly speculative.

A third study was based on the observation that individuals with PD present with impairments in the suppression of a strongly prepotent response, as measured in the HSCT. However, it was suggested that this task does not consider the influence of strategy generation as separate from suppression ability. A novel fMRI variation on the HSCT was therefore utilised to address this concern. Behavioural results again demonstrated no group differences, however the PD participants presented with altered patterns of activity in task-relevant frontostriatal circuits, including hyperactivation of the striatum and dorsolateral prefrontal cortex. This hyperactivation was interpreted as evidence of compensatory mechanisms, recruited to bolster disease-driven signal loss in these circuits.

The final study considered verbal selection. This process recruits cognitive control when a number of alternative linguistic units may appropriately fulfil a task requirement, and are thus in competition. Deficits in verbal selection have been identified in PD cohorts, however this evidence is largely drawn from studies of single-word processing. It was further noted that the HSCT only included sentence stems with few competing alternatives. The study therefore utilised a variation on the HSCT, combined with fMRI, which required participants to complete sentence stems with systematically varied selection demands. Again, behavioural results revealed no main effect of group (although a group-by-condition interaction indicated that control participants recorded a significant variation in accuracy between low and medium constraint, whereas PD did not). However, imaging data revealed a significant decrease in activity in the task-relevant ventrolateral prefrontal cortex and striatum in the PD group during conditions of increased selection demand. As this group were considered to be in a mild-moderate stage of disease severity and were taking dopaminergic medication, it was speculated that results may reflect an overmedication effect in frontostriatal pathways that were as yet unaffected by disease pathology.

The overall conclusion of this thesis was that verbal selection and suppression processes were largely intact in this cohort of individuals with mild-moderate PD, and this appeared to be supported by compensatory neural mechanisms, acting to bolster the output of frontostriatal circuitry. These findings help explain the heterogeneity of cognitive-linguistic deficits observed in PD, and could have future applications in the development of treatment protocols that capitalise on these compensatory mechanisms.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

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I would like to acknowledge the intellectual contributions of Professor David Copland, Associate Professor Katie McMahon, and Dr Anthony Angwin (Chapters 2, 3, 4, 5), and Professor Bruce Crosson (Chapters 4, 5) to the conceptualisation and experimental design of the studies contained within my thesis, and the review of associated manuscript drafts.

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None.

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This thesis is dedicated to my family.

Keywords

cognitive control, language, selection, inhibition, Parkinson's disease, prefrontal cortex, fMRI

Australian and New Zealand Standard Research Classifications (ANZSRC)

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F0R code: 1702, Cognitive Sciences 60%
FoR code: 1109, Neurosciences 20%
FoR code: 1199, Other Medical and Health Sciences 20%

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List of Abbreviations

3T	3 tesla
ACC	anterior cingulate cortex
ANOVA	analysis of variance
BA	Brodmann area
BGTC	basal-ganglia-thalamo-cortical
BNT	Boston Naming Test
BOLD	blood-oxygen-level dependent
CELEX	Centre for Lexical Information
CI	confidence interval
DARTEL	diffeomorphic anatomical registration through exponentiated lie algebra
DBS	deep brain stimulation
DCM	dynamic causal modelling
dlPFC	dorsolateral prefrontal cortex
dpi	dots per inch
EEG	electroencephalogram
EPI	echo planar imaging
F	F-statistic
F	female
FLAIR	fluid-attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FOV	field of view
FWE	family wise error
GDS	Geriatric Depression Scale
GLM	generalised linear model
GP	globus pallidus
GPe	globus pallidus external
GPi	globus pallidus internal
HSCT	Hayling Sentence Completion Task
HY	Hoehn and Yahr rating scale
IFG	inferior frontal gyrus
IPNP	International Picture Naming Project
IQ	intelligence quotient
ISI	interstimulus interval
k	cluster size
LEDD	levodopa equivalent daily dosage
LMM	linear mixed model
LOF	lateral orbitofrontal cortex
M	male
M	mean
MCI	mild cognitive impairment
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
mSFG	medial superior frontal gyrus
MTG	middle temporal gyrus
n	number of cases
NA	not applicable
NART	National Adult Reading Test
NART_FISQ	National Adult Reading Test Full Scale IQ
NHMRC	National Health and Medical Research Council
p	probability
PCgC	posterior cingulate cortex
PD	Parkinson's disease
PD-CRS	Parkinson's Disease Cognitive Rating Scale

PET	positron emission tomography
PFC	prefrontal cortex
pMFC	posterior medical frontal cortex
preSMA	pre-supplementary motor area
PWI	picture-word interference
r	Pearson's correlation coefficient
ROI	region of interest
SAS	supervisory attention system
SD	standard deviation
SE	standard error
SMG	supramarginal gyrus
SOA	stimulus-onset asynchrony
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
STG	superior temporal gyrus
STN	subthalamic nucleus
t	t-value
T1	longitudinal relaxation
tDCS	transcranial direct current stimulation
TE	echo time
TEA - EC	Test of Everyday Attention – Elevator Counting
TEA - ECD	Test of Everyday Attention – Elevator Counting with Distraction
TI	inversion time
TPC	temporoparietal cortex
TR	repetition time
U	Mann-Whitney test statistic
VBM	Voxel-based morphometry
vlPFC	ventrolateral prefrontal cortex
VS	ventral striatum
WSCT	Wisconsin Card Sorting Task
x^2	Chi square statistic
YOE	years of education
z	z-score
κ	Cohen's kappa

1 Chapter One

Introduction

In his seminal work, "An Essay on the Shaking Palsy*"* (1817/2002), James Parkinson provided the first documentation of the neurodegenerative condition that would later bear his name: Parkinson's disease (PD). His paper reported the physical manifestation of a disease that eventually rendered those afflicted immobile, speechless, and bereft of independent functioning. Of interest, Parkinson's early case notes, while detailed in their description of motor impairments, made limited reference to any deficits beyond those that could be physically observed. He reported that patients were able to comprehend their predicament, though unable to express this as a result of degraded articulation skills. It can be argued that this picture of a person affected by "the Shaking Palsy" may be considered a relatively accurate reflection of the distribution of scientific attention in this field for most of the twentieth century. Much of the published literature concerned the observable motor symptoms of the disease, with limited discussion or acknowledgement of non-motor features. Recent decades have seen a considerable shift toward characterisation of the cognitive impairments associated with PD, however much remains unresolved. Furthermore, though Parkinson himself alludes to declining communicative function, there is still limited knowledge regarding the impact of the disease upon the related realm of language processing.

This chapter will provide an overview of the current state of knowledge concerning the cognitive-linguistic impairments associated with PD, and consider the broader implications of this knowledge in understanding language processing in the adult brain. The chapter commences with a brief description of the pathology of PD (1.1), before reviewing available evidence for cognitive disturbances in PD (1.2). The remainder of the review will focus on critical evaluation of language production in PD and associated neural substrates (1.3 to 1.5), with the aim of identifying the avenues of investigation that will be subsequently undertaken in this thesis. Relevant models of cognitive and linguistic processing will be considered throughout the review as required. Finally, a summary of current limitations (1.6) and an outline of the aims and hypotheses of this thesis will be provided (1.7).

1.1 Pathophysiology of Parkinson's Disease

The primary pathology of PD is the degeneration of nuclei in the midbrain that results in a dopamine deficiency within the nigrostriatal system (Bartels & Leenders, 2009; Mink, 1996; Obeso et al., 2000). This chemical imbalance alters the operation of a series of parallel frontostriatal circuits, termed basal-ganglia-thalamo-cortical (BGTC) circuits, which deliver feedback to-and-from cortical regions. Early research described five topographically segregated circuits (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000) and while several other connections have since

been postulated (for example see Di Martino et al., 2008; Ford et al., 2013; Leh, Ptito, Chakravarty, & Strafella, 2007; Ullman, 2006), these five remain the most well characterised. Each circuit arises and terminates in a distinct region of the frontal lobe, and subserves a motor or non-motor function associated with this seed region. The five primary circuits are labelled the motor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate circuits. An illustration of the non-motor circuits and overview of their function is depicted in Figure 1.

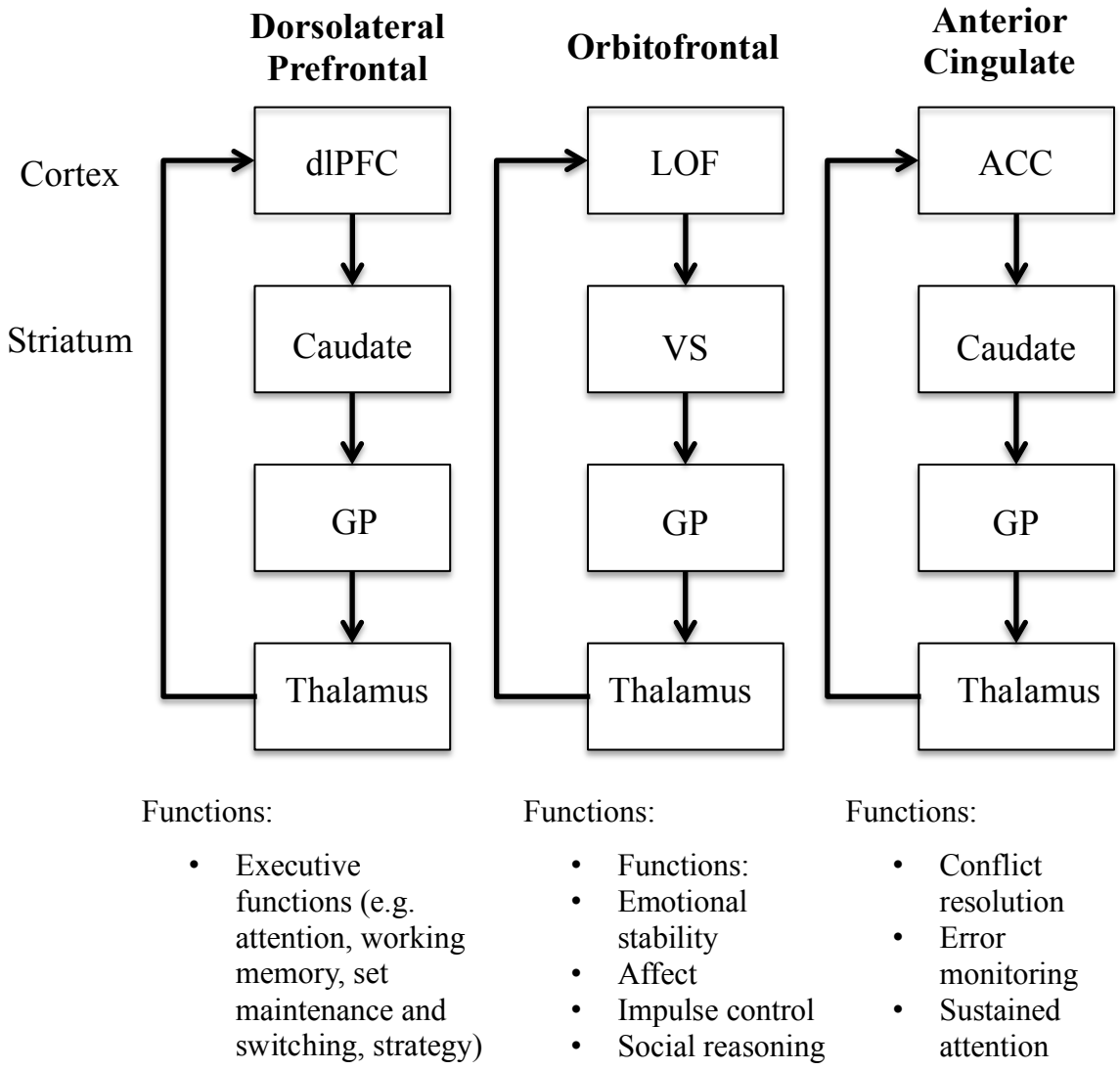

Figure 1. Simplified schematic of non-motor BGTC circuits and their associated functions. Functions adapted from "A Review of the Cognitive and Behavioral Sequelae of Parkinson's Disease: Relationship to Frontostriatal Circuitry" by D.J. Zgaljardic, J.C. Borod, N.S. Foldi, & P. Mattis, 2003, Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology, 16, p. 193. ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; GP = globus pallidus; LOF = lateral orbitofrontal cortex; VS = ventral striatum.

1.1.1 Intrinsic Circuitry of the Basal Ganglia

The intrinsic connections of the basal ganglia have also been well documented, though advances in imaging technology and in-vivo stimulation are driving constant updates and reconfigurations of their organisation. The basal ganglia are a group of structures embedded deep within the brain, and include the subthalamic nucleus (STN), globus pallidus (internal [GPi] and external [GPe] segments), striatum (comprised dorsally of the caudate nucleus and putamen, and ventrally of the nucleus accumbens), and substantia nigra (Lanciego, Luquin, & Obeso, 2012). As DeLong and Wichmann (2010) note, it is generally accepted that the striatum and STN receive feedback from widespread cortical regions. The striatum then gives rise to two primary pathways connecting selected nuclei of the basal ganglia. A direct pathway connects striatum → GPi, while an indirect pathway connects striatum → GPe → STN → GPi. The GPi then directs output to the thalamus, which exerts either a net excitatory or inhibitory effect over a specific region of the cerebral cortex. Activity in the direct pathway ultimately increases thalamocortical activity, while activity in the indirect pathway ultimately decreases thalamocortical activity. These changes in thalamocortical output may be described in simplistic terms as a "go" signal (facilitating behaviour) or a "no-go" signal (inhibiting behaviour). Nambu, Tokuno, and Takada (2002) have also provided evidence of a third, *hyperdirect* pathway that directly connects the cortex → STN → GPi, bypassing the striatum entirely. Though less understood relative to its direct and indirect counterparts, the hyperdirect pathway is thought to provide initial inhibitory output to the cortex.

The balance of activity in direct and indirect pathways is modulated by the differential influence of dopaminergic projections, originating in the substantia nigra pars compacta, upon the striatum. When dopamine is released in the striatum, activity in the direct pathway is increased and activity in the indirect pathway is decreased. In PD, the depletion of dopaminergic projections in the substantia nigra results in aberrant signalling within the basal ganglia, and subsequently within the frontostriatal loops facilitating communication with the cerebral cortex (DeLong & Wichmann, 2009). In the motor realm, this manifests as difficulty in the selection and initiation of appropriate motor plans and inhibition of competing alternatives and gives rise to the cardinal symptoms of the disease such as tremor, rigidity, and bradykinesia (Mink, 1996).

At this point, it is important to note that while PD is often used as a model of basal ganglia dysfunction, it is recognized as a complex, multisystem disease that affects a network of brain regions, including nuclei of the midbrain, brainstem, cerebral cortex and peripheral nervous system (Braak et al., 2006). Thus, in addition to the primary dopaminergic depletion, a number of satellite pathologies are also present and may worsen as the disease progresses (Halliday & McCann, 2010). These may include Lewy-related pathologies, deficiencies in a number of critical neurotransmitters in addition to dopamine, and structural atrophy of cortical and subcortical regions (Bartels &

Leenders, 2009; Braak & Del Tredici, 2008; Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004). For the purposes of the present thesis, discussion will focus primarily on behaviours arising from disruption of the nigrostriatal dopaminergic system, however, given the description above, it is acknowledged that conclusions drawn may not be solely attributable to this locus of pathology.

As stated above, much of the work concerning the changes in neural circuitry associated with PD has focused on those pathways that facilitate movement. However, the anatomical structure of BGTC circuits subserving cognitive functions has been shown to mirror that of the motor circuits, leading authors to hypothesise that the non-motor circuits function in a manner analogous to the motor circuits (Frank, 2006; Redgrave, Prescott, & Gurney, 1999). That is, the selection and suppression of "cognitive actions". This review will now consider the cognitive impairments associated with PD, and their relationship with frontostriatal circuitry.

1.2 Cognitive Impairment in Parkinson's Disease

Recent meta-analyses suggest that approximately a quarter of individuals diagnosed with PD will meet criteria for mild cognitive impairment (MCI; Aarsland et al., 2010). MCI is described as an impairment in cognitive function beyond that considered normal for age (Goldman & Litvan, 2011). Figures suggest that 15-20% of individuals with PD present with MCI as early as the time of disease diagnosis (Aarsland, 2016). Furthermore, MCI frequently occurs prodromal to dementia, with longitudinal studies demonstrating that 78% of a sample of 238 people with PD developed dementia over the course of 8 years (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003) progressing to 83% over 20 years (Hely, Reid, Adena, Halliday, & Morris, 2008). Furthermore, the risk of dementia has been observed to increase with an older age of onset of PD and lengthier disease duration (for reviews see Aarsland & Kurz, 2010; Meireles & Massano, 2012).

The cognitive sequelae associated with PD are of clinical significance, given the potential impact upon day-to-day functioning. For example, in their population-based study, Schrag, Jahanshahi, and Quinn (2000) identified a significant correlation between results on the Mini-Mental State Exam (Folstein, Robins, & Helzer, 1983) and the Parkinson's Disease Questionairre-39 (a PD specific measurement of quality of life; Peto, Jenkinson, & Fitzpatrick, 1998). A similar relationship between cognitive decline and quality of life has also been replicated more recently by Olchik, Ayres, Ghisi, Schuh, and Rieder (2016). In addition, the presence of significant cognitive deficits has been linked to greater caregiver distress or burden (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Lawson et al., 2016; Leroi, McDonald, Pantula, & Harbishettar, 2012) and higher incidence of nursing home admission (Aarsland, Larsen, Tandberg, & Laake, 2000).

The cognitive deficits observed in PD have often been likened to those observed in patients with frontal lobe damage, with memory, attention, and, in particular, executive functions implicated. This has led to the use of the term *dysexecutive syndrome* to describe the nature of the

impairment (Ceravolo, Pagni, Tognoni, & Bonuccelli, 2012; Dubois & Pillon, 1996). A large corpus of literature has been amassed demonstrating impaired performance on measures of cognitive flexibility, planning/problem solving, working memory, strategy generation, and inhibitory processing in the PD population (for reviews see Dirnberger & Jahanshahi, 2013; Dubois and Pillon, 1996; Kudlicka , Clare, & Hindle, 2011; Watson & Leverenz, 2010; Zgaljardic et al., 2003). Furthermore, these impairments have been correlated with decreased dopaminergic signalling in those BGTC circuits facilitating communication with the frontal cortex (Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, 2004; Zgaljardic et al., 2006), and their onset and severity has been linked to the dorsal-to-ventral progression of dopaminergic depletion through the striatum and migration to peripheral neural systems (Cools, 2006; Hanganu, Provost, & Monchi, 2015).

Collectively, many of the skills described above may also be referred to under the umbrella term of *cognitive control*. This term encapsulates those abilities required for goal-directed, adaptive behaviour in response to changing external and internal stimuli (Miller & Cohen, 2001). Cognitive control is required when conditions arise that are novel or require non-habitual responses, for example: the selection of an appropriate response from amongst multiple, competing alternatives; the suppression of a strongly prepotent or habitual response in order to select a task-relevant response; or the selection of a response in the face of interference from irrelevant stimuli. It must be acknowledged that the literature reflects lack of agreement concerning the conceptual definition of cognitive control, and a number of alternative perspectives have been proffered (Morton, Ezekiel, & Wilk, 2011). For the purposes of this thesis, mental operations that will be referred to under the term *cognitive control* include response selection and suppression/inhibition, performance monitoring, and cognitive flexibility. This collection of processes reflects the conceptualisation of cognitive control provided by Miller and Cohen (2001), upon which this thesis is largely based (discussed further in Section 1.2.1). These functions represent the highest level of behavioural organisation and are widely believed to be anatomically subserved by the frontal lobes and in particular, the prefrontal cortex (PFC).

1.2.1 Models of Cognitive Control

A popular model of cognitive control outlined by Miller and Cohen (2001) designates the PFC as fundamental in orchestrating top-down control over the execution of a response when this behaviour must be guided by internal states or intentions. Miller and Cohen propose a guided activation theory, in which the PFC maintains representations of information relevant to the achievement of internal goals. This information is used to exert influence over more posterior regions of the cortex in order to bias the selection and execution of a particular response, in line with internal goals.

Miller and Cohen (2001) briefly describe a potential role for phasic dopamine in a gating system that allows for updating of representations held in the PFC, however do not specifically refer to the participation of the basal ganglia in their model. Chatham, Frank, and Badre (2014) provide further elaboration on this notion, describing an expansion of guided activation theory that includes input and output gating mechanisms controlled by structures of the basal ganglia. Input mechanisms utilise dopaminergic frontostriatal pathways to allow for selective updating of the representations that are maintained in the PFC, in response to changes in the contextual environment. The output mechanism uses these same pathways to amplify particular representations within the PFC. These amplified representations are then able to exert the top-down bias described above, in order to influence activity in posterior cortical regions. Further specification of how the intrinsic connections of the basal ganglia participate in these gating mechanisms is yet to be determined. However, Chatham et al.'s work does suggest that the basal ganglia are indeed involved in cognitive control via connections with the prefrontal cortex. This is consistent with the anatomically established pathways existing between these two neural regions, in the form of the BGTC circuits described above, most notably the dlPFC circuit.

While guided activation theory has not been directly extrapolated for use in language processing, an early study by Cohen and Servan-Schreiber (1992) attempted to use its theoretical premise to explain language deficits associated with schizophrenia, a neurological condition also associated with disturbances in dopaminergic signalling and basal ganglia morphology (for review see Perez-Costas, Melendez-Ferro, and Roberts, 2010). Using an ambiguity resolution task, Cohen and Servan-Schreiber noted that individuals with this disease were limited in their ability to utilise contextual information across longer temporal windows. This resulted in errors in the selection of appropriate meaning. In line with guided activation theory, it was suggested that language deficits in this population may therefore arise as a result of impaired ability to maintain and utilise internal contextual representations in order to control subsequent actions. Though the pathophysiology that characterises this clinical population differs to that of PD, the study does provide a demonstration of how guided activation theory may be practically applied in the interpretation of language operations. Given the breadth of knowledge available concerning the pathophysiology of PD, exploration of language impairments in this population may provide additional insight into the interaction between cognitive control and language production, further developing the explanatory power of theories such as guided activation.

1.3 Language Impairment in Parkinson's Disease.

A measure that has been repeatedly included in batteries assessing executive functioning in PD is verbal fluency. However, this task is somewhat unique relative to the other executive functions described above, as it provides insight into the intersection of cognition and language. As

a higher order cortical function, language is closely entwined with cognitive processes (Bastiaanse & Leenders, 2009). Indeed, with reference to the prior description of cognitive control, verbal communication can be described as a goal-directed behaviour (Snyder, 2011). Speakers select and combine linguistic units from the vast mental lexicon in order to communicate a specific intention, and thus controlled selection and suppression processes must be at play in order to ensure that only the most appropriate units are produced. Verbal selection and suppression may therefore be described as processes involved in the cognitive control of spoken language production. Given the cognitive impairments (described above) observed in individuals with PD, it may be expected that language processing in this population will be compromised.

Individuals with PD have been observed to present with deficits in measures of semantic priming (Angwin et al., 2009; Angwin, Chenery, Copland, Murdoch, & Silburn, 2003, 2004; Arnott et al., 2010; Arnott, Chenery, Murdoch, & Silburn, 2001; Chenery, Angwin, & Copland, 2008; Copland, 2003), confrontation naming (Cotelli et al., 2007; Herrera & Cuetos, 2012; Rodríguez-Ferreiro, Menéndez, Ribacoba, & Cuetos, 2009), verbal fluency (for meta-analysis see Henry & Crawford, 2004), sentence processing (Angwin, Chenery, Copland, Murdoch, & Silburn, 2005; Colman, Koerts, Stowe, Leenders, & Bastiaanse, 2011; Grossman et al., 2002; Grossman, 1999), and higher-level language (for review see Altmann & Troche, 2011), though the nature and severity of these impairments appears to be somewhat inconsistent. In a review, Murray (2008) summarised the linguistic profile of PD and concluded that although many of the language impairments documented are associated with the onset of dementia, subtle alterations in the processing of linguistic stimuli are present even in the early stages of the disease, and these deficits are not exclusive to a single domain of language. The review aggregates evidence demonstrating the presence of impairments in morpho-syntax, lexical-semantic processing, and higher-level language. Murray further observed that these impairments have frequently been correlated with aberrant cognitive functioning, lending support to the notion of a generalised cognitive-linguistic disorder. Furthermore, she argued that decreased performance is commonly observed during those tasks that require a high level of controlled processing compared to automatic processing.

Based on the above, it can be surmised that those language tasks requiring an increased degree of cognitive control appear particularly vulnerable in PD (Caballol, Marti, & Tolosa, 2007; Murray, 2008). This description of a cognitive linguistic impairment reflects current understanding of the role of the basal ganglia in language production. Converging evidence amassed through observation of language performance in various patient-based studies have demonstrated that the basal ganglia do not play a primary role, with core language functions largely intact (Crosson et al., 2003; Hillis et al., 2002; Nadeau & Crosson, 1997). Rather, as described above, deficits appear to arise secondary to the interaction between cognitive control and linguistic processes.

1.3.1 Models of Subcortical Language Processing

Models of subcortical language processing have been developed largely in isolation from models of cognitive control and have undergone considerable reconfiguration in the past decades. As mentioned above, the cognitive control of spoken language production is generally considered to encompass the processes of verbal selection and suppression. A number of authors have suggested that selection and suppression are two sides of the same coin (Desimone & Duncan, 1995; Mostofsky & Simmonds, 2008). Interestingly, the process of selection emerges as a common theme among various reproductions of subcortical language processing models. An early model proposed by Wallesch and Papagno (1988) suggested that the subcortex participated in a cortico-subcortical loop together with anterior and posterior language regions with the role of selecting between competing lexical alternatives. This was achieved by monitoring the parallel processing of each alternative, and integrating task-relevant information such as internal motivational factors and external constraints in order to select the most appropriate response. A role in selection was also considered in Crosson's (1985) model, though here the language units referred to involved a phrase or short clause. The model posited that these language fragments are formulated in anterior language regions and then transmitted to posterior language regions for verification of their semantic accuracy. The basal ganglia were postulated to control an output gating mechanism, which allowed the verified fragment to be released for motor programming. Nadeau and Crosson's (1997) review of subcortical aphasia also makes references to selection processes, though this model focuses more so on thalamic mechanisms with little discussion of basal ganglia involvement. More recently, Crosson, Benjamin, and Levy (2007) mapped the execution of a verbal fluency task to specific activity patterns in intrinsic basal ganglia pathways, describing how the output of these pathways drove the selective enhancement or suppression of linguistic units. This model will be discussed in further detail below (see section 1.3.3).

Significant advances in imaging technology and the development of non-invasive neural modulation as an investigative tool have allowed for the development of alternative accounts of language processing in the brain, bringing a new perspective to the debate. For example, the evolution of *in vivo* language mapping during deep brain stimulation has led to the development of the hodotopical, dynamic model (Duffau, Moritz-Gasser, & Mandonnet, 2014), which holds that language is organised in parallel, segregated large-scale networks encompassing cortical and subcortical structures. However, despite these technological advances, models of language processing in the subcortex remain largely underspecified, and in turn, so too does the underlying source of language impairment in PD. Elucidating this information requires the systematic decomposition of performance on measures that capture the interaction of cognitive and linguistic processing. In previous literature, verbal fluency was widely utilised for this purpose.

1.3.2 Verbal Fluency and the Cognitive Control of Language.

Verbal fluency tasks involve the time-restricted generation of a set of semantically or phonemically related lexical items. Reports of performance on verbal fluency tasks in PD have been inconsistent. A surge of studies published in the eighties and nineties documented a variety of results even in the non-demented PD population. Findings have varied from impaired semantic and phonemic fluency relative to controls (Bayles, Trosset, Tomoeda, Montgomery, & Wilson, 1993; Flowers, Robertson, & Sheridan, 1995), to a selective deficit in semantic fluency (Auriacombe et al., 1993; Raskin, Sliwinski, & Borod, 1992), and to comparable performance between control and PD groups (Piatt, Fields, Paolo, Koller, & Troster, 1999; Taylor, Saint-cyr & Lang, 1986; Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998). Furthermore, additional contention has arisen regarding the specific impairment that can account for degraded performance. Given the number of processes underlying a verbal fluency task, specifying a point of breakdown presents a considerable challenge. Indeed, Costafreda et al. (2006) have commented that the vast array of neurocognitive variables at play are likely to hinder investigation.

Henry and Crawford (2004) performed a meta-analysis of 68 studies observing verbal fluency in participants with PD (with and without dementia) relative to healthy controls in order to address the aforementioned inconsistency. In addition, the authors sought to determine the underlying deficit, be it generalised executive functioning impairment, or difficulties with semantic memory. Semantic memory is defined here as the storage and retrieval of information related to meaning, understanding, and concepts. Henry and Crawford commented that previous studies had failed to control for heterogeneity among the PD population surveyed, especially with regards to the presence of dementia, and had not included measurements of cognitive-linguistic skills that could be considered to be covariates. The meta-analysis weighted studies based on sample size and applied a random-effects model in order to provide more generalisable results. The results of the meta-analysis demonstrated that both phonemic and semantic fluency were significantly impaired in non-demented PD patients, with a moderate effect size (Henry & Crawford, 2004). Furthermore, semantic fluency was found to be significantly more impaired that phonemic fluency, leading the authors to conclude that this impairment was best accounted for by retrieval from semantic memory.

The meta-analysis revealed a number of additional findings. Relative to measures of verbal intelligence quotient (IQ), deficits in phonemic and semantic fluency did not differ significantly, suggesting that generalised verbal intelligence impairment may contribute to overall decreased performance for participants with PD relative to controls. In addition, there was support for the *bradyphrenia* hypothesis (a generalised slowing of mental processes), although only a small number of studies included a measurement of cognitive speed and thus this effect may have been over-

exaggerated. However, these factors failed to account for why semantic fluency was impaired to a greater extent than phonemic fluency, given that both tasks were considered to place equivalent demands upon cognitive speed and other executive processes. To address this issue, the authors compared performance across the verbal fluency tasks to performance on the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001): a confrontation naming task that imposes only minimal demands upon speeded and effortful retrieval. It was found that the effect size of the deficit identified by this naming test was comparable to the effect sizes associated with deficits on both the phonemic and semantic fluency tasks. This finding was suggested to indicate that even when speed and retrieval loading was minimised, a semantic memory impairment continued to be discernible. However, the study was unable to determine whether this hypothesised semantic memory impairment was characterised by degradation of the concepts and representations stored within semantic memory, or by difficulty in the retrieval of these items. Given the lack of other converging behavioural evidence of degradation in semantic representations in PD, the former appears unlikely, and Henry and Crawford (2004) similarly supported the notion that the deficit most likely reflects problems in retrieval.

To explore this issue further, it is appropriate to discuss the component processes inherent in a verbal fluency task. For many years, verbal fluency tasks were considered to measure word retrieval. Perret (1974) was the first to argue that the task recruits a considerably larger number of processes. His conclusions were derived from a finding that performance on a Stroop Colour-Word Interference task was strongly correlated with phonemic fluency performance in a group of patients with left frontal lobe lesions. Perret postulated that a common cognitive denominator must be present in both tasks, subserved by the left frontal lobe. His suggestion was that both tasks involve a degree of response suppression. Namely, that a habitual behaviour must be suppressed in the face of novel demands. In the Stroop task, this habitual process was reading a written word (as opposed to naming the colour of the text), and in the phonemic fluency tasks, searching for a word based on initial sound (rather than conceptual meaning). Though this matter is not fully resolved, Perret's (1974) study did effectively demonstrate the importance of considering all the underlying component process at play during a verbal fluency task. Contemporary studies now consider performance on verbal fluency tasks to reflect a complex interplay of skills including lexical search strategies, retrieval, effortful response initiation, suppression of competing alternatives, selection of a response, and self-monitoring (Ruff, Light, Parker, & Levin, 1997; Shao, Janse, Visser, & Meyer, 2014) and these must be considered when interpreting data in the PD population.

Returning to Henry and Crawford's (2004) meta-analysis, an alternative explanation for impaired performance on semantic fluency tasks in the PD population may therefore relate to the ability to suppress an unwanted or irrelevant response. For example, when completing a semantic

fluency task for the category of *birds*, it is expected that a number of competing alternatives will be activated which are linked to the concept of bird (e.g., pigeon, eagle, crow) in line with current theories of semantic activation (Collins & Loftus, 1975; Levelt, Roelofs, & Meyer, 1999; Roelofs, 1992). Presumably, the option that is the most strongly activated will be selected, however in order for this to occur, the competing alternatives must be suppressed. It is possible that people with PD have difficulty with this stage of the process.

1.3.3 Verbal Selection and Suppression as a Locus of Language Deficits in Parkinson's Disease

An impairment in the ability to select an appropriate response and suppress irrelevant or competing alternatives would be in line with converging evidence from a large corpus of semantic processing studies in PD, which have provided indirect evidence for altered inhibition of semantic representations (Angwin et al., 2004; Arnott et al., 2010; Copland, Sefe, Ashley, Hudson, & Chenery, 2009; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Marí-Beffa, Hayes, Machado, & Hindle, 2005). Furthermore, a revised model of subcortical language processing outlined by Crosson et al. (2007) mapped the successful execution of a verbal fluency task to the balance of activity in the intrinsic basal ganglia pathways, and in doing so implicated verbal suppression as a critical task component. This model was based upon theoretical extrapolation of data provided by Nambu et al. (2002) that measured electrical signalling along motor pathways in the rat brain. Briefly, an initial wave of inhibition travels via the hyperdirect pathway with the effect of "re-setting" the system. This is followed by a facilitatory wave travelling via the direct pathway that acts to enhance possible responses to a point near activation threshold. A third wave carrying inhibitory signals then arrives and suppresses competing alternatives, allowing one response to be elevated above threshold and subsequently activated or "selected". Crosson et al. (2007) applied this to verbal fluency by suggesting that, for example, when items must be generated in the category of birds the initial inhibitory wave from the hyperdirect pathway resets the system by suppressing any concepts with residual activation. The facilitatory wave from the direct pathway then activates a set of possible responses e.g., pigeon, eagle, pelican. One of these responses, e.g., "pigeon", may be enhanced to a greater degree of activation than the others, due to the effects of frequency or familiarity etc. The inhibitory wave from the indirect pathway then suppresses the nodes representing eagle and pelican, allowing pigeon to be selected as the response.

Though theoretically plausible, experimental evidence for this model has yet to be provided. However, a growing body of literature does implicate intrinsic basal ganglia pathways in verbal fluency performance. For example, a decline in verbal fluency skills has been widely reported as an outcome of deep brain stimulation targeting the STN (Cilia et al., 2007; Cozac et al., 2016; Højlund, Petersen, Sridharan, & Østergaard, 2017; Parsons, Rogers, Braaten, Woods, & Tröster, 2006;

Wyman-Chick, 2016). This would be consistent with disrupted functioning of the indirect pathway, responsible for providing inhibitory signalling to cortical regions, as described above by Crosson et al. (2007).

Further downstream, relevant BGTC circuitry and associated regions of the frontal cortex have also been implicated in studies of verbal fluency. A review conducted by Zgaljardic et al. (2003) suggested that verbal fluency performance was consistently associated with impaired function in the dorsolateral prefrontal circuit in PD cohorts. They suggested that this was due to the role of the dorsolateral prefrontal cortex (dlPFC) in the maintenance and updating of a response set. This notion is corroborated by data obtained from healthy controls in a functional magnetic resonance imaging (fMRI) study conducted by Birn et al. (2010). This investigation examined the neural correlates of phonemic and semantic fluency, with automatic speech (naming months of the year) utilised as a control task. Significantly increased activity was observed in the left middle frontal gyrus (MFG), left caudate/thalamus, and left inferior frontal gyrus (IFG) when the fluency tasks (collapsed across phonemic and semantic) were compared to the automatic speech task. Furthermore, activation of left MFG and left superior temporal gyrus (STG) was greater during semantic fluency relative to phonemic fluency. The left MFG broadly encompasses the dlPFC. Its involvement in verbal fluency, simultaneously with caudate activity, is suggestive of involvement of the dlPFC circuit. Finally, Pereira et al. (2013) utilised transcranial direct current stimulation (tDCS) over the left dlPFC vs. left temporoparietal cortex (TPC) in a cohort of individuals with PD immediately prior to completion of phonemic and semantic verbal fluency tasks inside an fMRI scanner. Stimulation of the left dlPFC significantly enhanced functional connectivity in task-related networks, relative to stimulation of the left TPC. This may be taken to suggest that the dlPFC plays a critical role in facilitation of verbal fluency, in conjunction with the classical posterior language regions.

Though a considerable body of evidence supports involvement of lateral PFC regions in verbal fluency, as described above, it must be noted that other studies of word generation have identified alternative frontostriatal circuitry facilitating task execution. Crosson et al. (2003) employed a combination of word generation measures, including phonemic and semantic variations, in healthy controls with the intention of elucidating the involvement of subcortical structures in these processes. Results demonstrated the consistent recruitment of a frontostriatal loop involving the left pre-supplementary motor area (pre-SMA) and adjacent Brodmann area (BA) 32, left dorsal-caudate nucleus, and left ventral anterior thalamus in those tasks requiring lexical retrieval (based on either phonological or semantic cues). Based on the established connectivity of these regions, Crosson et al. (2003) suggested that these findings most obviously implicated this frontostriatal loop in the retrieval of lexical items from pre-existing stores, though a number of alternative

accounts were also proffered. Though these findings have yet to be replicated in a PD population, it is important that the involvement of a pre-SMA loop is considered in future investigations, in addition to the more widely acknowledged involvement on the PFC.

Identifying the locus of verbal fluency disruption in PD is critical not only for the consolidation of language processing models, but also for informing the long-term management of patients with the disease. A longitudinal study conducted by Williams-Gray, Foltynie, Brayne, Robbins, and Barker (2007) identified semantic fluency as a key clinical predictor of global cognitive decline in PD. Interestingly, they describe this task as having a basis in more posterior cortical function. However, as the evidence discussed above suggests, the cognitive control processes associated with frontostriatal circuitry appear to play a role in execution of such tasks. Specifying the precise breakdown underlying impaired verbal fluency performance in terms of verbal selection, suppression, and associated processes may lead to development of a more accurate predictor of cognitive decline, however the nature of a verbal fluency task does not allow these individual processes to be reliably isolated.

1.4 The Hayling Sentence Completion Task

Identifying the need for a more sensitive tool than fluency tasks to measure verbal selection and suppression, Burgess and Shallice (1996) developed the Hayling Sentence Completion Task (HSCT). This task comprises two components, each designed to measure an isolated ability. In Part A, response selection or 'initiation' is measured by asking subjects to provide a single word to accurately complete a high cloze probability sentence stem (e.g., The captain stayed with the sinking…"ship"). In Part B, high cloze probability sentence stems are again presented, however the subject must provide a word that is completely unrelated to the context of the sentence (e.g., The captain stayed with the sinking…"banana"). Verbal suppression (response inhibition) is measured by subtracting the score on Part B from the score on Part A. The HSCT is now a common inclusion in neuropsychological batteries as a measure of lexical response inhibition and selection.

1.4.1 The Hayling Sentence Completion Task in Parkinson's Disease

Though widely administered in healthy adults, there is a scarcity of PD studies utilising the HSCT. Given the cognitive-linguistic impairments outlined above, it would appear reasonable to assume that performance on the HSCT may be impaired in this population. Bouquet, Bonnaud, and Gil (2003) administered the HSCT and verbal fluency and trail-making tasks to a cohort of individuals with PD. Like Burgess and Shallice (1996), Bouquet et al. quantified response inhibition by subtracting response times on Part A from response times on Part B, stating that this would eliminate factors associated with response initiation or motor speech. The results demonstrated that PD participants were slower at generating an unrelated response for Part B relative to controls, however their generation of related responses in Part A was comparable

(Bouquet et al., 2003). Qualitative evaluation suggested that there was no significant difference between the groups in relation to the number of errors, or the use of strategies to complete Part B of the task. The authors concluded that impaired performance on Part B of the HSCT in PD occurred primarily as a result of disrupted inhibitory processes.

Obeso et al. (2011a) were intrigued by their observation of an overlap between inhibitory dysfunction in PD in both motor and cognitive domains and aimed to delineate this relationship in non-demented PD patients using a conditional stop-signal task (motor), and three cognitive tasks (Stroop, HSCT, and random-number generation). Errors on Part B of the HSCT were classified as either being connected to the sentence (referred to here as Type I), or somewhat related to the sentence (referred to as Type II). The difference in latency between Parts A and B was significantly larger in the control group, whereas the PD group failed to modulate their response times as a function of HSCT section. Furthermore, the PD group made significantly more Type I and Type II errors. In agreement with Bouquet et al. (2003), the authors interpreted these results as demonstrating that in PD, the ability to suppress a highly prepotent response is impaired. Based on the nature of errors made during the Stroop, stop-signal, and random-number generation tasks, it was concluded that this impairment was reflective of a generalised inhibitory deficit. Obeso et al. defined the common variable underlying these tasks as "volitional inhibition". That is, intentional and effortful inhibition, required for behavioural self-control. It encompasses the executive control that must be recruited in conditions with conflict or interference from competing responses.

O'Callaghan et al. (2013b) examined HSCT performance in non-demented PD participants. As expected, the PD group recorded more inhibition-related errors on Part B, however their response times did not differ significantly to controls. It must be noted that in contrast to earlier studies, O'Callaghan et al. did not observe a slowing of response times on Part B in the PD group relative to controls. This may be related to the manual administration of the assessment, as manual recording of response time may not capture performance with millisecond accuracy.

In a related study, O'Callaghan, Naismith, Hodges, Lewis, and Hornberger (2013a) also utilised voxel-based morphometry (VBM) to determine the grey matter correlates of HSCT performance in a group of 25 individuals with PD, relative to 15 age-matched controls. Similar to the previous study (described above), O'Callaghan et al. did not observe a difference in response latency between groups, however the PD group did record a significantly greater number of inhibition-related errors. Structural imaging analysis revealed that grey matter atrophy in the medial orbitofrontal cortex, the right lateral orbitofrontal cortex, the insular, and the inferior frontal cortex co-varied with total error score in this group. The authors concluded that structural abnormalities in these areas contribute to the deficits in inhibitory control observed in PD, however as it has been previously established that VBM requires large samples in order to produce reliable data, this

finding needs to be viewed with caution. Nevertheless, it is of interest to note that the regions implicated in O'Callaghan et al.'s (2013a) analysis are in line with current understanding of basal ganglia involvement in cognitive functions, as both the orbitofrontal cortex and inferior frontal cortex participate in frontostriatal circuits (Ford et al., 2013; Middleton & Strick, 2000).

1.4.2 Imaging Studies of the Hayling Sentence Completion Task in Healthy Adults

With the exception of O'Callaghan's et al.'s (2013a) VBM study, few authors have observed performance of the HSCT in a PD population in combination with neuroimaging. However, positron emission tomography (PET) and fMRI studies undertaken in healthy controls have provided some insight into the neural mechanisms subserving Part A and Part B of the task, and this has informed hypotheses regarding the specific cognitive-linguistic processes involved in each.

Nathaniel-James, Fletcher, and Frith (1997) employed a combined PET and behavioural paradigm in order to observe the neural regions activated during completion of the HSCT in six young adult males. When compared to a reading baseline, both Parts A and B of the HSCT were associated with increased regional cerebral blood flown in the frontal operculum, the left IFG and the right anterior cingulate cortex (ACC). Interestingly, comparison between Parts A and B revealed increased activity in the MTG (middle temporal gyrus) and the left IFG during response initiation only. Given that the HSCT Part B is typically considered to place greater demands on semantic search, retrieval and suppression processes, this result is not consistent with predictions. The authors suggested that the lack of activation represented either a deactivation of word generation networks that were inappropriate during the suppression task, or inhibition processes present during Part A that were involved in suppressing automatically activated words. It was proposed that the left IFG may be involved in word search strategy in the absence of the external cue and supports intrinsic word generation, particularly as the area is also frequently observed in studies examining word retrieval (Costafreda et al., 2006; Hirshorn & Thompson-Schill, 2006; Moss et al., 2005).

Collette et al. (2001) also employed the HSCT in a combined PET and behavioural paradigm, designed to elucidate the neural substrates underpinning initiation and suppression. These authors defined inhibition as "the processes which allow restraining access of strong but situationally inappropriate responses". Their study was based on the design of Nathaniel-James et al. (1997) however the interstimulus interval (ISI) was manipulated, in order to maximise the inhibitory loading of the task. In addition, strategies that supported response generation for Part B were provided to participants, and they were asked to avoid their use. Such strategies included naming of objects in sight, naming of category members, or use of a response provided previously during Part A or the baseline reading condition. Here lies a clear distinction between Collette et al.'s (2001) paradigm and that of previous authors. It could, however, be argued that this step may

have confounded performance, due to increased cognitive loading. For example, in addition to suppressing those alternatives automatically activated in response to the sentence string, the participants must also recall and suppress any responses that could be consistent with an aforementioned strategy. Post-test questioning was also conducted in order to verify that subjects had not used self-formulated strategies to complete the task.

In line with the findings of Nathaniel-James et al. (1997), Collette et al. (2001) observed a significant increase in activation in the left frontal operculum in the initiation condition vs. reading. However, contrary to these previous studies, when inhibition and initiation were compared Collette et al. found increased activation in the MFG and the IFG during the suppression component. Activity in the left IFG was significantly higher in the inhibition condition than all other tasks. In addition, activity in the left MFG was increased during the inhibition task and relatively decreased in the initiation task relative to the baseline condition. This is in direct contrast to Nathaniel-James et al. (1997), who observed increased activity in the left IFG during the initiation component of the task only. Collette et al. concluded that the left IFG is involved in generic semantic retrieval operations, and there is a considerable body of evidence supporting this view (Binder, Desai, Graves, & Conant, 2009). This may offer some explanation as to the discrepancy between studies. Collette et al. (2001) commented that due to the extended inter-stimulus interval present in Nathaniel-James et al.'s design, there was a period of uncontrolled cognitive processing which may have served to mark the distinction between inhibition and initiation processes. If the left IFG is involved in generic semantic operations (Hirshorn & Thompson-Schill, 2006; Moss et al., 2005), it may have been active during this time as participants reflected on their responses or considered alternatives. Collette et al. (2001) also performed correlational analysis in order to determine the relationship between response time and cerebral metabolism for each task. Results demonstrated a specific, positive correlation between response time and metabolism in the MFG bilaterally, the left superior parietal cortex and the left cuneus. The left dlPFC and left IFG (ventrolateral PFC portions) were also implicated in both suppression and initiation conditions relative to rest in an fMRI study of the HSCT conducted by Allen et al. (2008). Activation in the left dlPFC was significantly greater during the suppression condition, relative to initiation.

The imaging studies described above commonly implicated regions of the PFC, including the dlPFC and left IFG (interchangeably termed the left ventrolateral prefrontal cortex [vlPFC]), in parallel activation with posterior language regions (e.g., STG, MTG) during execution of Parts A and B of the HSCT. These findings are consistent with Miller and Cohen's (2001) model of cognitive control, in which prefrontal activity influences the generation of a response in more posterior cortical regions. Both the dlPFC and vlPFC (IFG) have been demonstrated to share reciprocal connections with the basal ganglia (Di Martino et al., 2008; Leh et al., 2007; Middleton

& Strick, 2000; Ullman, 2006). Taken together with the widely documented deficits experienced by individuals with PD when completing the task, this may be suggestive of a role for the basal ganglia in verbal selection and suppression, via frontostriatal circuitry.

1.5 Critical Appraisal of the Hayling Sentence Completion Task

As stated, the HSCT has been widely utilised as a measure of verbal selection and suppression and is a frequent inclusion in neuropsychological batteries. However, it can be argued that the task is limited in its capacity to provide a complete picture of these skills. Critical appraisal and dissection of the HSCT will serve as the basis for the development of four complementary studies of cognitively controlled spoken language production in PD in this thesis, each examining a specific aspect of processing. The following subsections will address each aspect in turn and provide a brief overview of how the identified limitations may be addressed methodologically.

1.5.1 Semantic Inhibition and the Influence of Task Design

The HSCT utilises a sentence completion design to measure inhibition of a prepotent response, however it has been demonstrated that syntactic processing may be taxing upon attention and working memory resources (Lee, Grossman, Morris, Stern, & Hurtig, 2003; Walsh & Smith, 2011). The demands associated with syntactic processing could contribute to difficulty in generating a response. It may be difficult to isolate the efficiency of inhibitory mechanisms based purely on this task, due to variable delays between the activation of prepotent concepts, their suppression, and the generation of an alternative response, as this could be subject to the length of the sentence and the individual's parsing of clausal elements within. A verbal suppression task that utilises single-word stimuli may be necessary in order to address these potential confounds.

As it stands, a large number of methodologies that consider single-word processing have been employed in the study of inhibition in PD including semantic priming (generally incorporating lexical decision), picture-word interference (PWI), and negative priming paradigms. However, a brief review of the current literature reveals considerable inconsistency regarding performance on these tasks in PD, and hence the integrity of suppression mechanisms in this population (see Chapter 2 for an elaborated discussion).

Negative priming represents an alternative means of investigating semantic inhibition, and allows consideration of single word production without the above sentence-based influences. However, when a version of this task that utilises visuospatial stimuli (location and identity priming) has been administered in PD cohorts, results have been conflicting. While some authors have identified enhanced negative priming in PD (difficulty overcoming residual inhibition; Stout, Wylie, Simone, & Siemers, 2001; Wylie & Stout, 2002) others have reported absence of negative priming in this population, despite its presence in control groups (Filoteo, Rilling, & Strayer, 2002; Troche, Trenkwalder, Morelli-Canelo, Gibbons, & Rammsayer, 2006).

Appraisal of the semantic priming, negative priming, and PWI literature identifies several elements of task design that may account for the discrepancies in findings. Variation in characteristics such as input modality (e.g., visuospatial vs. picture stimuli vs. written word), response requirements (lexical decision vs. overt naming), and the specific nature of the inhibition itself all emerge as potential points-of-difference across studies that report contrasting findings. Several of these factors are exemplified in Castner et al.'s (2007b) study of lexical-semantic inhibition in individuals with PD who had undergone deep brain stimulation (DBS) surgery. The investigation utilised two assessments designed to measure lexical-semantic inhibitory mechanisms. The first was a PWI task, which required participants to name a target picture surrounded by distractor printed words. The second was the HSCT, administered as per the original instructions. Each task was administered twice, once when STN stimulators were switched on and once when they were switched off. During the off-stimulation condition, the PD participants demonstrated significantly slower response times and made a larger number of errors on the HSCT Part B relative to the on-stimulation condition and healthy controls. In contrast, the magnitude of the interference effect elicited by written distractor words in the PWI task was equivalent across PD participants and controls, irrespective of stimulation.

With reference to the issue of input modality, it is noted while both tasks required suppression of task-irrelevant representations, the PWI task utilised the naming of picture stimuli (visual input), while the HSCT utilised sentence completion (orthographic input). Cognitive neuropsychological models of single word processing consider visual and orthographic information to be parsed via distinct pathways prior to accessing the semantic system (Kay, Lesser, & Coltheart, 1992). Thus comparison across these two modalities may be inappropriate.

Castner et al.'s (2007b) observations also speak somewhat to the question of domain-specific vs. domain-general mechanisms of inhibition. Castner et al. attributed the differing performance on the PWI task and the HSCT to the underlying nature of the tasks. They suggest that the PWI task is a measure of interference control, which is relatively intact in PD, while the HSCT requires generation of a novel response and suppression of a stronger but inappropriate response, recruiting behavioural inhibition processes. It was argued that stimulation of the STN restored the function of such behavioural inhibition processes to a level comparable with controls. This is in line with the comments of Shao, Roelofs, Martin, and Meyer (2015) who discussed the possibility of multiple, independent mechanisms operating to support dissociable types of inhibition. From this perspective, there are qualitative differences between behavioural inhibition (the effortful suppression of a response) and interference control (the capacity to ignore or selectively divert attention from irrelevant stimuli). The distinction somewhat echoes the premise of previous authors who have described variability in cognitive performance in PD as a function of internally vs.

externally available cues (Bouquet et al., 2003; Brown & Marsden, 1988). This may explain Castner et al.'s (2007b) finding of poorer performance on the HSCT, requiring internal response generation, relative to the PWI, in which the response is available in the form of a picture.

The present thesis will seek to address these limitations in task design by examining the performance of PD subjects on an object-based negative priming experiment (Chapter 2). Input modality will be strictly controlled to include visual-semantic stimuli only, and participants will be required to overtly name these representations. Comparison of response latency between an item suppressed in the previous trial and an item unrelated to the previous trial will further allow for a more direct measure of inhibition success.

1.5.2 The Time-course of Inhibition in Parkinson's Disease

The HSCT only provides a relatively static view of inhibition, with the integrity of processes only considered from the offset of the sentence to the onset of the verbal response. This reflects an aspect overlooked in many studies of inhibitory processing both in healthy controls and clinical populations: the fate of a suppressed item over time. A study conducted by Wheeldon and Monsell (1994) in healthy controls demonstrated the importance of considering changes in priming effects as a function of time. Their study employed a competitor priming design that asked participants to alternatively provide a word in response to a given definition, and name pictures of items that were semantically related to the target word of definition trials. When the picture was presented immediately after the definition, a facilitatory effect occurred, as a result of spreading activation to nearby related concepts. When two intervening trials occurred before the target picture was presented a competitor priming effect was induced, which slowed the subsequent naming of semantically related items. This was hypothesised to arise from the inhibition of semantic competitors to the definition's target word, allowing the target word to be enhanced for production. These results suggest that the nature of activation in semantic networks may alter in a predictable fashion over time. However, the study did not consider the fate of those items that were initially and actively suppressed.

Semantic priming paradigms undertaken in PD cohorts have demonstrated that deficits in inhibitory processing appear to emerge when the interval between presentation of a prime and probe is lengthened to 1-2 seconds (Angwin et al., 2005; Arnott et al., 2011; Longworth et al., 2005; for further discussion see Chapter 3). Copland et al. (2009) examined ambiguity priming over several intervening trials and found that individuals with PD were impaired in their ability to maintain inhibition of a representation over this increased time period. However, these priming paradigms have employed lexical decision as their output requirement, and thus are unable to demonstrate how the production of a previously inhibited response may be affected as a function of time. In conversation, when one linguistic unit is suppressed either in favour of another in order to limit its

interference, it may be that the suppressed item must be retrieved and produced within proceeding utterances. This prompts the question as to how the suppression of representations is maintained and subsequently resolved over time, and further, whether this process is disrupted as a result of PD pathology. Determining the nature and integrity of lexical-semantic inhibition processes over time in people with PD could offer some insight into the discourse maintenance difficulties that are documented in this population (Copland, Chenery, & Murdoch, 2001; Murray & Stout, 1999).

A related issue arising from the design of the HSCT is that the integrity of the inhibition mechanism is only indirectly assessed as a presumed requirement for the production of an unrelated response. Measuring an individual's ability to produce this prepotent response subsequent to its supposed suppression will more directly capture the effect of inhibition, however such a study has yet to be undertaken. The present thesis will address this issue by investigating the performance of individuals with PD on a novel hybridisation of the HSCT and Wheeldon and Monsell's (1994) competitor priming paradigm (Chapter 3). Participants will be required to name a pictured representation of the prepotent response presumed to have been suppressed during execution of a preceding sentence completion trial (analogous to Part B of the HSCT). Response latency and accuracy will be measured when the picture trial occurs both immediately after the associated sentence trial, as well as when it occurs after several unrelated, intervening trials. This methodology is expected to enhance current understanding of the time-course of inhibition during spoken language production, and further elucidate the nature of inhibitory deficits in PD.

1.5.3 The Influence of Strategy Generation

A critical factor that Burgess and Shallice (1996) did not quantitatively account for in the design of the HSCT is the difference in underlying component processes present in each section of the task (Part A and Part B). They suggest that with the exception of the nature of the response, each is identical. However, it can be argued that this is not the case. Part B requires an additional step that is not present in Part A of the task, and that is the generation of an alternative set of possible responses. This process is presumably streamlined by the use of an internally generated strategy, for example, selection of a response from a semantic category (e.g., fruits), or naming of items in the visual field. It must be acknowledged that Burgess and Shallice did in fact note that strategy could be used to aid completion of Part B, however they did not account for this in their calculation of response suppression. Thus, the algorithm for determining the cognitive process of suppressing a prepotent response is not complete (for further discussion see Chapter 2 and Chapter 4).

It is acknowledged that many of the HSCT studies described above did attempt to account for the influence of strategy (Bouquet et al., 2003; Castner et al., 2007b; Collette et al., 2001; Obeso et al., 2011a), however this was achieved through the use of subjective, qualitative rating scales and

thus does not inform robust conclusions. As a result, studies that have referenced performance on the HSCT as evidence for an impairment in verbal suppression may be underspecified. This is particularly relevant when using the HSCT to observe verbal suppression in PD, as it has been previously established that this population present with deficits in strategy generation (Taylor et al., 1986). The possible influence of strategy generation has implications not only for utilisation of this task in determining the integrity of inhibition mechanisms, but also for the allocation of particular cognitive functions to neural regions observed to be active during Parts A and B of the task. For example, the conclusions of Nathaniel-James et al. (1997), Collette et al. (2001), and Allen et al. (2008) concerning neural substrates of verbal selection and suppression (described above, see Section 1.4.2) may relate to a number of potential sub-processes including strategy formation.

Recognising this significant limitation, de Zubicaray, Zelaya, Andrew, Williams, and Bullmore (2000) developed the Category Judgment and Substitution Task, a novel paradigm analogous to the HSCT, designed to measure verbal suppression and selection while quantitatively accounting for strategy use. This was combined with fMRI in order to elucidate underlying neural substrates. Results provided support for the notion that the processes of verbal response initiation and response suppression are subserved by unique cortical regions. The study also demonstrated the significant influence of strategy utilisation in generating an alternative response, analogous to Part B of the HSCT. In the suppression condition, 94% of responses were deemed to be generated based on the use of a strategy. Relative to the initiation condition, this was associated with increased activity in a network of frontal regions including the orbitofrontal cortex, left dlPFC and the anterior cingulate gyrus. Behaviourally, slower response times were noted in Part B (response suppression) relative to Part A (initiation). This correlated with more extensive activation of cortical regions, possibly indicative of the increased cognitive demand associated with effortful suppression. De Zubicaray et al. hypothesised that the dlPFC is involved in strategy implementation, as it was only observed to be active during Part B of their task and 94% of responses here were considered to be strategic.

De Zubicaray et al.'s findings (2000) support the suggestion that the HSCT's capacity to provide a measurement of verbal suppression may be confounded by the need to internally generate and implement a facilitating strategy. It therefore cannot be conclusively stated that people with PD exhibit impairment on Part B of this task as result of deficits in verbal inhibition, as has previously been claimed. Confirmation will require the investigation of these processes in a PD cohort. It must be noted that de Zubicaray et al.'s task employed single-word stimuli, and did not require the sentence-level semantic integration demanded by the HSCT. Furthermore, the authors suggest that knowledge of the high-frequency categories of animals, vegetables, and body-parts is specialised and highly robust, making these items less vulnerable to competition. Therefore, to more reliably

address the issue of interference from strategy generation in the HSCT paradigms must be developed that can tease apart disruptions in inhibitory processing of lexical-semantic representation from compromised internal strategy generation and implementation, while otherwise minimising departures from the traditional HSCT design. In response to these issues, the present thesis will include an experiment that compares performance on Parts A and B of the HSCT to a novel condition designed to eliminate the need for strategy generation when producing an unrelated response (Chapter 4).

1.5.4 The Influence of Contextual Constraint Upon Verbal Selection

The HSCT uses sentences which have had the final word removed. An important variable to consider with regards to the difficulty of the task is the cloze probability value of the sentence stem. When a sentence stem has a high cloze probability it means that the most common response to complete the sentence occurred with a high frequency in the normative population. As a result, the number of possible alternative responses likely to be activated is fairly limited. This allows the researcher to ensure that in Part A, significant suppression demands are not introduced. For example, in a low cloze probability sentence such as "The man who was arrested was very …" there are a large number of words that could logically complete the sentence. As a result, response selection will be slowed due to increased competition, and thus increased suppression requirements. The original HSCT only includes sentences with high cloze probability (Burgess & Shallice, 1996). However, though several of the studies discussed above utilised an expanded version of the task, the authors have not disclosed the cloze probability of the sentences they have employed, and do not make mention of how any variation has been controlled.

The potential for variability in performance on Part A of the HSCT as a function of contextual constraint warrants further investigation. As discussed above, cognitive control mechanisms are thought to be recruited for those language processes that require a departure from automatic processing in order to align behaviour with the maintenance of an internal goal. This is the case when more than one word may appropriately fulfil task-demands, as occurs when a sentence stem carries low contextual constraint.

The selection of an appropriate linguistic unit from amongst multiple alternatives is a process that has received considerable attention in the healthy control literature. While initially only defined by the concept of "choosing one from among many", extensive investigation of the process has led to revision of its theoretical mechanism. Badre, Poldrack, Pare-Blagoev, Insler, and Wagner's (2005) two-pronged model of selection emphasises the importance of considering both selection among multiple alternatives (termed *post-retrieval selection*, occurring when numerous appropriate concepts are activated by the available contextual information) and *controlled retrieval* (the bottom-up selection of linguistic units required when insufficient contextual information is

available to facilitate top-down activation of relevant concepts). The vlPFC has been widely associated with facilitation of these processes (Badre et al., 2005; Nagel, Schumacher, Goebel, & D'Esposito, 2008; Snyder et al., 2011), though a growing body of evidence also implicates the striatum (Argyropoulos, Tremblay, & Small, 2013; Crosson et al., 2003; Ketteler, Kastrau, Vohn, & Huber, 2008) and to a lesser extent, the pre-SMA (Crosson et al., 2003).

Given the proposed involvement of both the vlPFC and the striatum in frontostriatal circuitry (Di Martino et al., 2008; Leh et al., 2007), it would appear reasonable to assume that controlled selection may be affected by the pathology of PD. Furthermore, several of the models of subcortical language function, outlined above, make reference to a role for the basal ganglia in the selection and/or release of linguistic units (Crosson, 1985; Crosson et al., 2007; Nadeau & Crosson, 1997; Wallesch & Papagno, 1988). Despite this, little exploration of verbal selection under conditions of increasing demand is evident in the PD literature to date. Several authors have demonstrated the existence of a verb generation impairment (and, to a lesser degree, noun generation, see Crescentini, Mondolo, Biasutti, and Shallice [2008]) in this population (Boulenger et al., 2008; Fernandino et al., 2013; Peran et al., 2009; Rodríguez-Ferreiro et al., 2009), which has been attributed to the greater number of competing alternatives that may be associated with verbs, thus reflecting a selection deficit. (Note however that an alternative hypothesis suggests the verb generation impairment in PD can be explained via the theory of semantic embodiment [Cardona et al., 2013]. This issue will be discussed further in Chapter 5).

Notably, studies exploring verb generation in PD have been limited to use of single word stimuli. If an impairment in selection among competing alternatives is the locus of this deficit, it might be logically hypothesized that any stimuli that elicit such conditions may be expected to induce disruption. Furthermore, generation of selection demands as a result of a contextually constrained sentence may provide a better indication of how such a deficit may manifest in functional communication. To address these issues, the present thesis will incorporate a study examining the influence of variable contextual constraint on response generation in a task analogous to Part A of the HSCT (sentence completion) and its underlying neural substrates (Chapter 5).

1.6 Summary of Limitations in the Current Literature

Converging evidence suggest that individuals with PD may present with impairments in specific aspects of spoken language production as a result of underlying deficits in cognitive control, arising from aberrant frontostriatal activity. However, the precise nature of these impairments remains unresolved, and this reflects similar limitations in current models of subcortical language processing. Though several accounts have been proffered, a unified model describing the interaction of subcortical processes with cortical language control mechanisms has

yet to be fully specified. Systematic evaluation of the complementary processes of verbal selection and verbal suppression in a PD cohort is required in order to address outstanding issues. Existing literature in this field has been limited by potential confounds associated with input modality (picture vs. orthographic stimuli) and syntactic processing demands (single words vs. sentence-based stimuli). The time course of semantic inhibition has received little attention in PD, and those studies that have addressed this issue have not observed impact on single-word production (instead utilising lexical decision paradigms, which require no verbal output. Note that this limitation will be discussed further in Chapter 2). Although the HSCT, designed to measure verbal inhibition and selection, has been administered in PD cohorts, the potentially confounding influence of strategy formulation upon generation of an unrelated response in Part B has not been considered. The selection of a word to correctly complete the sentence stem, as in Part A has also not been investigated when sentence stimuli carry increased selection demands. Finally, there has been limited utilisation of combined behavioural and neuroimaging paradigms in this population, thus limiting the extent of knowledge concerning possible changes in underlying neural circuitry.

1.7 Thesis Aims and Hypotheses

This thesis aims to determine whether the language deficits reported in PD can be explained by underlying disruptions to verbal selection and verbal suppression, and elucidate the associated functional changes in the neural mechanisms responsible. In addition, comparison with a cohort of age-matched healthy controls will advance current understanding of how the subcortex participates in language processing in the adult brain. This will be achieved through the completion of four complementary studies, designed to address the limitations outlined above, that will utilise a combination of behavioural and neuroimaging methodologies. It is expected that findings derived from these studies may contribute to the refinement of current models of language processing.

The study described in Chapter 2 will determine the ability of individuals with PD to inhibit an irrelevant visual-semantic representation by measuring differences in response latency when naming a picture that was previously ignored relative to a picture that has not been previously encountered. This will be achieved using an object-based negative priming paradigm, based on that developed originally by Tipper (1985). Additionally, response latency will also be measured when naming items semantically related to a previously ignored object, in order to indirectly observe the spread of inhibition throughout the semantic network. This study design will address a number of limitations present in the literature, by strictly controlling input modality, limiting syntactic demands with the use of single-word stimuli and responses, and providing insight into how a previously suppressed word is retrieved and produced by requiring an overt naming response, rather than a lexical decision. Based on reports of impaired ability to inhibit irrelevant representations in

the PD literature (Marí-Beffa et al., 2005) it is hypothesised that the PD group will not exhibit a negative-priming effect.

Chapter 3 will examine the time-course of semantic inhibition and its integrity in PD by adopting a novel hybridisation of the HSCT and a competitor priming paradigm. Participants will be required to read a high cloze probability sentence with the final word removed, and overtly provide a single word that is completely unrelated to the context of the given sentence, as per HSCT Part B. These trials will be interleaved with picture naming trials, in which a participant must correctly name a black and white line drawing of an object. The relationship between the prepotent response presumed to have been suppressed in the sentence completion trial and the pictured item will be manipulated to include items that are identical, semantically related, or unrelated. A lag will also be incorporated in order to observe the maintenance of inhibition over time. Thus, picture items will be presented either immediately after the corresponding sentence trial, or after a delay of two intervening trials. Based on evidence suggesting that individuals with PD have difficulty maintaining inhibition over time, and converging evidence of disrupted signalling in frontostriatal pathways thought to support cognitive control, it is hypothesised that the PD participants will not record a significant difference in response time for items that are unrelated to the suppressed prepotent response relative to items that are identical or semantically related, after the long delay.

Chapter 4 will employ a novel variation on the traditional HSCT design in order to determine whether the deficits in completing Part B of this task (frequently reported in PD cohorts) are indeed the result of impaired ability to suppress a prepotent response, or whether they arise from difficulty generating a strategy to facilitate the production of an unrelated response. This study will also utilise fMRI in order to elucidate the neural substrates subserving these processes. In addition to the standard Part A (verbal initiation/selection) and Part B (verbal suppression) components of the HSCT, a novel condition will be introduced with the intention of eliminating the need to generate a task-facilitating strategy. This will be achieved by providing participants with a cue (in the form of a semantic category) after the sentence stem is given, from which a member can be named as the 'unrelated' response. It is hypothesised that impaired performance in the PD group relative to controls on Part B will be accompanied by decreased activity in frontostriatal circuitry (namely, the dlPFC circuit). It is further hypothesised that if impairment is the result of difficulty generating an appropriate strategy, performance will improve in the novel condition of the task, in which the need to develop a strategy is eliminated.

Finally, Chapter 5 will determine the influence of contextual constraint upon the ability to select a word that correctly completes a given sentence stem (as per Part A of the HSCT). A variation on the HSCT will be employed, in which participants are only required to either provide a single word that completes the sentence stem, or read the word already provided that completes it

(this will serve as a baseline condition). The contextual constraint of the sentence stems in the complete condition will be manipulated to include low, medium, and high levels of constraint. In this way, selection demands will be varied, resulting in greater or fewer numbers of competing alternatives. Given that individuals with PD have previously presented with deficits in word generation attributed to difficult selecting among competing alternatives, it is hypothesised that this cohort will present with increasing response times and errors rates in parallel with increasing selection demands. Furthermore, as regions of the PFC and striatum have been implicated in verbal selection, it is expected that this behavioural performance will be accompanied by decreased activation in related frontostriatal circuitry.

2 Chapter Two

The Suppression of Irrelevant Semantic Representations in Parkinson's Disease

The following chapter aimed to address inconsistencies in the literature concerning the integrity of inhibition mechanisms in individuals with PD. Variability in the parameters of task design (including input modality, syntactic properties of stimuli, and response requirement) was identified as a potential source of this inconsistency. The study in Chapter 2 utilised an object-based negative priming paradigm that required participants to name a target image while ignoring a distractor item. The semantic relationship between the distractor item and the subsequent target item was manipulated in order to observe the level at which suppression took place (categorical or word level). It was hypothesised that the PD group would not exhibit a negative priming effect, and would instead present with enhanced positive priming (reflecting an inability to suppress an irrelevant representation).

2.1 Introduction

Parkinson's disease (PD) may influence the inhibition of inappropriate or irrelevant stimuli, however, this issue is a point of contention. Even within the body of work that suggests an impairment *is* present, the magnitude and nature of the disruption varies considerably between paradigms and modalities (Bokura, Yamaguchi, & Kobayashi, 2005; Gauggel, Rieger, & Feghoff, 2004; Grande et al., 2006; Obeso, Wilkinson, & Jahanshahi, 2011b; Seiss & Praamstra, 2006). Shao et al. (2015) note that inhibition is a general term used to refer to a large number of processes recruited under specific circumstances. The inhibitory processes affected in PD have yet to be agreed upon, and doing so will require the development of tasks that can reliably isolate different aspects of inhibition.

This issue of inhibitory processing is readily manifest in the literature concerning lexical-semantic mechanisms in PD, which is the focus of the present study. Many studies have provided substantial evidence for altered performance across a variety of lexical-semantic tasks including verbal fluency (Auriacombe et al., 1993; Henry & Crawford, 2004; Herrera, Cuetos, & Ribacoba, 2012; Piatt et al., 1999; Tröster et al., 1998), semantic priming (Angwin et al., 2009; Arnott et al., 2001; Copland, 2003; Filoteo et al., 2003; Murdoch, Arnott, Chenery, & Silburn, 2000), and confrontation naming (Cotelli et al., 2007; Rodríguez-Ferreiro et al., 2009). Disrupted semantic inhibition may represent a common underlying deficit that can account for these impairments, and attempts have been made to develop paradigms that test this hypothesis.

A tool that has been previously employed to test semantic inhibition in PD is the Hayling Sentence Completion Test (HSCT), developed by Burgess and Shallice (1996). This task is designed to allow for isolation of verbal selection from verbal suppression. Participants are presented with a high cloze probability sentence stem that has had the final word removed and are asked to provide a word that either completes the sentence (Part A) or is unrelated (Part B). For example, for the sentence stem "The captain stayed with the sinking…" a word which would complete the sentence is "ship" while an unrelated word might be "banana". Part A and Part B are said to measure verbal selection and verbal suppression, respectively. A consistent finding in the literature is that PD participants record slower response times and decreased accuracy on Part B of the task relative to controls while performance on Part A appears relatively commensurate across the two populations (Bouquet et al., 2003; Copland et al., 2012; O'Callaghan et al., 2013b; Obeso et al., 2011a). Castner et al. (2007b) further demonstrated a possible association between altered semantic inhibition mechanisms and PD pathology by administering the HSCT to a group of PD participants who had undergone DBS surgery targeting the subthalamic nucleus (STN) bilaterally. Slower response times were evident for PD participants in Part B when the stimulators were

switched off relative to the on-stimulation condition and healthy controls, and were commensurate with controls when the stimulators were switched on.

At a surface level, these studies appear to suggest that PD is associated with deficits in the inhibition of a strongly prepotent verbal response, and that this function may be subserved by nuclei of the basal ganglia known to be affected in PD. However, it is difficult to draw broad conclusions regarding verbal inhibition abilities from studies that employ the HSCT. It can be argued that this test is unable to reliably isolate the individual processes of selection and suppression. In order to successfully complete Part B, a participant must first suppress the prepotent response and any related concepts that have become partially activated, then generate an alternative set of possible responses and select a response from within this set. The ability to internally develop and implement a strategy that facilitates the generation of an alternative response is critical to successful task execution. The HSCT collapses each of these individual processes under the umbrella of verbal suppression and as a result cannot isolate the source of any indicated impairment. Identifying the source of impairment is particularly important in PD given that executive functions, including strategy generation, are often compromised in this population (Dirnberger & Jahanshahi, 2013; Taylor et al., 1986).

Interestingly, the HSCT's authors acknowledged this limitation in their original paper (Burgess & Shallice, 1996), and indeed Castner et al. (2007b), Obeso et al. (2011a), and Bouquet et al. (2003) all considered the possibility of impaired strategy generation in PD. Each of these studies attempted to rule out the possibility of a core deficit in strategy generation by subjectively rating the participant's individual responses as strategic or non-strategic, however, further investigation is required to confirm this suggestion. Furthermore, the design of the HSCT may introduce additional confounds which could interfere with its capacity to reliably index verbal suppression. It could be argued that the task incorporates a substantial delay between activation, suppression, and response generation, as the participant may begin to invoke activation of the prepotent response while reading the sentence stem. Syntactic processing may also introduce additional attention and working memory demands (Grossman et al., 2003; Grossman et al., 2002; Lee et al., 2003; Walsh & Smith, 2011). With these limitations in mind, it would appear that elucidating the mechanisms of verbal suppression may be best achieved through the use of paradigms that eliminate the need for internal response generation and strategy development, and which strictly measure single-word production.

Castner et al. (2007b) provided an example of such a task in their aforementioned study of PD patients tested on and off STN stimulation. A picture-word interference (PWI) task was administered, which involved presenting pictures of target items simultaneously with a distractor word. The distractor word either had a high- or low- level semantic association with the target

picture, or was unrelated. Overall, the PD group recorded significantly slower response times across all conditions relative to controls, and these were slowest when off stimulation. A significant semantic interference effect (i.e., slower response times when there was a high association between the target and the distractor) was also observed, which was commensurate across the control and PD group (on and off stimulation). These results suggest that the PD participants were able to process the lexical distractor at least to a categorical level, and that, similar to controls, the activation associated with this semantically associated distractor interfered with their ability to name the target.

It could be suggested that the difference in performance between the PWI task and the HSCT task in PD relates to the availability of externally cued responses in the PWI task, which are not available in HSCT, or the need to generate and implement an internal strategy in the HSCT. Alternatively, Castner et al. (2007b) attributed their results to differences in the underlying inhibitory mechanisms assessed by each task, outlining a difference between interference control and behavioural inhibition. In the HSCT, participants must actively suppress a strong prepotent response (behavioural inhibition), whereas in the picture-word interference task they must ignore irrelevant stimuli (interference control). Performance on these tasks may also differ as a result of the temporal parameters of the task. The PWI task presents a distractor simultaneously with the target, and cannot therefore demonstrate how inhibition may resolve over time. Comparatively, it is difficult to index the temporal dynamics of selection and inhibition in the HSCT as this task employs sentence stems rather than single words.

Negative priming tasks provide a useful tool for examining the influence of ignored distractors over time. In a negative priming task, the prime display includes a target item and a distractor item that must be ignored. In the subsequent probe display the target item to-be-named is either the previous distractor item itself, or a semantically related item. The negative priming effect occurs when the distractor item presented with the prime, either identical or semantically related to the probe, subsequently interferes with the naming of the probe. The effect is assumed to occur as a result of inhibition processes called into play to suppress the representation of the distractor and its related concepts, thus allowing for naming of the prime that shares the display with the distractor. When the subsequent probe is semantically identical or related to this distractor, the residual inhibition must be overcome in order to retrieve the appropriate response, thereby slowing responses to the probe word.

Marí-Beffa et al. (2005) employed a negative priming task to observe the processing of irrelevant stimuli in people with PD and healthy age-matched controls. They created a lexical decision task that manipulated the semantic relatedness between a distractor word in the prime display, and the subsequent target word in the probe display. Participants were encouraged to ignore

the peripheral distractor word, and the probe display was presented once the participant had responded to the prime such that the stimulus-onset asynchrony (SOA) was variable across trials. Unrelated prime distractor and probe pairs were compared with either semantically related pairs (Experiment 1) or identical pairs (Experiment 2). In the first experiment, trials where the prime distractor was semantically related to the probe were significantly faster compared to unrelated trials in the PD group, however no significant priming was evident in controls. In the second experiment, the PD group showed significant positive priming for trials where the distractor was identical to the subsequent probe, while the control group showed significant negative priming under this condition. The authors suggested that these findings support the proposal that the underlying cause of the facilitatory priming effect observed in the PD group was a failure to successfully ignore the irrelevant distractor items, thus allowing these representations or their semantic relations to be more rapidly retrieved in subsequent probe trials.

These results contrast with those of Castner et al.'s (2007b) PWI task study, which suggested that people with PD are able to initiate suppression of a related distractor in a similar manner to controls. There are a number of factors that may explain the differential results found across the HSCT, negative priming and PWI tasks. Firstly, the response requirements of each differ considerably. Both the HSCT and the picture-word interference task require a verbal response and retrieval of a word or object name. Comparatively, Marí-Beffa et al.'s (2005) negative priming task involved lexical decision, and thus only required a nonverbal yes/no response. Secondly, the differing temporal parameters between tasks may suggest that the inhibition difficulties experienced by people with PD vary as a function of time, a possibility suggested by previous studies in this population (Copland et al., 2009). Finally, it must be noted that Castner et al.'s (2007b) study only recruited PD participants who had undergone DBS surgery and these individuals may not have been representative of the broader PD population. It may also be inappropriate to assume that the performance of the DBS group when off stimulation would be equivalent to that of a non-surgical PD group, as the surgery itself and the resulting change in medication regime may have altered the baseline performance of the DBS group.

The performance of people with PD across the different tasks described above suggests that while semantic inhibition appears to be affected by PD, the nature and magnitude of the disruption may be dependent upon task conditions such as temporal parameters and response requirements. Accordingly, PD participants need to be assessed using tasks that can systematically isolate and test each of these parameters. The present study administered a classic negative priming task (Tipper, 1985) that used a picture-in-picture paradigm. In this task, participants are presented with two line drawings superimposed over each other, one coloured red and the other green. They are asked to name the red image and ignore the green image. The relationship between the green distractor

image and the red target image of the subsequent trial is manipulated so that the green distractor is either unrelated, semantically related, or identical to the subsequent red target. When administered in young healthy controls, this task elicited a negative priming effect (Tipper, 1985).

By only using visual stimuli this paradigm allows for control of input modality, and the manipulation of semantic relatedness will allow for observation of the level to which distractor items are processed. The negative priming design introduces a delay between expected suppression of the distractor and naming of the target so that the resolution or maintenance of inhibition over time can be measured. Unlike Marí-Beffa et al.'s (2005) task, this paradigm requires naming production, but not the internal generation of a response or a strategy (as required in the HSCT).

The present study aimed to determine whether people with PD are able to suppress irrelevant semantic information and maintain that suppression across a trial, using a negative priming task with visual objects. It was hypothesised that the PD participants would show faster reaction times for targets that were semantically related or identical to the preceding distractor item as a result of difficulty suppressing irrelevant semantic information, while the control group would demonstrate a negative priming effect (slower response times for related and identical targets). While the identity condition will examine suppression of the visual-conceptual representation and its lexical form, slowing of related targets will be consistent with inhibition within the lexical-semantic network.

2.2 Methods

2.2.1 Participants

Sixteen adults (9 females, mean age = 62.9 years [*SD* 6.3], mean years of education [YOE] = 13.6 [3.7]) with a diagnosis of idiopathic PD (diagnosis confirmed using Calne, Snow, and Lee's [1992] criteria) were recruited. Years spent undertaking primary, secondary, bachelor, post-graduate, and diploma/certificate studies were tallied to calculate YOE. Participants were right-handed, confirmed with the Annett Hand Preference Questionnaire (Annett, 1970), with English as a first language and no history of neurological surgery, trauma or substance abuse. Fifteen neurologically healthy adults (8 females, mean age 68 years [10.1], mean YOE = 16.1 [2.8]) were recruited to act as controls, and were matched to the PD group for age ($p = .106$) and sex ($x^2 = 1.0$), however the control group had marginally greater years of education ($p = .043$). Control participants were also right-handed (Annett, 1970), with no history of neurological disease, surgery, trauma, or substance abuse. All participants had normal or corrected-to-normal vision and hearing.

Participants in the PD group completed the Parkinson's Disease Cognitive Rating Scale (PD-CRS; Pagonabarraga et al., 2008). Those who achieved a score below 64 were excluded from further involvement in the study, as this score is considered to be indicative of significant cognitive impairment or dementia (Kulisevsky & Pagonabarraga, 2009). The Montreal Cognitive Assessment

(MoCA v7.1; Nasreddine et al., 2005) was employed as a basic cognitive screener in order to broadly detect the presence of cognitive impairment in the control group (mean total score = 26.9 [3.6]). Control participants were required to score within the normal range for their age as identified by Rossetti, Lacritz, Cullum, and Weiner (2011) in order to be included in the study. The Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was administered to all PD participants. A score greater than eight on the GDS is considered indicative of major depressive disorder in PD (Dissanayaka, O'Sullivan, Silburn, & Mellick, 2011; Dissanayaka et al., 2007), hence those participants scoring in this range were excluded unless they reported current use of anti-depressant medication or other medical treatment. The PD participants had a mean Hoehn and Yahr rating (HY; Hoehn & Yahr, 1967/2001) of 2.1 [0.3]. Levodopa Equivalent Daily Dosage (LEDD) was calculated for each PD participant according to the methods outlined by Tomlinson et al. (2010). Demographic, neurological, and cognitive performance data for the PD participants is provided in Table 1.

Table 1

Characteristics of Participants with PD

Participant	Age[a]	Sex	YOE	Disease duration[a]	LEDD	HY	PD-CRS	GDS
1	60	M	16	0.5	400	2	102	1
2	66	F	18	2	280	2	122	0
3	70	M	5	18	614	2	85	1[b]
4	63	F	12	9	348	2	113	10[b]
5	73	M	13	10	400	2	114	0
6	63	F	11	4	0	3	94	1
7	56	M	12	6	325	2	96	1
8	62	F	15	3	100	2	100	3
9	71	M	12	10	800	2	100	1
10	60	F	14	6	550	2	111	3[b]
11	57	F	18	5	550	2	114	0[b]
12	60	F	16	5	394.5	2	112	3
13	59	M	12	10	1660	3	90	10[b]
14	71	F	12	2	400	2	107	1
15	50	F	11	4	950	2	111	1
16	65	M	21	6	549	2	117	3
M	**62.9**	NA	**13.6**	**6.3**	**520**	**2.1**	**105.5**	**2.4**
SD	*6.3*		*3.7*	*4.2*	*383.44*	*0.3*	*10.5*	*3.1*

Note. YOE = Years of Education; LEDD = Levodopa Equivalent Daily Dosage (mg/day); HY = Hoehn & Yahr rating. PD-CRS = Parkinson's Disease Cognitive Rating Scale (total score). GDS = Geriatric Depression Scale; M = male; F = female.
[a]Age and Disease duration are reported in years.
[b]Participant was taking anti-depressant medication at time of testing.

The study was approved by the University of Queensland Human Research Ethics Committee and was conducted in accordance with the ethical standards laid down in the 2007 NHMRC (National Health and Medical Research Council) National Statement on Ethical Conduct in Human Research. Informed written consent was obtained from participants prior to their inclusion in the study. Financial reimbursement was provided to all participants.

2.2.2 Experimental Design and Stimuli

A picture in picture task was designed to elicit semantic inhibition as a result of simultaneous presentation of a red line drawing superimposed over a green line drawing. Participants were required to name the red image aloud as quickly as possible and ignore the green image. A superimposed pair of images collectively referred to as the prime was presented first (red prime image and green distractor image), followed by the corresponding probe pair (red probe image and green distractor image). Stimuli were drawn from the International Picture Naming Project database (IPNP; Szekely et al., 2004). The converged red and green images were created using Adobe CC Photoshop software (v2014.4.0), with the red image superimposed over the green image. The task design manipulated the relationship between the red target item in the probe pair and the green distractor item in the prime pair immediately preceding it.

A total of 144 superimposed images were developed, each containing a red target image and a green distractor image. For the purposes of this text, one superimposed image is referred to as one trial. These superimposed images were divided equally into three condition sets (identical, related, and unrelated), each containing 48 trials (with 24 primes and 24 corresponding probes). The green distractor image in the prime stimulus was identical to the red image in the subsequent probe stimulus in the identical condition, semantically related to the red probe image in the related condition (achieved by selecting images from the same semantic category), or semantically unrelated in the unrelated condition (achieved by ensuring the two images were from distinct semantic categories as judged independently by two researchers). An example of stimuli from each condition is provided in Figure 2. The mean naming latency (IPNP; Szekely et al., 2004) and the Centre for Lexical Information (CELEX) spoken word frequency (obtained from the N-Watch Database; Davis, 2005) of stimuli in each condition are presented in Table 2. These values did not differ significantly between the conditions ($p = .173$ and $p = .592$, respectively).

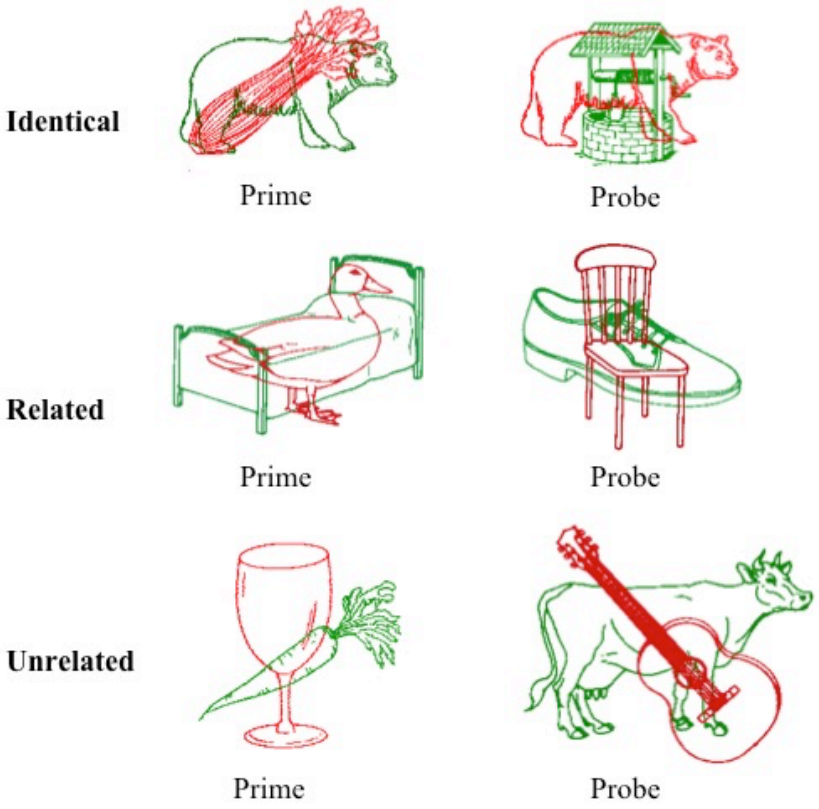

Figure 2. Example of prime and probe stimuli from the three conditions of the negative priming task. Participants were required to name the red item and ignore the green item. Images were adapted from the International Picture Naming Project, see "A new on-line resource for psycholinguistic studies," by A. Szekely, S. D'amico, A. Devescovi, … E. Bates, 2004, *Journal of Memory and Language, 51*, 247-250.

Table 2

Psycholinguistic Properties of Picture Stimuli

Condition		CELEX spoken word frequency	Naming latency (ms)
Identical	*M*	82.46	1010
	SE	*70.98*	*25*
Related	*M*	16.96	952
	SE	*4.36*	*19*
Unrelated	*M*	12.28	952
	SE	*5.72*	*23*

Note. CELEX (Centre for Lexical Information) spoken word frequency obtained from the N-Watch database (Davis, 2005). Naming latency obtained from the International Picture Naming Project, see "A new on-line resource for psycholinguistic studies," by A. Szekely, S. D'amico, A. Devescovi, … E. Bates, 2004, *Journal of Memory and Language, 51*, 247-250.

2.2.3 Procedure

Stimuli were presented using a laptop with the screen set to 640 x 480 bit-depth resolution and positioned approximately 60 cm from the seated participant. The experiment was realised using Cogent graphics software (Wellcome Department of Imaging Neuroscience, 2013) via a Matlab platform (MathWorks, 2013). The task involved the presentation of superimposed red and green line drawings on a white square of 300 x 300 pixels in the centre of the screen. A single trial started with a fixation cross that was displayed for 100 ms followed by a red/green picture (superimposed stimulus) for 500 ms. A mask was then displayed immediately following presentation of this stimulus for 5000 ms in order to discourage controlled processing of the image. This mask was a nonsensical image made from multiple line drawings superimposed over each other in red and green, such that no individual shape or picture could be easily discerned. During this 5000 ms period, the subject was required to name the red image as quickly as possible and the audio was recorded using a headset microphone. The task was self-paced, requiring participants to press the space bar after providing their response in order to progress, and thus the SOA was variable across trials.

Three alternative pseudo-randomisations of stimuli were generated to minimize order effects. Within each randomization it was ensured that a minimum of one intervening prime-probe presentation occurred between trials of the same condition. The experiment was conducted in a quiet room with minimal environmental distractions. The task was completed in one run with no rest breaks between trials and took approximately 20 min.

2.3 Results

2.3.1 Scoring

Response times were manually extracted from the voice recordings and were measured from the onset of the picture stimulus to the onset of the participant's response. Accuracy was scored by two independent raters according to the following criteria: A correct response required the red image to be accurately named in a single word utterance (items with a two-word name e.g., washing machine were also permitted). Any response that contained multiple words, excessive interjections or false starts, self-corrections, or inaccurate names was scored as incorrect. Cohen's kappa (κ) was run to determine the inter-rater agreement and results indicated an acceptable level of agreement, $\kappa = 0.956$ (95% CI 0.95, 0.96), $p < .001$.

2.3.2 Behavioural Results

Two participants from the control group presented with 10 or fewer valid trials across multiple conditions and were excluded from further analysis. A total of 16 PD and 13 control participants were included in the final statistical analysis reported below. The significance of the

group differences in age and gender balance did not change as a result of this exclusion, however, the marginal difference in YOE was eliminated ($p = .081$). Of the total trials, non-responses accounted for 18.2% in the PD group and 12.9% in the Control group. Of the remaining trials, only those in which naming latency was between 250 ms and 2500 ms were included in the latency and accuracy analysis. As a result, 1.7% of these trials in the PD group and 0.98% of these trials in the control group were discarded.

2.3.2.1 Naming response time.

Only those trials for which both the prime and the probe met criteria for a correct response were included. This resulted in discarding 24.7% of trials in the PD group and 16.9% of trials in the control group. An independent samples t-test confirmed that the difference in error rates between groups was not significant [$t (27) = 1.757$, $p = .09$). A Shapiro-Wilks test of normality demonstrated that the data for both PD and control groups was not normally distributed ($p < .001$) and visual inspection revealed extreme positive skewness. A reciprocal transformation (1/x) was performed and the data again submitted to a linear mixed model (LMM) analysis. Skewness and kurtosis figures indicated that this transformation substantially improved the distribution of the data for each group. Transformed response times for probe trials were submitted to an LMM. Fixed effects were group (PD and control) and condition (related, unrelated, and identical). Participant was included as a random effect.

The results of the LMM revealed a significant main effect of condition for response time (F [2, 1340] = 7.351, $p = .001$). A Bonferroni-adjusted pairwise comparison was performed and identified that when response time was collapsed across groups, participants were significantly faster ($p < .001$) in naming the target image in trials where the preceding prime distractor image was unrelated to the subsequent target image (unrelated condition), compared to trials where the preceding prime distractor was identical to the subsequent target image (identical condition). This result suggests the presence of a negative priming effect across both groups. Further analysis confirmed that this significant difference in response time between unrelated and identical conditions was present independently in both the PD and control groups ($p = .02$ and $p = .027$ respectively. These results are presented in Figure 3 in their untransformed state, for ease of interpretation. No difference between related and unrelated conditions was observed for either group. No main effect of group ($p = .782$) or significant interaction ($p = .811$) was observed.

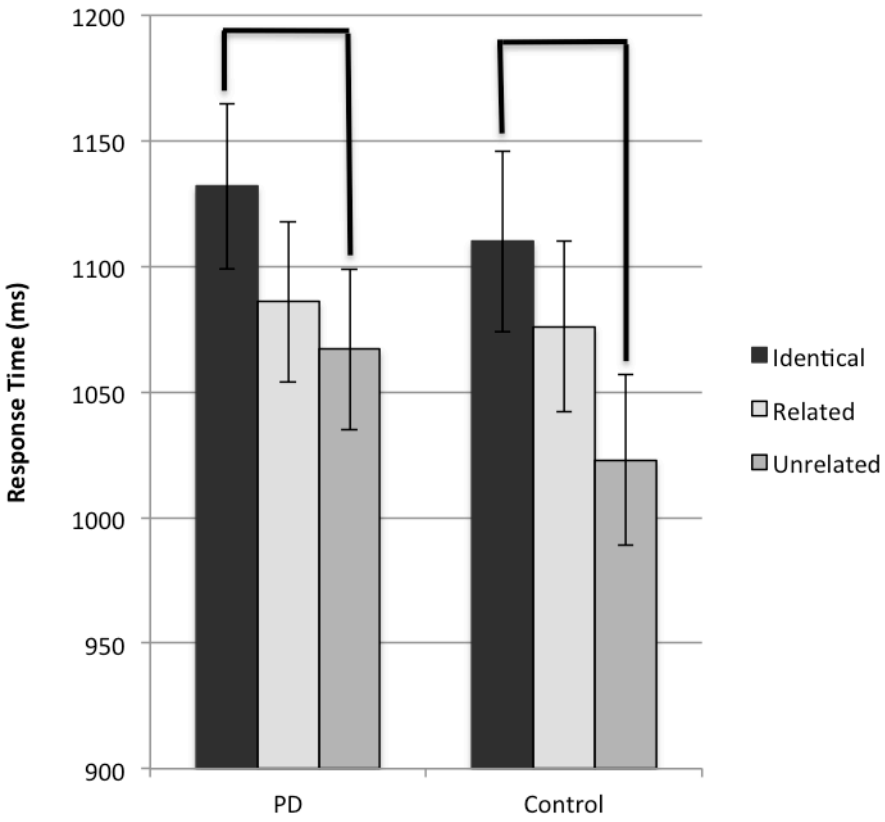

Figure 3. Mean response time (ms) for probe responses in identical, related, and unrelated conditions for PD and control groups. Brackets indicate significant differences ($p < .05$). Error bars indicate mean standard error.

2.3.2.1.1 Prime trials. In order to confirm the validity of the negative priming effect detected for both groups in the analysis of response times for probe trials, the transformed response times for correct prime trials were also submitted to a LMM with group modelled as a fixed effect and participant number as a random effect. Results of this analysis demonstrated no group differences in response time for prime trials ($p = .729$).

2.3.2.2. Naming accuracy.

The accuracy analysis considered probe trials for which the prime was named correctly. As a result, 24.4% of trials for the PD group and 16.6% of trials for the control group were discarded. The percentage of target trials named correctly in each condition was submitted to a LMM analysis with fixed effects of group and condition, and participant included as a random effect. A Shapiro-Wilks test indicated that the data for the PD group was normally distributed ($p = .41$) while the control group did not achieve normality ($p = .001$). However, skewness and kurtosis values for the control group were considered acceptable.

The LMM analysis revealed a significant main effect of condition, $F(2, 58) = 11.05$, $p < .001$. Bonferroni-adjusted pairwise comparisons indicated that when collapsed across group, participants were significantly more accurate in responding to the unrelated condition relative to the

identical condition ($p < .001$), and in responding to the related condition relative to the identical condition ($p = .002$). However, when analysed independently, only the control group demonstrated the later effect (controls $p = .001$, PD $p = .877$). There was no main effect of group ($p = .128$) or significant interaction ($p = .145$). Results are presented in Figure 4.

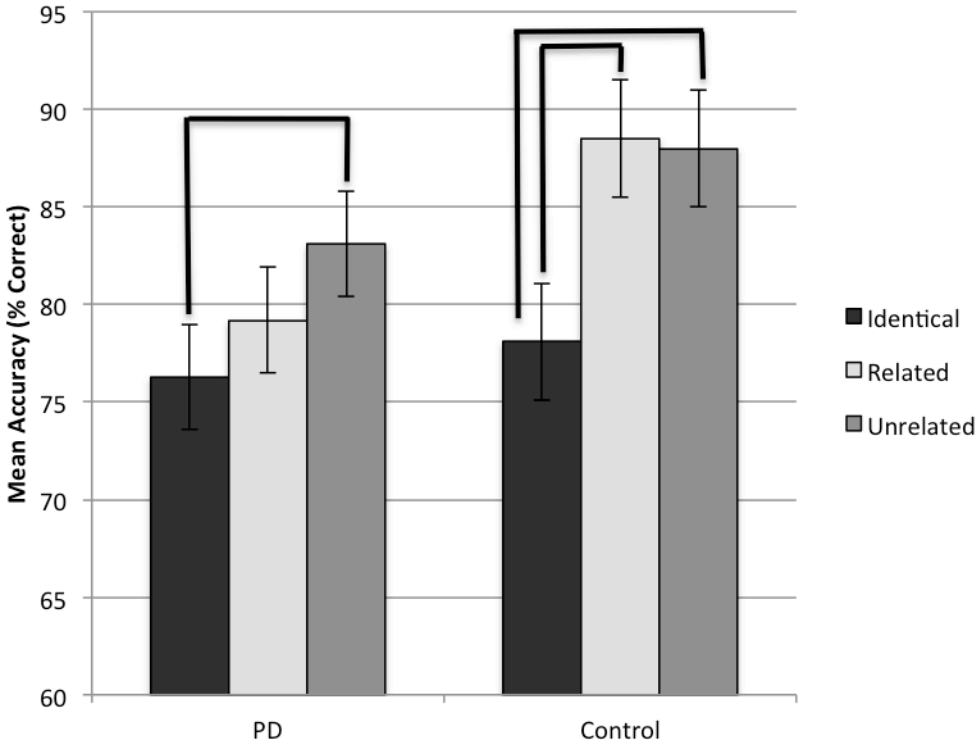

Figure 4. Mean accuracy (percentage correct) for probe responses in identical, related, and unrelated conditions for PD and control groups. Only those trials where the prime was named correctly were included. Brackets indicate a significant difference ($p < .05$). Error bars indicate mean standard error.

2.4 Discussion

The present study used an object-based negative priming task to determine whether people with PD are able to suppress irrelevant semantic information and maintain that suppression in a naming task. The PD group performed similarly to controls across all conditions in terms of naming latency, demonstrating that the retrieval of an object's name was slowed when it had previously been ignored. This finding suggests that the ability to suppress the distractor image and its related concepts was intact in PD participants. A similar pattern of performance was observed in both groups with regards to naming accuracy, where the identical condition was significantly less accurate than the unrelated condition. However, in contrast to controls, the PD participants demonstrated no significant reduction in accuracy for the identical condition relative to the related condition.

The results obtained for the control group are in line with existing literature concerning negative priming of objects, where response time is consistently slower for trials where the

distractor in the prime display is identical to the subsequent probe (de Zubicaray, McMahon, Eastburn, Pringle, & Lorenz, 2006; Schrobsdorff, Ihrke, Behrendt, Herrmann, & Hasselhorn, 2012; Tipper, 1985). Furthermore, it has been recently established that identity or object-based negative priming is not influenced by age and the effect appears to remain constant across the lifespan (for reviews see Frings, Schneider, & Fox, 2015; Gamboz, Russo, & Fox, 2002). It is therefore appropriate to make comparisons between the results found in the present study, and studies in younger healthy populations. In contrast, the finding of negative priming effects for trials where the distractor is semantically related to the probe has been less consistent in the healthy population (Frings et al., 2015; MacLeod, Chiappe, & Fox, 2002; Tipper, 1985). In the present study, the control group were significantly more accurate in the related condition, relative to the identical condition. This result was not accompanied by significant differences in response time, which will be discussed further below.

Previous studies of negative priming in the PD population have generally manipulated visuospatial stimuli, observing the processing of location (spatial) and identity (object) features. However, results have rarely been replicated across studies. Stout et al. (2001) found evidence for enhanced negative priming in PD on a visuospatial task, and Wylie and Stout (2002) later replicated these findings. The latter study reported enhanced negative priming in PD relative to controls for location, identity and location-identity conditions, suggesting that people with PD have greater difficulty overcoming residual inhibition compared to controls. In contrast, Filoteo et al. (2002) administered a visuospatial negative priming task to PD and healthy control groups, and found no evidence of any negative priming effect in the PD participants, despite its presence in the control group. Likewise, Troche et al. (2006) found no evidence of negative priming in control or PD groups when identity was manipulated, however both groups recorded a significant negative priming effect for trials where location was manipulated. This inconsistency across studies has sparked some commentary and the suggestion that this discrepancy could be explained by differences in a number of design features, including the nature of the stimuli and the response demands of the task (Stout, Wylie, & Filoteo, 2002).

Possin, Filoteo, Song, and Salmon (2009) further evaluated the lack of agreement in the literature around attention/inhibition tasks in PD and noted that much of the contention appeared to surround the distinction between spatial processing and object or identity processing. Possin et al. (2009) proposed that attention/inhibition is not a unitary mechanism, and that specialised components exist that can be impaired or spared independently. These authors developed a task to control for spatial-parameters and assess object-based attention in isolation from location-based attention. Their task used picture-based stimuli depicting common objects, and participants were shown a target and comparator and asked to indicate whether these two objects were the same or

different. A distractor image was presented in the same display, slightly overlapping with the target. PD participants performed at a level commensurate with controls across all conditions, demonstrating equivalent degrees of both negative and positive priming in the ignored repetition (analogous to the present study's identical condition) and attended repetition trials, respectively. The authors interpreted this to suggest that object-based attention processes are intact in PD, while spatial (location) processing may be disrupted. Possin et al.'s study provides support for the current results, as it manipulated stimuli that might be expected to activate visual-semantic representations, and found no impairment in the PD group relative to the controls with respect to latency. Furthermore, the suggestion that attention/inhibition processes are not represented by a single mechanism goes some way toward explaining the conflicting results found in the previous negative priming PD literature, and indeed between this literature and the present study.

After evaluating the vast catalogue of negative priming studies since the emergence of the paradigm in 1966, a recent review by Frings et al. (2015) reached a similar conclusion. These authors proposed that it is inappropriate to make comparison between studies of negative priming in spatial-location and identity paradigms, as it appears likely that the mechanisms underlying each may differ to some degree. Indeed, the possibility of multiple, independent attention/inhibition mechanisms is a notion supported by a growing cohort of publications (Grande et al., 2006; Miyake et al., 2000; Nigg, 2000; Shao et al., 2015). If each type of inhibition is affected differentially in PD, this could explain the inconsistent performance observed across paradigms. The results of the present study certainly appear to support this conclusion, however further investigation is required regarding this hypothesis. It may therefore be of value to consider the present results within the domain of cognitive-linguistic processing and hence, lexical-semantic inhibition. This view may allow for speculation as to an alternative explanation for the differences found between the performance of people with PD on the present picture-based negative priming task, and Marí-Beffa et al.'s (2005) word-based negative priming task.

PD participants were observed to perform at a level commensurate with controls in the present study in terms of latency and negative priming, while PD participants in Marí-Beffa et al.'s (2005) study demonstrated positive priming under circumstances where controls demonstrated either no priming at all, or negative priming. Two key factors that warrant consideration when examining the differences between the present study and that of Marí-Beffa et al. are the use of picture-based stimuli, and the response requirement. Firstly, the current study required naming of a target picture, in the presence of a distractor image. In contrast, Marí-Beffa et al.'s task only used word-based stimuli for both targets and distractors, and required a yes/no button press regarding the lexicality of the prime or probe target. As previously discussed, Stout et al. (2002) commented on the importance of considering differing response input and output modalities in the visuospatial

domain. It may therefore also be appropriate to consider the possibility of a similar effect in the lexical-semantic domain. Furthermore, the reviews of negative priming conducted by Frings et al. (2015) and Fox (1995) concluded that ignored items are processed only to the level that is required by the demands of the task. Frings et al. (2015) went on to suggest both retrieval and inhibition processes play a role in successful completion of negative priming, but that each may be recruited to different degrees depending on the task design. Balota, Cortese, and Wenke (2001) have also suggested that differing task goals will engage distinct processing pathways and that these can impact performance downstream. It is therefore important that task design is considered when interpreting the present results.

Indeed, the differing input modalities and response requirements in the Marí-Beffa et al. (2005) task and the present task may have given rise to the contrasting results. For example, in Marí-Beffa et al.'s task participants were required to ignore written distractors in order to make a lexical decision about a central target word. It has been demonstrated that participants with PD have difficulty inhibiting automatic word reading processes (Henik, Singh, Beckley, & Rafal, 1993). On this basis, it could be assumed that the PD group were unable to effectively ignore the written distractor words in the task, and that these lexical units activated their semantic representations. It has been suggested that PD participants also have reduced lateral competitive inhibition (Arnott et al., 2010; Copland, 2003; Gurd & Oliveira, 1996). It is therefore possible that the activation of distractor word representations also spread to related concepts. However, it may be argued that completion of the lexical decision task does not necessitate the suppression of the distractor representation, as this may not interfere significantly with the lexical level of processing. PD participants are then able to make a successful lexical decision, but the additional activation of the distractor and its related concepts allows for speeded decisions when these words are repeated as the target in the subsequent probe display. In contrast, controls are able to effectively ignore the distractor words, or at least do not automatically process them to a categorical (semantic) level as the task requirements do not necessitate accessing the semantic system. They therefore demonstrate no significant priming effect for related trials, and demonstrate negative priming for repeated trials (where the distractor becomes the target) due to previous inhibition of the word form at a lexical level, not its semantic representation.

Comparatively, the use of a picture-naming design in the present study evokes different processing pathways. Visual stimuli access the semantic system following perceptual feature analysis (Humphreys & Forde, 2001), and this must take place prior to retrieval of lexical representations (also see Kay et al., 1992; Lesser & Milroy, 1993; Morton, 1980). Several authors have also demonstrated that abstract representations are still accessed for ignored objects (Dell'Acqua & Grainger, 1999; Morgan & Meyer, 2005) and indeed this has been demonstrated in

object/identity based negative priming paradigms (de Zubicaray et al., 2006; Tipper & Driver, 1988). It may therefore be suggested that in the present study, both control and PD groups automatically access the abstract representation of the ignored picture in the semantic system. However, the semantic representation of the target image must also be accessed in order for its name to be retrieved. This task requires the representation of the distractor to be inhibited, in order to resolve completion at the semantic level and allow the target image to be named. The present study demonstrated that the PD group were capable of executing this deliberate suppression. Both groups then experienced delayed naming latency and increased errors when they had to subsequently name this distractor in the probe display. Also of note is the decreased accuracy in the identical condition present in the control group relative to the related condition. This effect was not observed in the PD group, and was not accompanied by significant corresponding differences in response time. The cause of this discrepancy is presently unclear, however in the PD group one possible explanation relates to difficulty in maintaining the focus of inhibition within the semantic network, analogous to the difficulties this population has in controlling the spread of activation (Arnott et al., 2010).

The notion that deficits in negative priming in PD relate to the demands of the task design, and not to a specific impairment in semantic inhibition, gains some support from the semantic priming literature. Specifically, a large body of semantic priming literature that frequently reports disruptions to inhibition processes in PD and such research typically employs lexical decision tasks (Angwin et al., 2005; Arnott et al., 2001; Boulenger et al., 2008; Castner et al., 2007a; Copland, 2003; Fernandino et al., 2013; McDonald, Brown, & Gorell, 1996). Examining multiple tasks with contrasting demands within the same PD cohort would further verify this account.

Neuroimaging provides additional insight into the negative priming effect that may aid in interpreting the present results. In an fMRI study of negative priming using a similar paradigm to the current study, de Zubicaray et al. (2006) observed increased left anterior temporal cortex activity in the repetition-ignored condition (analogous to the present study's identical condition). This region of the brain is generally thought to be responsible for the processing of abstract semantic representations (e.g., see Price, Devlin, Moore, Morton, & Laird, 2005). Whilst cortical pathology has been observed in PD, this region has not been implicated, suggesting that performance on tasks involving abstract semantic processing may be largely preserved in this population.

A final explanation for the present findings may relate to the use of colour-cues in the present study. It has been demonstrated in the motor realm that people with PD appear to benefit from external cues and demonstrate better performance on externally cued tasks relevant to internally cued tasks (Lim et al., 2005; Rocha, Porfirio, Aguiar, Ferraz, & Trevisani, 2014;

Spaulding et al., 2013). Indeed, Castner et al. (2007b) offer this as a possible explanation for the differential performance of people with PD on the HSCT and PWI tasks, as the HSCT relies on internal response generation while the correct response for the PWI is cued by the presented image. Brown and Marsden (1988) employed a variation of the Stroop task to demonstrate that PD participants were more impaired when the task demanded greater internal control. These authors suggested that impairment to cognitive functions like inhibition emerge when task demands exceed the capacity of the supervisory attentional system, and that the resources of the system were reduced in PD. In addition to using images as stimuli, the present study also provided a colour-cue. Participants were always required to name the red image and ignore the green. In contrast, the lexical decision task used by Marí-Beffa et al. (2005) required internal evaluation and generation of a yes/no response. These differing task requirements may therefore also have contributed to the results observed.

2.5 Limitations and Future Directions

The present study was unable to speak to the influence of dopaminergic medication on performance in the PD group. All but one of the PD participants were medicated when they completed the task. Previous studies of semantic processing have demonstrated differential performance in PD groups when on and off levodopa (Angwin et al., 2009; Angwin, Copland, Chenery, Murdoch, & Silburn, 2006; Arnott et al., 2011; Pederzolli et al., 2008). It is therefore possible that any deficit in inhibitory processing could have been ameliorated by medication. Similarly, PD participants in the present study were all judged to be mildly-moderately affected by the disease. It is possible that cognitive processes such as the inhibition assessed here are relatively intact at this stage of the disease, as striatal dopamine depletion has yet to progress to those regions thought to be associated with these cognitive functions (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001).

Some evidence for the notion that individual mechanisms of attention/inhibition may exist for different cognitive domains has been generated by the results of the present study. However, obtaining conclusive support for this hypothesis will require systematic evaluation of each domain in isolation. Furthermore, it appears that within each domain, input modality and response requirements must be strictly controlled in order to tease apart the precise conditions under which different types of inhibition are evoked.

2.6 Conclusions

In conclusion, the present study suggests that PD participants are largely unimpaired in their ability to suppress irrelevant semantic information evoked by a picture, and that this suppression is maintained across a one-trial interval. It can be further speculated that inhibition processes are subserved by specialised mechanisms unique to individual cognitive domains (e.g., visuospatial vs.

lexical-semantic), and these mechanisms may be differentially affected by the pathology of PD. These results suggest that inhibitory mechanisms related to the processing of visual-semantic stimuli may be largely intact in PD. Further investigation using paradigms that strictly control for the influence of lexical-semantic input and output is required in order to elucidate the integrity of such mechanisms.

3 Chapter Three

Investigating the Time-Course of Lexical-Semantic Inhibition in Parkinson's Disease

The study in Chapter 2 aimed to determine the ability of individuals with PD to suppress an irrelevant representation and maintain that suppression over an intervening period of one trial. An object-based negative priming paradigm was employed. Results demonstrated no significant group difference in response time or degree of accuracy between control and PD participants. A main effect of condition was present, characterised by a significant negative priming effect in both groups. That is, items that had previously served as distractors were named more slowly than unrelated items. These findings were taken to suggest that this PD cohort were unimpaired in their ability to suppress an irrelevant representation and maintain that suppression across a trial.

It was noted that this study only explored a brief temporal window of 1-2 seconds. Similarly, the HSCT only provides a measure of suppression ability from the offset of the sentence stem to the subsequent provision of a response. This reflects a broader issue in the literature concerning the mechanisms of semantic inhibition in PD: That is, the nature and integrity of this system over time. Little is known of the fate of a suppressed representation, however elucidating this information in PD may provide valuable insights into inhibitory processing. The study in Chapter 3 therefore aimed to determine the time-course of semantic inhibition in PD, by observing the downstream processing of a representation presumed to be suppressed during a typical trial in the unrelated condition (Part B) of the HSCT.

3.1 Introduction

In recent decades, aberrant lexical-semantic inhibition has emerged as a probable locus of the cognitive-linguistic impairments observed in PD (Angwin et al., 2005; Arnott et al., 2010; Grossman, 1999; Marí-Beffa et al., 2005). This proposal is in line with the argument that the frontostriatal networks known to be disrupted in PD contribute to attention-based semantic processes, including inhibition (Copland, 2003; Tinaz, Schendan, & Stern, 2008). Studies of semantic priming in PD have frequently reported that failure of inhibitory processes emerges most consistently when controlled processing is invoked by lengthening the interval between presentation of the prime and probe stimuli, referred to as the inter-stimulus interval (ISI; Angwin et al., 2005; Arnott et al., 2011; Castner et al., 2007a; Copland, Chenery, & Murdoch, 2000; Longworth et al., 2005). However, these studies typically only observe a temporal window of 1- 2 seconds. Thus, the time-course of lexical-semantic inhibition in the PD population remains unclear. Furthermore, semantic priming tasks typically do not require the production of verbal responses. This is of relevance, as deficits in spoken language production have been widely reported in PD (Cotelli et al., 2007; Herrera & Cuetos, 2012; Liu et al., 2015; Murray, 2008; Rodríguez-Ferreiro et al., 2009) and may be the result of underlying impairments in lexical-semantic inhibition.

For example, verbal fluency has been frequently reported as disrupted in PD (for meta-analysis see Henry & Crawford, 2004) and aberrant lexical-semantic inhibition may be at the root of this problem. However, confirming this hypothesis has proven difficult, due to the challenges associated with isolating verbal suppression from other cognitive-linguistic processes such as search, selection and retrieval. The Hayling Sentence Completion Task (HSCT; Burgess & Shallice, 1996) was designed to distinguish between some of the processes involved in verbal fluency. It requires participants to read a high cloze probability sentence stem and provide either a word that completes the sentence (measuring verbal selection) or a word that is unrelated (measuring verbal suppression). Participants with PD have consistently recorded slower response times and increased error rates on the suppression component of the task relative to healthy controls (Bouquet et al., 2003; Copland et al., 2012; O'Callaghan et al., 2013b; Obeso et al., 2011a). Castner et al. (2007b) found that bilateral stimulation of the subthalamic nucleus (STN) returned this performance to a level commensurate with that of controls. Together, these findings have led to the suggestion that PD is associated with an impaired ability to inhibit a strong prepotent response in favour of a task-appropriate response, due to frontostriatal circuit dysfunction.

However, successful completion of the suppression component of the HSCT requires not only verbal suppression, but also internal strategy generation and selection among competing alternatives. It cannot therefore be concluded that lexical-semantic inhibition is impaired in PD based on these studies. Furthermore, even if the task is completed successfully, the level at which

the assumed suppression takes place (i.e. the word form level or the semantic category level) is unclear.

With the exception of studies using semantic priming paradigms, the time course of lexical-semantic activation and inhibition in PD has received minimal attention. In the healthy population, Wheeldon and Monsell (1994) developed a novel competitor priming task that asked participants to name a word in response to a definition, and subsequently name a semantically related picture (e.g., the participant provides the word "whale" in response to the definition "the largest creature that swims in the sea" and must subsequently name a picture of a shark). Naming latency in response to the probe was measured across a number of intervals including immediate presentation (lag = 0 trials), after two intervening trials (lag = 2 trials) and several minutes later (lag > 38 trials). The study found that healthy participants were slower to respond in picture naming trials when a semantically related word had been previously produced in response to a definition. This effect was enhanced after the lag = 2 interval (approximately 12 s) relative to lag = 0, and was no longer present after 38-100 trials (4-8 min). The authors attributed these findings to the influence of different kinds of priming. An immediate facilitatory effect occurs as the result of automatic spreading activation through a network of semantic concepts. However, this effect decays quickly, followed by a longer-lasting inhibitory effect that slows the naming of semantically related items termed *competitor priming*. This is assumed to result from inhibition of semantically related competitors to allow for enhanced activation of the most appropriate response. In the previous example, this would mean that a number of competing alternatives that share features with "whale" were activated in response to the given definition, but these were suppressed in order to allow for "whale" to be selected for production. This powerful inhibition is relatively long lasting, resulting in slowed retrieval of the word "shark" in response to a picture several trials later. Wheeldon and Monsell (1994) localised this competitor priming effect at the level of lemma selection, after activation of semantic representations has taken place but prior to retrieval of a phonological form. Here, the lemma that best matches the semantic concept must be selected from among several competing alternatives.

In the PD population, the efficiency of these downstream mechanisms of lexical-semantic processing is relatively unknown. Copland et al. (2009) administered a lexical ambiguity repetition priming task to this population, with a lag of 8, 10 or 12 intervening word-pair trials. Unlike Wheeldon and Monsell's (1994) paradigm, this task required participants to make a speeded lexical decision indicated by a button press rather than generate a verbal response. Lexical ambiguities were first presented with a target word that biased either the dominant or subordinate meaning, and the ambiguity was then presented again after a lengthy interval, this time paired with a different target word that biased the same or the alternative meaning. Overall, the PD group had difficulty

sustaining facilitation of the appropriate congruent meanings and inhibition of incongruent meanings over a period of several intervening trials, extending previous findings of deficits in the controlled processing of lexical-semantic representations in this population. However, in this case it was also noted that impairment of the ability to select and suppress competing meanings was compromised as a function of the frequency and familiarity features of the first-biased representation. Thus it can be concluded that the failure of lexical-semantic inhibition mechanisms under controlled processing conditions is not absolute in PD, but varies with the properties of the stimuli and the context in which they are encountered.

While some conclusions can be drawn from the Copland et al. (2009) and Wheeldon and Monsell (1994) studies regarding the downstream processing of previously suppressed stimuli, definitive statements cannot be made as these paradigms have varied in terms of ISI, input modality, and response requirements (i.e. single-word production or lexical decision). Primarily, those discussed above have focused on the influence of representations that were initially attended to. To the best of the author's knowledge, there is currently no available evidence concerning the processing of suppressed lexical-semantic stimuli beyond a one trial interval in a verbal production task in PD.

Some inferences regarding the fate of suppressed items may be drawn from classic object-based negative priming tasks. Possin et al. (2009) observed the ability of people with PD to make a same/different judgement about two pictured objects, while ignoring a distractor object which overlapped with one of the targets. The PD group performed at a level commensurate with controls when the distractor item subsequently became the target in the next trial. In this instance, both groups recorded a negative priming effect. That is, they were slower to name the item when it had previously served as a distractor. This finding suggests that the short-term ability to suppress a lexical-semantic representation may be intact in PD. However, it must be noted that negative priming tasks are considered to provide a measurement of an individual's ability to ignore a presented item. While there is some evidence to suggest that ignoring irrelevant stimuli is not passive in nature but does in fact require active processing (Schrobsdorff et al., 2012), the mechanisms underlying this process may differ to those recruited to suppress a prepotent verbal response (as in the HSCT). Furthermore, it has been suggested that PD participants are aided by the availability of external cueing, and that cognitive performance in this population appears to fail more consistently when internal self-cueing is required (Brown & Marsden, 1988; Dubois & Pillon, 1996; Pollux & Robertson, 2002). Given that negative priming provides an external cue in the form of a picture it may be that when a response must be internally generated and suppressed, as in the HSCT, performance is altered.

In order to clarify the nature of lexical-semantic inhibition and its integrity over time in PD, the present study will employ a novel hybridisation of the HSCT and the competitor priming paradigm. This will involve providing participants with a high cloze probability sentence stem and asking them to overtly provide an unrelated word in the place of the prepotent response. This prepotent response will be subsequently presented as a picture that the participants will be required to name. Picture trials that require the naming of items semantically related to the prepotent response will also be included in order to observe whether suppression takes place at the word form level or the semantic category level. Presentation of subsequent picture stimuli will occur either immediately following the response to the definition, or after a lag of one or two intervening, unrelated trials in order to examine the time-course of inhibition.

Given that people with PD have demonstrated difficulties with maintenance of inhibitory control over longer ISIs (Copland et al., 2009), it is hypothesised that this group will demonstrate no difference in response times for previously suppressed items and their semantic relations relative to unrelated items. In contrast, it is hypothesised that controls participants will exhibit delayed latencies in response to these trials. The present study also aims to address the question of whether the generation of an alternative unrelated response in the place of a highly prepotent response requires the suppression of that representation at the word form level or the semantic category level. If occurring at the level of the semantic category, it would be expected that the subsequent presentation of an item semantically related to the suppressed item would also invoke a delay in naming retrieval. However, if naming latency is only delayed for items that are identical to the suppressed item, it may be assumed that suppression is taking place at the word form level only (Howard, Nickels, Coltheart, & Cole-Virtue, 2006; Tipper, 1985; Wheeldon & Monsell, 1994).

3.2 Methods

3.2.1 Participants

Fourteen adults with mild-moderate idiopathic PD (diagnosis confirmed using Calne et al.'s [1992] criteria) were recruited to participate in the study (7 females, mean age = 63.79 years [7.3], mean YOE = 13.5 [4.2]). Years spent undertaking primary, secondary, bachelor, post-graduate, and diploma/certificate studies were tallied to calculate YOE. Fifteen neurologically healthy adults were recruited to act as control subjects (9 females, mean age = 66.4 years [10], mean YOE = 16.2 [2.8]. Student t-tests indicated that these participants did not differ significantly from the clinical group in terms of age ($p = .422$) or education ($p = .05$). Fisher's exact test indicated no significant difference between the groups in terms of gender distribution ($x^2 = 0.715$). All participants were required to meet the following inclusion criteria: (a) no history of neurological disease, trauma or surgery (other than PD in the clinical group); (b) no history of alcohol or substance abuse; (c) right-handed, confirmed with the Annett Hand Preference Questionnaire (1970); (d) English as a first language;

and (e) normal or corrected-to-normal eyesight and hearing. The Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was administered to participants in the PD group and individuals were excluded if they scored greater than eight. Such scores are considered indicative of major depressive disorder in PD (Dissanayaka et al., 2011; Dissanayaka et al., 2007). The Parkinson's Disease Cognitive Rating Scale (PD-CRS; Pagonabarraga et al., 2008) was administered to PD participants in order to obtain a baseline measurement of cognitive function. Participants with a score less than or equal to the cut-off score of 64 were excluded from further involvement (Kulisevsky & Pagonabarraga, 2009). Levodopa Equivalent Daily Dosage (LEDD) was calculated for all medicated PD participants according to the methods outlined by Tomlinson et al. (2010). Demographic, neurological, and cognitive characteristics of the PD participants are presented in Table 3.

Table 3

Characteristics of Participants with PD

Participant	Age[a]	Sex	YOE	Disease duration[a]	LEDD	HY	PD-CRS	GDS
1	60	M	16	0.5	400	2	102	1
2	66	F	18	2	280	2	122	0
3	70	M	5	18	614	2	85	1[b]
4	73	M	13	10	400	2	114	0
5[+]	56	M	12	6	325	2	96	1
6[+]	62	F	15	3	100	2	100	3
7	60	F	14	6	550	2	111	3[b]
8	57	F	18	5	550	2	114	0[b]
9	60	F	16	5	394.5	2	112	3
10	50	F	11	4	950	2	111	1
11[+]	65	M	21	6	549	2	117	3
12[+]	63	M	10	7	400	2	107	1[b]
13	75	F	10	21	1030	3	85	4[b]
14	75	M	10	8	955	2	92	0
M	**63.7**	**NA**	**16.12**	**7.25**	**535.54**	**2.1**	**104.86**	**1.5**
SD	*7.5*		*2.7*	*5.75*	*273.62*	*0.27*	*11.78*	*1.4*

Note. YOE = Years of Education; LEDD = Levodopa Equivalent Daily Dosage (mg/day); HY = Hoehn & Yahr rating. PD-CRS = Parkinson's Disease Cognitive Rating Scale (total score). GDS = Geriatric Depression Scale; M = male; F = female.

[+]Participant subsequently excluded prior to data analysis.

[a]Age and Disease duration are reported in years.

[b]Participant was taking anti-depressant medication at time of testing.

The Montreal Cognitive Assessment (MoCA v7.1; Nasreddine et al., 2005) was administered to all controls and those scoring below the recommended cut-off for typical functioning within their age range (Rossetti et al., 2011) were excluded from further testing. The mean total MoCA score for the control group was 27.6 [2.6]. Informed written consent was obtained from participants prior to inclusion. The study received ethical approval from the University of Queensland's Human Research Ethics Committee and was therefore in accordance with the 2007 NHMRC National Statement on Ethical Conduct in Human Research. Participants received financial reimbursement for their participation.

3.2.2 Experimental Design and Stimuli

The task developed for this study was a hybridised version of tasks developed by Burgess and Shallice (1996) and Wheeldon and Monsell (1994). The first component involved a sentence completion task identical to Part B of the HSCT (Burgess & Shallice, 1996) in which participants were presented with a high cloze probability sentence stem and required to respond with a completely unrelated word. This presumably necessitated the suppression of the strong, prepotent response (the word that would usually be expected to complete the sentence stem) and generation of an acceptable alternative. Sixty-eight cloze probability sentences were drawn from the database compiled by Block and Baldwin (2010). Sentences were limited to 6-11 words in length, with a cloze probability greater than 0.75. Fourteen of these sentences were designated as fillers and the rest as experimental trials.

The second component of the paradigm was a picture naming task that required participants to name a black-and-white line drawing of an object. Sentence stem and picture naming trials were interleaved throughout the task in an A-B-A-B design. Each sentence stem was paired with a corresponding picture according to three experimental conditions. In the unrelated condition, the picture was semantically unrelated to the prepotent response associated with the sentence stem. In the related condition the picture was semantically related to the prepotent response. In the target condition the picture was identical to the prepotent response. A lag of zero or two trials was incorporated between the sentence stem and the corresponding picture. When lag = 0, the corresponding picture was presented immediately after the sentence stem. When lag = 2, the sentence stem and its corresponding picture were separated by an intervening picture trial and an intervening sentence stem. This design was hypothesised to allow for observation of the duration and decay process associated with inhibition within a semantic network.

The black-and-white line drawings were drawn from multiple sources including the International Picture Naming Project (IPNP) database (Szekely et al., 2004) and Snodgrass and Vanderwart (1980). In order to determine words that were deemed to be semantically related, the sentence stem's prepotent response was entered into the Edinburgh Associative Thesaurus (Kiss,

Armstrong, Milroy, & Piper, 1973) and the top five closest results were shortlisted. This was then cross-referenced against words that were represented as line drawings in at least one picture database (described above). Words that were classified as unrelated did not appear in the Edinburgh Associative Thesaurus list and were from a contrasting semantic category compared to the target word. These items were also present in at least one picture database. Judgment of relatedness was performed in accordance with these guidelines by two independent raters. No prepotent response or picture appeared more than once. A total of 68 pictures were employed, and 14 of these images were designated as fillers. The naming latency (IPNP; Szekely et al., 2004) and CELEX spoken word frequency (obtained from the N-Watch database; Davis, 2005) of the pictured objects did not differ significantly between the conditions ($p = .657$ and $p = .171$, respectively).

The complete task involved 164 trials (68 sentence stem trials, 68 corresponding picture-naming trials, 14 filler sentence stems and 14 filler pictures). The stimuli were pseudorandomised into three alternative runs to minimise order effects, with at least one intervening trial occurring between the repetitions of the same condition. In each pseudo-randomisation, each sentence occurred in a different condition. For example, the sentence "Susan went to the bakery to buy a loaf of …" would occur in each pseudorandomisation once, but in a different condition (related, unrelated, or target) each time.

3.2.3 Procedure

Testing was conducted in a quiet room. The task was presented on a laptop computer positioned approximately 60 cm from the seated participant. Participants wore a microphone attached to a headset that recorded verbal responses. The experiment was presented using Cogent 2000 graphics (Wellcome Department of Imaging Neuroscience, 2013) via a Matlab 2011b platform (MathWorks, 2011). Text was presented in Arial size 50 font. Images were 300 x 300 pixels 72 dpi set against a white background.

To begin, a fixation cross was displayed for 250 ms followed by presentation of the sentence stem, which appeared one word at a time from left to right across the screen (500 ms per word). A blank line (e.g., _____) was presented in the place of the final word of the sentence. The complete sentence then remained on screen for 5000 ms during which time the participant was required to provide their verbal response. The sentence was then replaced by a picture (black-and-white line drawing) that remained on screen for 5000 ms while the participant provided a verbal response. This was followed by a blank screen that appeared for 500 ms before a fixation cross appeared and the sequence commenced again.

Participants were asked to provide their responses as quickly as possible. The researcher provided verbal instructions in addition to written instructions presented on screen. Participants completed five practice trials prior to commencing the task in order to familiarise themselves with

the nature of the stimuli and the responses required. During this time, participants were reminded to provide single words only, and avoid using the same word more than once for the sentence completion trials. The task took approximately 20 min to complete.

3.3 Results

3.3.1 Scoring

Response times were manually extracted from the audio recordings and were measured from the offset of the blank line to the onset of the participant's response in sentence completion trials, and from the onset of the picture to the onset of the participant's response in picture naming trials. Two independent raters scored responses for accuracy according to pre-established criteria. Scoring of responses for the sentence completion task was based on the original HSCT scoring criteria (see Burgess & Shallice, 1996). In short, responses were required to be a single word that was completely unrelated to the sentence stem. In the picture-naming task, participants were required to correctly name the image. For both tasks, responses that involved excessive interjections or false starts, self-corrections, or multiple words were considered incorrect. Cohen's kappa was run to determine the level of inter-rater agreement for sentence completion and picture-naming scores. There was very good agreement between the two raters' judgements, $\kappa = .897$ (95% CI 0.883, 0.911), $p < .001$.

3.3.2 Behavioural Results

Initial exploration of the data set revealed several participants in each group (4 PD, 4 control) who had achieved less than 50% accuracy in all three conditions of the picture naming trials. These participants were excluded from further analysis, as this error rate was considered to be evidence that the individuals were unable to perform the required task. Their exclusion did not affect the significance of the difference in age, gender, or YOE between groups. The final analysis therefore included 10 participants from the PD group and 12 participants from the control group. Overall, 3.08% of trials in the PD group and 1.34% of trials in the control group were recorded as non-responses in the picture naming trials and subsequently discarded.

3.3.2.1 Picture naming response time.

Analysis of response time in the picture naming condition was only considered for those trials in which the picture naming response time was greater than 250 ms and less than 2500 ms. As a result, 1.21% of trials in the PD group and 1.25% of trials in the control group were excluded. Filler trials were also discarded for this analysis.

Response time data for picture naming trials was to be evaluated as a function of a specific set of criteria in order to observe the influence of successful or unsuccessful suppression on picture naming. These were to include the following combinations:

A. Sentence Correct and Picture Correct

B. Sentence Incorrect and Picture Correct

However, it was found that once the criteria for each of these combinations was applied to the data, the remaining number of trials available was deemed to be unsuitable for statistical analysis. For combination A, only 42.96% of total trials administered to the PD group and 43.06% of total trials administered to the control group were valid for consideration. For combination B, only 19.4% of the PD responses and 23.6% of the control responses were valid. These figures were then further reduced when attempting to examine the effects of condition and lag on response time data. Hence, further interpretation and exploration of this response time data was abandoned. Raw response time data for each group is presented in Table 4.

Table 4

Mean Picture Naming Response Time (ms) for PD and Control Groups as a Function of Lag and Condition

Group	Condition	Lag	*M*	*SD*
PD	Related	0	1221.2	462.4
		2	1110.8	421.6
	Unrelated	0	1137.5	380.9
		2	1018.7	328.7
	Target	0	1176.6	376.4
		2	1170.5	395.9
Controls	Related	0	1145.2	480.9
		2	1059.9	392.0
	Unrelated	0	1011.0	302.0
		2	1051.9	358.3
	Target	0	1101.0	405.9
		2	1083.0	387.8

3.3.2.2 Picture naming accuracy.

Picture naming accuracy data was extracted for each participant, per condition and lag, both when the sentence component of the task was correct and when it was incorrect. A large ceiling

effect was observed in both groups, resulting in abnormal distributions. An Arcsine transformation did not improve the normality of the distribution. Non-parametric methods were therefore employed to analyse the accuracy data.

A series of Mann-Whitney U tests were performed in order to detect between-subject differences across combinations of sentence trial accuracy and lag when condition was collapsed, A Bonferroni adjustment for multiple comparisons was performed and returned a corrected alpha value of p = 0.0125. There was only one significant difference between groups, and this occurred when the sentence trial was incorrect and lag = 0 (U = 313.5, z = -2.778, p = .005), wherein the PD group was significantly less accurate than the control. A Friedman test was run for each group to determine whether this difference in accuracy was specific to a particular picture naming condition (related, unrelated, target). Results indicated no significant differences between conditions for the PD or control groups at the uncorrected alpha value of 0.05 (x^2 = 1.75, p = .417, and x^2 =1, p = .607, respectively). Means, medians, and interquartile ranges for accuracy are presented in Table 5.

Table 5

Picture Naming Accuracy Scores (% Correct) for PD and Control Groups as a Function of Sentence Accuracy and Lag

	M *[SD]* No. Sentences Correct	M *[SD]* No. Pictures Correct	M *[SD]* Percentage Pictures Correct	Median (%)	Interquartile Range (%)
PD					
Sentence Correct Lag=0	18 *[4.4]*	15.9 *[4.1]*	81.44 *[25.64]*	100	34
Sentence Correct Lag=2	8.4 *[3]*	7.3 *[2]*	88.89 *[22.92]*	100	8
Sentence Incorrect Lag=0*	-	6.7 *[4.8]*	76.17 *[35.9]*	80	50
Sentence Incorrect Lag=2	-	3.8 *[2.5]*	84 *[27.8]*	100	0
Controls					
Sentence Correct Lag=0	17.8 *[4.6]*	16 *[4.7]*	88 *[18.03]*	100	25
Sentence Correct Lag=2	7.9 *[3.4]*	7.3 *[3.1]*	94.22 *[13.6]*	100	0
Sentence Incorrect Lag=0*	-	8.3 *[4.1]*	88.7 *[20.41]*	100	14
Sentence Incorrect Lag=2	-	4.9 *[2.6]*	93 *[16]*	100	0

*p < .05

Freidman tests were then performed to observe within-subject effects of condition (related, unrelated, target) on picture naming accuracy across all combinations of sentence accuracy and lag. Results demonstrated no overall main effect of condition when collapsed for group, across any combination. Each test was repeated separately for the PD and control group. No main effect of condition was detected for either group for any combination of sentence accuracy and lag.

It must be noted that for each analysis that considered both accuracy for the sentence completion trial and accuracy for the picture naming condition, the number of valid trials was low. In the analysis of picture naming accuracy, less than 50% of the total trials administered to each participant were valid for consideration under any combination of sentence accuracy and lag. Furthermore, the loss of trials across groups was not always consistent, resulting in unbalanced sample sizes. In addition to the initial removal of eight participants, this loss of trials must be noted as considerably impacting the validity of the results obtained.

3.3.2.3 Isolated sentence stem response time and accuracy.

A separate analysis of sentence response time and accuracy was conducted in order to determine whether the PD and control groups differed in their ability to perform the sentence completion trials. This analysis only considered those trials in which the response to the sentence stem was given within 250 ms and 2500 ms and resulted in removing 7.2% of overall trials for the PD group, and 4.7% of overall trials for the control group. As the requirements of the sentence completion trial remained constant throughout the experiment, condition was not included as a factor.

Initial exploration revealed a lack of normality in the distribution of response times for both groups, and this was not resolved through log, square root, or reciprocal transformation. Non-parametric measures were therefore applied. A Mann-Whitney U test demonstrated that the PD and control groups did not differ in their mean response time *(M* = 1210 [34] ms*, M* = 1480 [29] ms, respectively) when providing an unrelated word in response to the sentence stem (U = 64141, z = -1.166, p = .244).

The mean percentage of correct responses per participant was extracted. Again, this data was not normally distributed for either group and non-parametric measures were employed for the analysis. A Mann Whitney U test revealed that there was no difference in accuracy between the PD and control groups (*M* = 0.75 [0.038] and *M* = 0.73 [0.032], respectively) for the sentence completion trials (U = 515, z = -0.322, p = .747).

In order to rule out order or practice effects, sentence trials were divided into four equal blocks of 17 trials and response time and accuracy data submitted to non-parametric analyses. A Mann-Whitney test was run to determine whether PD and control groups differed in mean sentence

response time (for correct trials only) as a function of block. This test returned no significant results ($p > .05$ for all blocks). A Friedman test also demonstrated no significant differences in response time between blocks when collapsed across groups ($x^2 = 1.8$, $p = .615$). A second Mann-Whitney test was performed in order to identify group differences in sentence accuracy as a function of block. No significant differences were detected ($p > .05$ for all blocks). Finally, a second Freidman test was run to determine whether there was a significant difference in sentence accuracy between blocks when collapsed for group. This test found no significant difference ($x^2 = 6.59$, $p = .086$).

3.4 Discussion

The aim of the present study was to elucidate the nature and integrity of lexical-semantic mechanisms over time in PD. A secondary aim was to determine whether the generation of an unrelated word in response to a high cloze probability sentence stem, as assessed by the HSCT, indeed requires the suppression of a prepotent response at the word level or at the semantic category level. Analysis of the results suggested that the complexity of the experimental design and task difficulty may have significantly diminished the reliability of results due to the limited number of valid trials available under given conditions. Any conclusions must therefore be treated with considerable caution. The primary finding of the study was that the PD group were significantly less accurate in naming the picture when they had been unsuccessful in suppressing the strongly prepotent response and/or its related concepts across all conditions, but only when lag = 0. This difference was not detected for any other combinations of sentence completion accuracy and lag. For these trials, the PD group's median accuracy was equivalent to that of the controls (median = 100%). This result suggests that when the PD group were unable to successfully suppress a prepotent response they had increased difficulty in immediately naming a subsequent picture image (related, unrelated or identical to the prepotent response), however when given additional time (lag = 2) their performance was restored to a level commensurate with controls.

Given the limited scientific validity of the results obtained, the following discussion may be more appropriately viewed as a speculative, theoretical exploration of the descriptive difference observed in the performance of the PD group, rather than a robust interpretation and description of its significance. Sections 3.4.1 – 3.4.3 will cautiously consider the possible interpretations of the difference in performance observed in the PD group in the context of existing literature, and Section 3.5 will proffer some alternative explanation for the limited outcomes of this study.

3.4.1 Integrity of Inhibition Mechanisms

An initial intention of this study was to observe the integrity of inhibition mechanisms over time in the PD population. Analysis of response time and accuracy data for the sentence trials revealed that PD participants performed at a level commensurate with controls in the component of the task that replicated the HSCT verbal suppression task. Rather, the effect of errors on the

subsequent picture naming trial was discrepant between the groups. It may therefore be suggested that PD pathology does not appear to affect the inhibition of a prepotent verbal response in this cohort of participants.

This finding is in contrast to previous studies that have administered the HSCT in a PD population. Studies conducted by Bouquet et al. (2003), Obeso et al. (2011a), and O'Callaghan et al. (2013b), all demonstrated that PD participants recorded slower response times on Part B of the HSCT relative to a control group. These findings were interpreted as evidence for the impairment of verbal response suppression in this population. A number of factors may explain this discrepancy. The present study involved a considerably greater number of trials relative to the original HSCT. The original only contains 15 trials in which participants are required to provide a semantically unrelated response, while our study contained 68. It is possible that increased exposure to the suppression task allowed participants the opportunity to develop strategies that facilitated improved execution of the task, a possibility that has been previously proposed by Robinson et al. (2015). However, analysis of the effect of block order demonstrated that this was not the case in the present study, with no group differences in performance as a function of order, or evidence of linear changes in performance over time. An alternative explanation for the lack of group differences in suppression of a prepotent response may be the overall heterogeneity of the PD population, which has been well established (Monchi, Hanganu, & Bellec, 2016). Taken together, the finding of no group differences in response time or accuracy for the sentence completion component suggests that the decreased accuracy observed for picture trials following *unsuccessful* suppression of the prepotent response is not indicative of compromised inhibition mechanisms in the PD group.

3.4.2 Cognitive Flexibility

Cognitive flexibility is the capacity to respond and adapt appropriately to changing conditions in the environment. It is commonly subsumed under the umbrella term of cognitive control, and is thought to be largely mediated by regions of the prefrontal cortex (Miller & Cohen, 2001; Watson & Leverenz, 2010). Disruptions to cognitive flexibility may result in a greater number of errors and/or increased switching costs (delayed response times) when required to cease responding to one perceptual dimension and begin responding to another. In the present study, there is no evidence to suggest that cognitive flexibility is a generalised or consistent problem in this sample of PD participants as, under most circumstances, there were no significant differences detected between groups in terms of accuracy or response time deficits across the two components of the task. However, given that errors arose in the picture naming trials when they immediately followed an incorrect sentence completion trial, it could be speculatively suggested that cognitive flexibility is disrupted in the PD group only in the face of increased cognitive loading. That is, when an error in one component of the task was detected, this conflict and the response processes that it initiated

exhausted resources such that the system was unable to transition effectively into the new set of task requirements. While the effect was immediately present post-error, the PD group were able to restore their ability to switch between sets when allowed time for the conflict to resolve (presuming there are no intervening error trials), explaining why the effect was no longer present at lag = 2. Of course, it must be noted that this explanation is dependent upon the PD participants being aware of their errors when they occurred (a parameter that was not documented).

Though speculative, this explanation is consistent with reports of disrupted cognitive flexibility in the PD population. Such deficits are one example of the myriad of cognitive impairments thought to be associated with disrupted communication between the basal ganglia and the frontal lobes (Cools et al., 2001; Dirnberger & Jahanshahi, 2013). Cognitive flexibility has been traditionally tested through administration of set-switching tasks, similar to and including the Wisconsin Card Sorting Task (WCST). This task asks participants to match a set of cards based on a classification rule that is learned through response feedback. After a set number of correct matches, the classification rule is changed and thus "set" must be switched. Participants with PD have consistently demonstrated impairment on the WCST and similar tasks recording increased set-loss errors and/or perseverative errors (Bokura et al., 2005; Cools et al., 2001b; Lange et al., 2016; Monchi et al., 2004; Woodward, Bub, & Hunter, 2002; for systematic review see Kudlicka et al., 2011).

That cognitive flexibility may be disrupted in the face of additional processing demands in PD participants is a suggestion also supported by the findings of Cools et al. (2001b). These authors designed a task that minimized working memory and rule learning requirements, thus allowing for more isolated observation of set-switching capacity. Their task involved switching between naming a letter and naming a digit, with cross-talk and no-cross-talk conditions (i.e. interference and no-interference). Forty-three medicated participants with mild PD were compared to a group of matched healthy controls, and exhibited significantly increased switch costs in the cross-talk condition (which required inhibition of competing information). Moreover, this deficit was independent from impairments in concept formation, rule learning, working memory, or general cognitive slowing. The authors interpreted this result as suggesting that set-switching deficits only manifested when competing information was introduced (as in the cross-talk condition) and when the load on cognitive mechanisms was increased.

The suggestion of disrupted cognitive flexibility only in the face of increasing cognitive demands is also in line with the circulating multiple hit hypothesis of cognitive inflexibility in PD. Lange et al. (2016) identified that PD participants only recorded increased perseverative errors on a computerised version of the WSCT when at least two executive processes were compromised. They suggested that if the deficit underlying cognitive inflexibility is limited to only one executive

function, e.g., set-shifting, then the PD group may be able to compensate for this loss. Considering the multiple hit hypothesis in the context of the present study, it could be postulated that the limited cognitive resources available for set-switching are sufficient to perform the task, until additional resource demands are introduced in the form of error-processing (e.g., error-monitoring, feedback, resolution).

3.4.3 Integrity of the Anterior Cingulate Cortex's Function

It may be tentatively postulated that decreased accuracy following unsuccessful suppression in the PD group alternatively relates to the function of the anterior cingulate cortex (ACC). This region has long been associated with cognitive control functions, and a landmark series of papers have attempted to discern the specific nature of its role (Carter, Braver, Barch, & Botvinick, 1998; Cohen, Botvinick, & Carter, 2000; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001). These authors argue that the ACC is involved in conflict-monitoring, as a means of modulating cognitive control. It could be suggested that the ACC is relevant when discussing the present study due to its involvement in frontostriatal circuitry and the known disruption of these pathways in PD. It has been well established that a closed feedback loop exists which facilitates communication between nuclei of the subcortex and the ACC (Alexander et al., 1986; Middleton & Strick, 2000). That the ACC is dependent upon the integrity of signals it receives from the basal ganglia (and in turn the basal ganglia's processing of any return signals sent by the ACC), lends some credit to the argument that a disruption in ACC function may underlie the effect observed on the present task in the PD group. The loss of nigrostriatal dopamine projections as a result of PD is known to disrupt the function of frontostriatal circuitry (for review see Zgaljardic et al., 2003). Furthermore, evidence is beginning to emerge that demonstrates altered activity in frontal-attention networks, including the ACC, in PD patients when completing tasks that recruit cognitive control (Baggio et al., 2014; Rosenberg-Katz et al., 2016).

As discussed previously, humans only have a limited reserve of cognitive control (Dirnberger & Jahanshahi, 2013), and it is thus important that it is distributed or allocated in the most efficient way possible. The ACC assists in this process by detecting the presence of conflict on a trial-by-trial basis, and then re-directing or sharpening cognitive control resources for the subsequent trials to prevent recurrence (Botvinick, Cohen, & Carter, 2004). This explanation dictates that when the ACC is strongly engaged during a trial, the subsequent behavioural performance should reflect increased attention (top-down control), and likewise, weak ACC engagement will be followed by decreased attention. Kerns, Cohen, Macdonald, and Cho (2004a) provided confirmation of this hypothesis through observation of interference effects on the Stroop task following instances of strong ACC recruitment.

Studies employing electroencephalogram (EEG) and fMRI technology have also linked increased activity in the ACC to the occurrence of errors (Garavan, Ross, Murphy, Roche, & Stein, 2002; Holroyd et al., 2004; Iannaccone et al., 2015; Mathalon, Whitfield, & Ford, 2003; Swick & Turken, 2002). As previously stated, the disruption to PD performance in the present task appears to relate to the downstream effect of an error that has occurred during a sentence completion trial (failure to suppress the prepotent response) on the picture trial that immediately follows. With reference to the role of the ACC in conflict-monitoring as discussed above, it may be that the failure to successfully supress the prepotent response created an error-induced state of conflict, to which the ACC was required to respond. In the PD group, the ACC response was insufficient to prevent further errors. Yeung, Botvinick, and Cohen (2004) have proposed that a state of conflict can be induced when an error is made because even as responses to the error are being executed, ongoing processing of the stimulus continues, and this may lead to eventual activation of the correct answer. Thus there is a transient period in which both the correct and incorrect responses are activated, leading to conflict. This is also in line with our finding of no group differences in picture-naming accuracy following an incorrect trial when lag = 2, as the conflict evoked during the aforementioned transient period has subsided by this stage, allowing the correct name to be produced.

Involvement of the ACC may also be speculated based on the nature of each group's response to error. In the literature, response-time slowing has been observed following trials that invoke conflict and is thought to be the result of increased cognitive control. This post-error slowing has also been attributed to the influence of the ACC (Botvinick et al., 2004) and serves to improve performance on subsequent trials (Gehring & Fencsik, 2001). Due to the lack of valid trials in the present study we were unable to test whether the control and PD groups experienced differential changes in response time for picture naming trials following an incorrect sentence completion trial. However, another type of post-error adjustment thought to act as a compensatory control mechanism is post-error changes in accuracy, and a review conducted by Danielmeier and Ullsperger (2011) suggested that this can occur independently of post-error slowing. Such changes in accuracy have been observed as either improvements or lack of change in accuracy in the healthy population (Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011; Hajcak & Simons, 2008; Klein et al., 2007; Maier, Yeung, & Steinhauser, 2011; Themanson, Rosen, Pontifex, Hillman, & McAuley, 2012) and indeed the control group in the present study did not demonstrate a decrease in their picture naming accuracy following incorrect sentence trials. It may therefore be surmised that in the PD group, the integrity of the fronto-subcortical error-monitoring/resolution system was disrupted such that errors were followed by decreased accuracy.

3.5 Limitations and Future Directions

The present study was limited by the small number of participants in each group. These numbers were further impacted by the inherent complexity of the task and associated loss of valid trials, particularly when attempting to observe the influence of the sentence completion task on subsequent picture naming. Additionally, the heterogeneity of the PD population in terms of severity, response to medication, disease progression, and predominance of symptoms may have further confounded the distribution of the data.

Future studies may look to address these concerns by recruiting larger samples and increasing the number of trials per condition so as to lessen the overall impact of error or non-responses. Furthermore, tasks that aim to measure the interaction between cognitive control and language processing in PD should be designed to allow for the controlled, systematic increase of task demands. In this way, the relationship between cognitive-linguistic performance, and the allocation and availability of attentional resources may be explicitly observed.

3.6 Conclusions

In conclusion, the results of the present study suggest that the ability of people with PD to suppress a prepotent verbal response is largely intact in this cohort relative to healthy controls. However, it must be noted that, as a presumed result of the excessive difficulty experienced by both PD and control groups in executing the task, data analysis was based on an extremely limited number of trials. As such, the interpretation of these results should be considered speculative in nature. Instead, discussion has instead aimed to proffer some speculation as to how the observed pattern of performance in the PD group could align with existing literature, and outline the limitations inherent in the study's design. This theoretical exploration speculated that cognitive flexibility, conflict monitoring, or a combination of both processes may be disrupted in this population as a function of increasing cognitive control demands. However, considerable remodelling of the paradigm is required if these conjectural suggestions are to be substantiated.

4 Chapter Four

Functional Correlates of Strategy Formation and Verbal Suppression in Parkinson's Disease

The study in Chapter 3 aimed to determine the nature and integrity of the time-course of inhibition in PD. A novel hybridisation of the HSCT and a competitor priming paradigm was employed that required participants to respond to alternating sentence completion and picture naming trials. Sentence completion trials were akin to the suppression component (Part B) of the HSCT and thus asked participants to provide a word that was unrelated to a high cloze probability sentence stem, presumably requiring the suppression of a prepotent response. The relationship between this prepotent response and picture naming trials was then manipulated to be identical, semantically related, or unrelated. There was no significant group difference in sentence completion accuracy, however, the PD group did record significantly more errors in picture naming trials (regardless of condition) when the previous sentence completion trial was inaccurate (that is, when the prepotent response was not successfully suppressed). This effect was only identified when Lag = 0, and was no longer present at Lag = 2. It was speculated that these findings may reflect the effects of a compromised frontostriatal system, either as a result of disrupted cognitive flexibility, or error-processing faculties.

It must be noted that these hypotheses were highly speculative in nature, given the limited trials upon which analysis was based. Furthermore, analysis of behavioural performance was not accompanied by a neuroimaging investigation. The study in Chapter 4 therefore employed a combined fMRI and behavioural design in order to elucidate the participation of frontostriatal circuitry in the HSCT, and observe changes in activity accompanying PD performance on this task. A novel condition was also incorporated with the intent of determining whether generation of an unrelated response on Part B was influenced by the ability to internally formulate and implement a strategy: a factor not measured quantitatively in previous administrations of the task.

4.1 Introduction

Language disturbances have been widely documented in the PD population, including altered semantic priming, word-finding difficulties, impaired syntactic processing, and compromised high-level language performance (Angwin et al., 2003, 2004; Arnott et al., 2010; Arnott et al., 2001; Grossman, 1999; Ketteler et al., 2014; Liu et al., 2015; Murray, 2008; Peran et al., 2009; Vanhoutte, De Letter, Corthals, Van Borsel, & Santens, 2012). Parkinson's patients also perform poorly on verbal fluency tasks (Auriacombe et al., 1993; Bayles et al., 1993; Flowers et al., 1995; Henry & Crawford, 2004; Herrera et al., 2012; Piatt et al., 1999; Raskin et al., 1992). Problems in verbal fluency may reflect a deficit in efficient verbal selection and suppression. This is of particular clinical significance, as decreased verbal fluency performance has been linked to increased risk of dementia development (Jacobs et al., 1995; Levy et al., 2002; Williams-Gray et al., 2007). However, verbal fluency tasks are complex and require several skills including lexical search, selection, suppression, and retrieval (Perret, 1974; Ruff et al., 1997).

One task that has been employed to further understand and isolate some of these processes is the Hayling Sentence Completion Task (HSCT), developed by Burgess and Shallice (1996) to measure verbal selection and suppression. This task involves the presentation of cloze probability sentences that have had the final word removed. Participants are required to either provide a word that is congruent with the sentence (Part A) or provide a word that is incongruent (Part B). It is posited that Part A provides a measure of verbal selection while Part B provides a measure of verbal suppression. Burgess and Shallice also hypothesised that the ability to develop and apply a strategy would assist in generating an alternative response to complete Part B, and so developed a scoring system for the task that allowed for this to be qualitatively measured.

Participants with PD typically perform poorly on the HSCT. Bouquet et al. (2003) observed that while performance on Part A of the task was comparable between PD and controls, the PD participants were significantly slower than controls during Part B (suppression). Qualitative evaluation of responses did not reveal any significant difference between the groups in relation to error rate and the use of strategy to complete Part B (e.g., naming objects in the room, using a previous response or similar). In a later study, Obeso et al. (2011a) observed similar results. Their design additionally allowed for direct comparison of performance on motor and verbal tasks, including the HSCT. The PD group recording slower response times across both Part A and Part B relative to controls. Analysis of the difference between Part A and Part B scores also demonstrated that the PD group did not modulate response time as a function of condition (unlike controls who were significantly faster in Part A relative to Part B). Furthermore, the PD group made a greater number of errors on Part B that were either related or distantly related to the sentence stem. This performance was interpreted as demonstrating that the PD group were impaired in suppressing a

highly prepotent response in favour of a task appropriate response. The authors also observed deficits in the PD group across all tasks administered, leading them to conclude that a generalised inhibitory deficit was present.

Interestingly, Obeso et al. (2011a) defined the inhibition employed in the HSCT task as 'volitional inhibition' requiring intention and effort. This notion was also echoed in the conclusions of Castner et al. (2007b), who administered the HSCT to a group of PD patients receiving bilateral stimulation of the subthalamic nucleus (STN). These authors found that when off stimulation, the PD participants demonstrated significantly slower response times and made a larger number of errors on the HSCT Part B subtest, relative to the on-stimulation condition and healthy controls. This performance was improved to a level commensurate with healthy controls when the participants' stimulators were switched on. The results were considered to indicate a potential role for the subthalamic nucleus in modulating activity in the frontostriatal pathways responsible for facilitating aspects of verbal suppression or related processes. Castner et al. (2007b) additionally observed intact performance in the same cohort on a picture-word interference (PWI) task, which required participants to name a pictured object in the presence of a semantically related distractor word. The authors suggested that the differential performance on the HSCT and the PWI task, both of which are assumed to require some degree of lexical-semantic inhibition, can be explained by differences in the nature of the inhibition required. The HSCT was suggested to involve 'behavioural inhibition' - similar to Obeso et al.'s (2011a) 'volitional inhibition' - a function that appears to be disrupted by the pathology of PD. In contrast, the PWI task was suggested to involve less effortful 'interference control', a spared function in PD. This comparison also highlights differences in externally vs. internally mediated processes. It can be said that in Part B of the HSCT participants must generate an unrelated response internally, while in the PWI task, the response is available externally in the form of the picture to-be-named. Similarly, Brown and Marsden (1988), in their study of the Stroop inhibition task in a PD cohort, concluded that deficits arise when internally self-generated (rather than externally available) responses are required.

As this discussion demonstrates, the precise nature and origin of the verbal suppression deficits observed in the PD population is yet to be determined. It can be further argued that while the HSCT is a useful tool for investigation in this area, the conclusions that can be drawn from such studies are limited by the task's design and scoring. The method described by Burgess and Shallice (1996) for calculating and evaluating inhibition dictates that the score on Part B minus the score on Part A gives a measurement of "thinking time" on Part B, attributed to the demands of suppressing the prepotent response. This design does not account for the underlying component processes that are at play in each part of the HSCT, following the presentation of the sentence stem. In Part A, participants are presumed to activate a set of possible responses, enhance the activation of the most

appropriate response, suppress competing alternatives, and verbally produce the selected word. In comparison, Part B will initiate activation of a set of prepotent responses, one of which will likely be automatically enhanced as the most contextually accurate. All of these responses must then be suppressed. At this point, the participant is required to generate an alternative response and produce the selected word. It can therefore be noted that in addition to the likely differences in suppression of a non-prepotent (Part A) vs. a strongly prepotent (Part B) response, Part B also has an additional step involving the generation of an alternative response. It may be assumed that this process would be best facilitated by the development and application of a strategy that streamlines the search, retrieval and selection of an alternative word from within a large pool of possibilities. Internal strategy formulation is closely related to cognitive control, and has been previously identified as being impaired in PD (Taylor et al., 1986). It could therefore be suggested that either verbal suppression, strategy generation, or both of these cognitive functions underlie the difficulties observed on the HSCT in this population. As mentioned earlier, Burgess and Shallice (1996) only accounted for the possible contribution of strategy generation by subjectively rating the participant's responses based on whether they appear to be strategic in nature. While several subsequent authors (Bouquet et al., 2003; Castner et al., 2007b; Obeso et al., 2011a) have also employed this method, it is suggested that other task modifications may be more informative with reference to strategy generation and application during the HSCT.

De Zubicaray et al. (2000) developed a novel fMRI task termed the Category Judgement and Substitution Test, analogous to the HSCT, which was designed to allow for observation of verbal selection and suppression in isolation while also providing a means of quantifying the use of strategy. In young, healthy adult males they found that in the suppression condition, 94% of responses were generated based on use of strategy, and that relative to the initiation condition this correlated with increased activity in a network of frontal regions including the left dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC). This appears consistent with the hypothesised role of the dlPFC as a mediator of strategic processing. A current theory concerning the origin of cognitive control posits that the left dlPFC provides top-down signals that bias activity in other cortical areas in order to favour a weak but task-relevant response (Miller & Cohen, 2001). In the context of the findings of de Zubicaray et al. (2000) this would appear to support the notion that the dlPFC was recruited during the component of the task requiring participants to implement a strategy and generate an alternative, incongruent response. It therefore appears likely that administering the HSCT in the PD population in a manner that allows for quantitative measurement of the influence of strategy may offer further insight into the mechanisms underlying their difficulty with the task.

To date, assumptions regarding the mechanism underlying verbal selection and suppression differences between healthy controls and the PD population have been based on comparison of behavioural performance and known basal ganglia pathology in PD. However, direct evidence supporting the assumed role of the basal ganglia and associated circuits in these deficits is yet to be provided in the PD population. In healthy control subjects, functional neuroimaging has been employed to identify the underlying neural structures subserving the processes involved in this task. Recruitment of the frontal lobe during completion of both components of the task has been consistently observed, however the precise location varies. Typically, response times are associated with increased activity in the left inferior frontal gyrus (IFG) during both conditions, while mid-frontal and orbitofrontal activation is commonly observed during the Part B in parallel with slower response times relative to Part A (Allen et al., 2008; Collette et al., 2001; Nathaniel-James et al., 1997). It has been well established that regions of the frontal cortex are functionally connected to nuclei of the basal ganglia, via a number of parallel, closed-circuit feedback loops known as basal-ganglia-thalamo-cortical (BGTC) circuits or more generally, frontostriatal networks. In the motor realm these tracts allow the basal ganglia to provide top-down control over the selection and inhibition of competing motor plans in order to facilitate fluid movement (Alexander & Crutcher, 1990; Frank, 2006; Mink, 1996). The primary pathology of PD is the degradation of dopamine projections in the nigrostriatum, resulting in altered signalling along these BGTC pathways (Bartels & Leenders, 2009; Obeso et al., 2000). A large body of evidence exists describing the causal relationship between this disrupted signalling and motor symptoms, and people with PD have consistently demonstrated decreased performance on a number of tasks designed to measure the initiation and suppression of motor plans (Alegre et al., 2013; Bokura et al., 2005; Cooper, Sagar, Tidswell, & Jordan, 1994; Gauggel et al., 2004). Given that the subcortical circuitry believed to subserve cognitive functions is analogous to that of the motor realm, it has been hypothesised that their function may also be similar (Frank, 2006; Redgrave et al., 1999). Indeed, the role of frontostriatal circuitry in facilitating cognitive functions has now been widely documented (Lewis et al., 2003; Owens, 2004; Dirnberger & Jahashini, 2013). Furthermore, it has been speculated that the subtle impairments in language production associated with PD are the result of the interaction between cognitive processes (mediated by the frontostriatal networks) and linguistic processing in cerebral regions (for review see Altmann & Troche, 2011; Murray, 2008; Pell & Monetta, 2008).

For the present study, an fMRI paradigm was designed to examine brain activity associated with the component processes underlying the HSCT in individuals with PD relative to healthy controls. Specifically, the study aimed to test whether the altered performance of PD participants relative to controls on the HSCT was the result of deficits in verbal suppression, or strategy generation and implementation. This was achieved by comparing performance in the HSCT Part B

(requiring strategy formation) with a novel condition in which individuals were provided with a strategy for producing an unrelated word. Based on the literature reviewed above, it was hypothesized that the ability to formulate a strategy would place significant demands upon the dlPFC frontostriatal loop, and thus it was expected that activity here would be decreased in the PD group as a result of disease-driven dysfunction in this circuitry.

4.2 Methods

4.2.1 Participants

Thirteen participants (6 males) with idiopathic PD were recruited. All participants in the PD group were required to meet the following inclusion criteria: (1) diagnosis of idiopathic PD prior to inclusion in the study (diagnosis confirmed using Calne, Snow, & Lee's criteria [1992]); (2) right-handed, confirmed with the Annett Hand Preference Questionnaire (Annett, 1970); (3) English as a first language; (4) Hoehn and Yahr (1967/2001) rating of 1-3. Applicants were excluded if there was a history of substance abuse, head trauma, stereotaxic surgery and/or neurological disease other than PD. The Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was administered to screen for untreated clinical depression. A score greater than eight was considered indicative of major clinical depression in PD and any participants scoring in this range were excluded (Dissanayaka et al., 2011; Dissanayaka et al., 2007). The Montreal Cognitive Assessment (MoCA v7.1; Nasreddine et al., 2005) was administered in order to screen for significant cognitive impairment. Participants who achieved a score that was > 1 *SD* below the expected range for their age group (Rossetti et al., 2011) were excluded from further involvement in the study. Potential participants were also excluded if they presented with moderate-severe dysarthria (in order to minimise variation in response transcription due to poor intelligibility of speech) or an uncorrected hearing or visual impairment that could affect the validity of task performance (self-reported). Years of education (YOE) was calculated for each participant and included years spent undertaking primary, secondary, bachelor, post-graduate, and diploma/certificate studies. Levodopa equivalent daily dosage (LEDD) was calculated for each PD participant based on the procedures outlined by Tomlinson et al. (2010). The demographic and neurological characteristics of the PD participants are presented in Table 6.

Table 6

Characteristics of Participants with PD

Participant	Age[a]	Sex	Disease Duration[a]	YOE	HY	LEDD	MoCA	GDS
1	65	F	1	18	1	100	29	1
2	62	M	14	9	2	298	20	4
3[+]	59	F	4	16	2	364	27	8
4	55	F	3	20	1	512.5	26	0[b]
5	70	F	1	12	1	100	25	4
6	57	M	7	12	2	1787.5	23	5[b]
7	62	M	7	9	2	1050	24	5[b]
8	69	M	10	10	1	191	24	1[b]
9	73	M	4	17	2	500	26	4
10	49	F	2	11	1	600	24	3
11[+]	61	F	7	12	2	348	27	6[b]
12	58	F	4	14	1	450	26	0
13	69	M	6	17	1	349.5	24	0
M	**62.23**	NA	**5.39**	**13.62**	**1.46**	**511.58**	**25**	**3.3**
SD	*6.83*		*3.8*	*3.64*	*0.52*	*455.67*	*2.24*	*2.6*

Note. YOE = Years of Education; LEDD = Levodopa Equivalent Daily Dosage (mg/day); HY = Hoehn & Yahr rating. MoCA = Montreal Cognitive Assessment. GDS = Geriatric Depression Scale; M = male; F = female.
[+]Participant subsequently excluded prior to data analysis.
[a]Age and Disease duration are reported in years.
[b]Participant was taking anti-depressant medication at time of testing.

Eighteen neurologically healthy participants were recruited as controls (6 males, mean age = 68.06 years [9.52], mean YOE = 16 [4]). There was no significant difference between the control and PD groups for age (p = .07), YOE (p = .1) or gender (x^2 = .71). Controls were excluded if: (1) they were left handed (Annett, 1970); (2) they had a history of alcohol and/or substance abuse, neurological disease, surgery and/or trauma; (3) they had an uncorrected vision or hearing impairment that could affect validity of task performance; or (4) they achieved a score on the MoCA (Nasreddine et al., 2005) that was >1 *SD* below the expected range for their age group and level of education (Rossetti et al., 2011). The mean total MoCA score for the control group was 27 [1.8].

A battery of neurocognitive assessments was also administered to all participants in order to establish cognitive baselines. These assessments included the Boston Naming Test 2nd Edition (BNT; Kaplan, Goodglass, & Weintraub, 2000), selected subtests of the Test of Everyday Attention

(TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) including Elevator Counting and Elevator Counting with Distraction, the National Adult Reading Test (NART; Nelson & Willison, 1991), digits forwards and backwards, and verbal fluency (phonemic, semantic, and cued). Group performance on these assessments will be discussed below in Section 4.3.1.1.

The study was approved by the Human Research Ethics Committee of the University of Queensland and was therefore in accordance with the 2007 NHMRC National Statement on Ethical Conduct in Human Research. Participants provided written informed consent prior to their inclusion in the study. All participants were financially compensated for their participation in the study.

4.2.2 Experimental Design and Stimuli

The study employed a novel variation on the HSCT originally described by (Burgess & Shallice, 1996). This modification was required in order to differentiate between the processes of response inhibition, response initiation and strategy formation. Stimuli consisted of 120 high cloze probability sentences, 6-8 words in length (M_{length} = 7.2 [0.8]), with the final word removed. These were obtained from an expanded version of Bloom and Fischler (1980) sentence completion norms, compiled by Block and Baldwin (2010). This database comprises 400 high cloze probability sentences standardised against an undergraduate student population. N-watch software (Davis, 2005) was employed to determine the CELEX spoken word frequency of the final word (i.e. the most frequently provided 'most probable' response) in the high cloze probability sentences.

Three conditions were constructed termed complete, unrelated, and strategy. In the complete condition sentence stems were presented followed by the instruction "complete". Participants were required to provide a single word that accurately completed the sentence conceptually and grammatically. Participants completed this condition twice (60 trials in total), using alternative sets of stimuli. In the unrelated condition sentence stems were presented followed by the instruction "unrelated". Participants were required to provide a single word that was completely unrelated to the context of the sentence. Participants completed this condition once only (30 trials in total).

In the novel strategy condition sentence stems were presented followed by a semantic category cue (e.g., "fruit" or "transport") that was unrelated to the context of the sentence. Participants were required to generate a single word that is derived from the given category. Participants completed this condition once only. Eight high frequency semantic categories (six experimental and two for practice trials) were selected from the Battig and Montague (1969) norms. These included colour, transport, fruit, furniture, sport, and clothing for experimental trials, and tools and vegetables for practice trials. The Battig and Montague (1969) norms reported the mean total number of members generated for each of the experimental categories to be as follows: colour (M = 9.73 [3]), transport (M = 7.02 [23]), fruit (M = 7.82 [14]), furniture (M = 7.25 [18]), sport (M = 7.93 [13]), and clothing (M = 9.54 [5]). In order to minimize potential priming effects, categories

were unrelated to the context of sentence stems included in this condition, and did not relate semantically to any responses predicted for the complete condition. Semantic categories in the strategy condition were pseudo-randomized such that a minimum of five items separated repetitions of a category cue. Participants completed this condition once only (30 trials in total - each category appeared five times).Sentence stems were pseudo-randomized across conditions in order to minimise semantic associations existing between lexical items contained within each sentence stem, the most probable responses, and the selected semantic categories provided in the strategy condition (for example, exposure to the sentence stem "On Valentines day the women received a single red… " in the complete condition could potentially prime the response "red" in relation to the semantic category of colour when encountered in the subsequent strategy condition). One-way ANOVA demonstrated no significant differences between conditions with respect to sentence stem length (F [3, 116] = 0.744, p = .528), cloze probability (F [3, 116] = 0.134, p = .940), or CELEX spoken word frequency of the most probable response (F [3, 116] = 0.734, p = .534).

Participants completed two runs of 60 trials successively within one scanning session, with a short break in between. The first run examined the complete and unrelated conditions, with the second involving the complete and strategy conditions. This sequence of events was designed to prevent participants from using the semantic categories provided in the cued condition to aid response generation in the unrelated condition, and thus remained constant for each participant. Conditions were presented sequentially (five trials per block) within each experimental run in order to minimise cognitive set-switching demands.

4.2.3 Procedure

Prior to commencing each experimental run, participants received five practice trials of each condition in order to familiarise themselves with the task requirements. Practice trials for complete and unrelated conditions were presented prior to run 1 (outside of scanner), with trials for the strategy condition only presented prior to Run 2 (in scanner). This arrangement was designed to prevent participants from utilising the semantic category approach of the strategy condition to support completion of unrelated trials (note however that if that if participants spontaneously utilised this strategy independently during the unrelated condition their responses were still considered valid). Practice stimuli were selected such that the occurrence of semantic associations between practice and test items was minimized. During practice trials, corrective feedback was provided by the examiner as per the original HSCT protocol (Burgess & Shallice, 1996). For the novel strategy condition, participants were corrected if they provided a word that was unrelated to the sentence stem but did not belong to the given category. Importantly, the categories used during practice trials were not included in the experimental trials. Participants were discouraged from providing the same response to multiple items (e.g., providing "banana" for every item).

Stimuli were presented on a computer monitor using Cogent 2000 software (Wellcome Department of Imaging Neuroscience, 2013) operating via a Matlab R2011b platform (MathWorks, 2011) with a screen resolution of 1024x768, Arial font in size 50. The screen projected onto a monitor visible to the participants within the bore of the magnet. Each trial began with a fixation cross for 250 ms. Sentence stems appeared one word at time with an interval of 500 ms between each individual word. Then, 500 ms after the offset of the last word, a prompt "_____" appeared, followed by a written instruction that informed participants of the response required ("complete", "unrelated" or a semantic category cue e.g., "fruit"). This design was intended to discourage participants from ignoring or not processing the sentence and thus reducing suppression requirements. The sentence stem and instruction remained on screen for 5000 ms before automatically progressing to the beginning of the next trial, after which any responses were discounted. For each item, participants were asked to provide a response as quickly as possible following appearance of the response instruction.

The total time to complete both runs was approximately 20 min.

4.2.4 Image Acquisition

Imaging was acquired using a Siemens Trio (3T; Siemens AG, Germany). Functional imaging was conducted using a gradient echo EPI sequence (echo time [TE] = 36 ms, repetition time [TR] = 2500 ms, field of view [FOV] = 210 x 210 mm, flip angle 80, in-plane resolution of 3.6 x 3.6 mm, and 36 slices x 3 mm, with a 0.6 mm gap). In each run, 242 image volumes were collected. Three-dimensional T1-weighted images were also acquired in the same session, using a magnetisation-prepared rapid acquisition with gradient echo sequence (TE = 2.99 ms, TR = 2200 ms, inversion time [TI] = 900 ms, FOV = 256 x 256 x 192 mm, 192 phase encodings in the slice direction, isotropic voxel size of 1 mm^3). A fluid-attenuated inversion recovery (FLAIR) sequence was also included in order to remove signal from cerebrospinal fluid from resulting images (FLAIR TE/TR 93/7000 ms, TI = 2500 ms, resolution = 0.86 x 0.86 x 4 mm, FOV = 220 mm).

4.2.5 Imaging Data Processing

Raw imaging data was processed using Statistical Parametric Mapping Version 12 software (SPM12; Wellcome Trust Centre for Neuroimaging, 2014) operating through Matlab R2014b (Mathworks, 2014). Pre-processing steps included realigning and unwarping the fMRI time series, and applying slice time correction. Both sessions were then co-registered to a within-session, high-resolution T1 structural image. At this point, a motion finger-printing tool was employed in order to automatically assess and correct for the effects of motion within the fMRI time series, as described by Wilke (2014). T1 images were then segmented into grey matter, white matter and cerebrospinal fluid using a tissue classification method. The images were spatially normalised using DARTEL spatial normalisation (Ashburner, 2007). An 8 mm, full-width, half-maximum Gaussian kernel was

then be used to smooth the resulting images. A general linear model, ANOVA was constructed, regressing out global signal and motion, and modelling condition (complete, unrelated, and strategy) by group (PD and control). Independent t-tests were also developed to directly compare strategy and unrelated conditions across groups.

A hypothesis-driven region of interest (ROI) analysis was also conducted. A spherical ROIs (of 8 mm radius) capturing the left dorsolateral prefrontal cortex (dlPFC; -38 30 32) was developed within MNI atlas space using MarsBar ROI toolbox (Brent, Anton, Valabregue, & Poline, 2002) for SPM12 (Wellcome Trust Centre for Neuroimaging, 2014). As discussed above, the left dlPFC has been implicated in previous studies of the HSCT and its analogues (de Zubicaray et al., 2000; Nathaniel-James et al., 1997) and is a critical component of the cognitive frontostriatal loop (Middleton & Strick, 2000). Two anatomically derived ROIs were also obtained using WFU Pickatlas software (Maldjian, Laurienti, Kraft, & Burdette, 2003). These included the left dorsal striatum (caudate and putamen) and the left ACC, due to their participation in a cognitive frontostriatal circuits implicated in PD (Middleton & Strick, 2000).

4.2.6 Scoring of Behavioural Data

Audio files containing verbal responses were digitally filtered to reduce interference from scanner noise using Audacity software (v2.1.2) and response times were manually extracted. Response time was measured from the offset of the written instruction indicating required response (e.g. “unrelated”, “complete”, “colour”) to the onset of the participant’s verbal response (in order to avoid contamination from non-verbal artifacts such as coughing). The PD and control groups were compared in terms of both response latency and response accuracy. Responses were scored as either correct or incorrect. Responses were incorrect if they contained excessive interjections or false starts, or self-corrections. For the complete condition, a single word that completed the sentence in a way that made sense and was grammatical was considered to be a correct response. For the unrelated condition, each response was judged on how semantically related it was to the sentence, as outlined by Burgess and Shallice (1996), with a correct response being a single word that was unrelated to any component of the sentence. For the strategy condition, a correct response had to be a member of the cued semantic category. Repetitions in the unrelated and strategy conditions were not permitted. Response scoring was conducted by two markers. Cohen’s kappa was run to determine inter-rater agreement and returned an acceptable level of agreement, $\kappa = .781$ (95% CI 0.768, 0.794), $p < .001$.

4.3 Results

Initial exploration of ROI data (see Section 4.3.2.1) identified three significant outliers (2 PD, 1 control). Outliers were identified based on interquartile range. A data point (representing the mean percentage blood-oxygen-level dependent [BOLD] signal change) that fell below the 25th

percentile or above the 75th percentile was considered to be an outlier. These participants were excluded from all further analysis including whole brain results. These exclusions did not result in significant differences between groups in terms of age (p = .152), YOE (p = .128), or gender (p = .441).

4.3.1 Behavioural Results

4.3.1.1 Neurocognitive battery.

A series of independent t-tests were conducted in order to identify any significant differences between groups across the battery of neurocognitive measures. Results are presented in Table 7. Note that excluded participants, as discussed above, were not included in statistical analysis of this assessment data. For selected items, sample size is also reduced due to some participants being unable to complete the task as a result of fatigue or time constraints. No significant differences were identified.

Table 7

Baseline Measurements of Neurocognitive Performance of Participants with PD

Measure	Group	*n*	M_{Score}	*SD*	Significance
Semantic Fluency	PD	11	17.53	5.21	.079
	Control	17	20.84	3.25	
Phonemic Fluency	PD	11	13.88	4.48	.086
	Control	17	16.61	2.49	
BNT	PD	11	55.45	2.38	.988
	Control	17	55.47	3.10	
TEA - EC	PD	11	6.91	0.30	.758
	Control	17	6.94	0.24	
TEA - ECD	PD	11	9.18	2.96	.395
	Control	16	10.06	2.32	
Digits Forward	PD	10	7.20	1.03	.253
	Control	17	7.76	1.30	
Digits Backward	PD	10	5.30	1.25	.698
	Control	17	5.12	1.11	
NART_FISQ	PD	10	112.50	11.43	.228
	Control	17	117.53	6.80	
Cued Fluency	PD	11	22.64	3.96	.161
	Control	17	24.47	2.78	

Note. BNT = Boston Naming Test 2nd Edition; NART_FISQ = National Adult Reading Test Full Scale IQ; TEA – EC = Test of Everyday Attention - Elevator Counting; TEA – ECD = Test of Everyday Attention - Elevator Counting with Distraction.

4.3.1.2 Response time.

Only correct trials were included in the analysis of response time. Furthermore, only those trials in which a response was provided within a window 250 ms to 2500 ms were included. As a result, 26% of trials in the PD group and 20% of trials in the control group were also discarded. A Shapiro-Wilks test indicated a departure from normality in the distribution of the response time data for both groups. A square-root transformation was performed to rectify this and the resulting distribution was satisfactory. This transformed data was submitted to a Linear Mixed Model (LMM) analysis with group and condition modelled as fixed effects and participant number as a random effect.

Results demonstrated a significant main effect of condition, F (2, 2138) = 313.71, $p < .001$. Pairwise comparisons further demonstrated that significant differences were present between all conditions, with responses given faster in the unrelated condition relative to the strategy condition ($p < .001$), and faster again in the complete condition relative to both unrelated ($p < .001$) and Strategy conditions ($p < .001$). Independent testing of PD and control groups separately revealed that this pattern of performance was present and significant at the specified .05 level in both groups, see Figure 5. Results here are reported in raw form, for ease of interpretation. No main effect of group or group by condition interaction was detected.

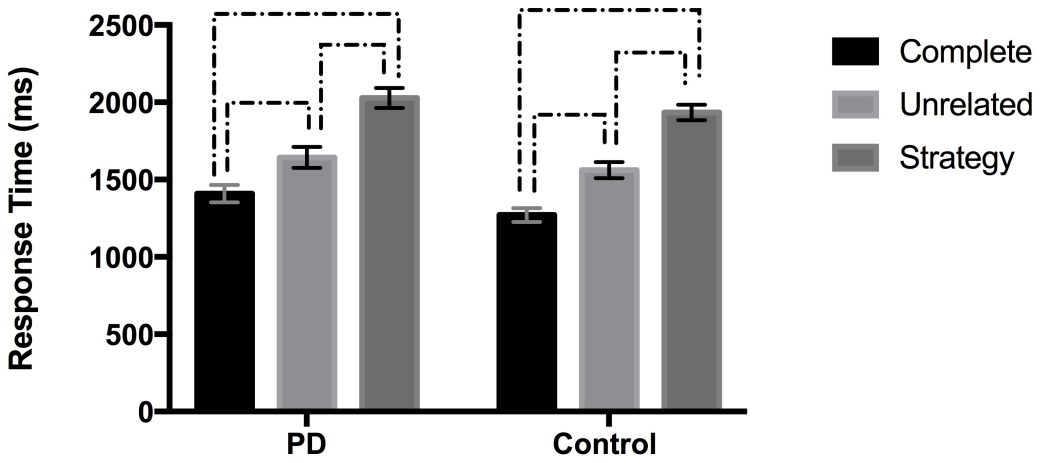

Figure 5. Mean response time (ms) for complete, unrelated, and strategy conditions by group. Brackets indicate significant differences ($p < .05$). Error bars indicate mean standard error.

4.3.1.3 Accuracy.

The mean percent correct responses per condition were generated for each participant and submitted to an LMM. Group and condition were modelled as fixed effects, and participant as a random effect. Results returned a main effect of condition, F (2, 56) = 82.64, $p < .001$. Pairwise comparisons confirmed significant differences between all three conditions, wherein complete was more accurate than unrelated ($p < .001$) and strategy ($p < .001$), and strategy was more accurate

than unrelated ($p < .001$). This pattern of performance was present independently in both PD and control groups (see Figure 6). No main effect of group or group by condition interaction was present.

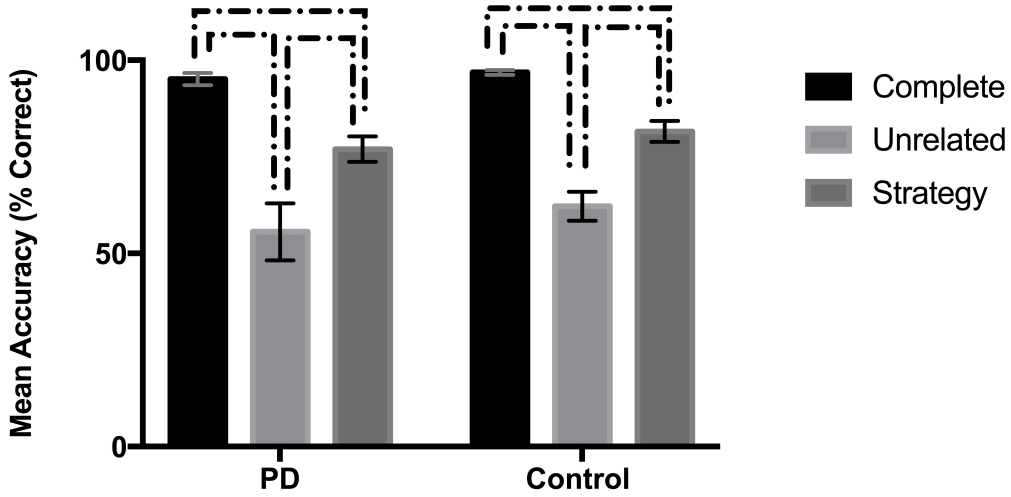

Figure 6. Mean accuracy (percentage correct responses) for complete, unrelated, and strategy conditions by group. Brackets indicate significant differences ($p < .05$). Error bars indicate mean standard error.

4.3.2 Imaging Results

4.3.2.1 Region of interest analysis.

In order to reliably compare performance across groups in the unrelated and strategy conditions, it was necessary to control for differences in the relative baseline. The complete condition was assumed to provide a baseline measure to control for speech production. Mean BOLD signal in the unrelated condition and strategy condition were therefore subtracted from the complete condition for each ROI (i.e. complete minus strategy and complete minus unrelated) and these figures submitted to a generalised linear model (GLM), repeated measures ANOVA in order to observe the effects of group and condition. Results indicated group by condition interactions in the left dlPFC (F [1, 26] = 7.417, $p = .011$, partial eta squared = .222) and left striatum (F [1, 26] = 11.125, $p = .003$, partial eta squared = .3). However, in order to interpret these findings accurately, it was necessary to ensure that the two groups did not differ significantly in their complete baseline measure. Independent t-tests demonstrated that the control and PD groups recorded equivalent baseline activations in the left dlPFC and left striatum ($p > .05$).

Significant group by condition interactions detected in the left dlPFC and the left striatum were further examined in order to define the nature of the interaction. An independent t-test revealed significant between-group differences in activation of the left dorsal striatum for both

unrelated (t [26] = -3.14, p = .004) and strategy conditions (t [26] = 3.08, p = .005). This difference was characterised by increased activation during the unrelated condition and decreased activation during the strategy condition in the control participants, while the opposite pattern (decreased during unrelated and increased during strategy) was observed in the PD group.

Independent t-tests also identified significant differences between groups in activation of the left dlPFC for both the unrelated (t [26] = -2.36, p = .026) or strategy conditions (t [26] = 2.76, p = .01). Paired t-tests examining the change in activation between unrelated and strategy conditions further revealed that only the control group significantly modulated recruitment of this region as a function of condition, t (16) =2.33, p = .033. This was characterised by a decrease in activity in the strategy condition relative to unrelated. The PD group did not record a significant change in left dlPFC activation across these conditions, t (10) = -1.74, p = .113. Significant findings in the left dlPFC and left striatum are plotted in Figure 7 and Figure 8 respectively.

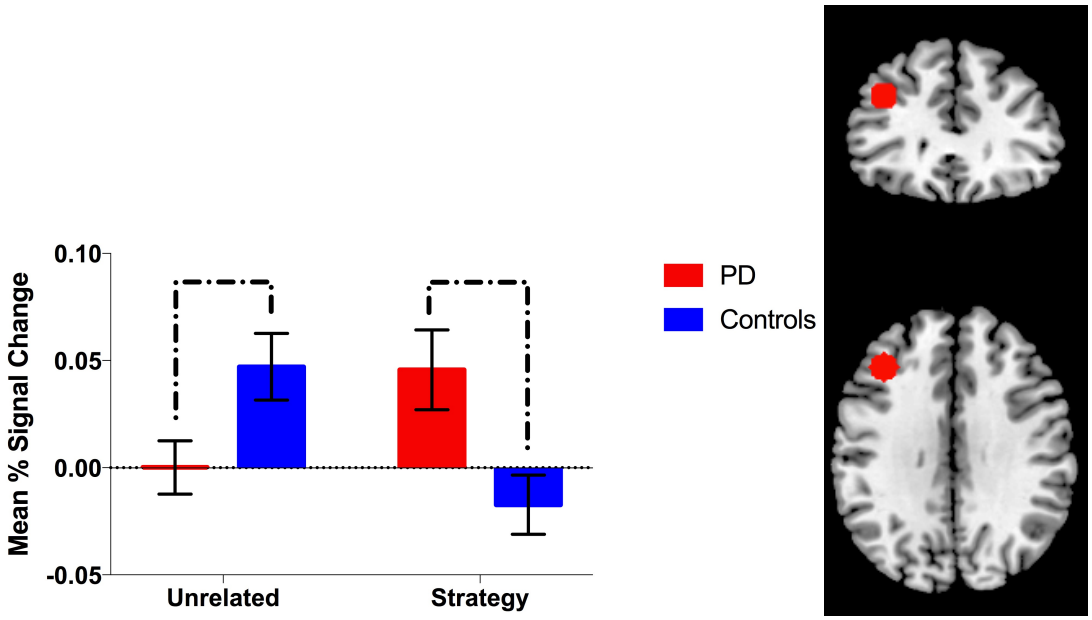

Figure 7. Region of interest analysis for the left dlPFC. Figure displays axial and coronal slices of a priori defined spherical ROI. Bar graph indicates relative mean percentage change in BOLD signal in left dlPFC as a function of condition (unrelated vs. strategy, each subtracted from the complete baseline). Brackets indicate significant between-group differences in activation ($p < .05$). Error bars indicate standard error mean.

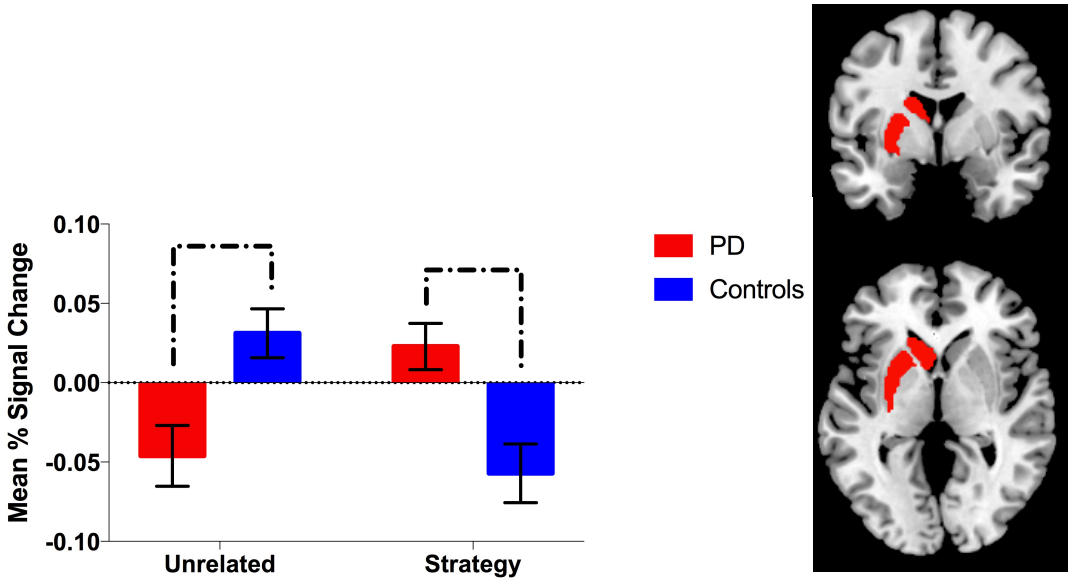

Figure 8. Region of interest analysis for the left striatum. Figure displays axial and coronal slices of a priori defined anatomical ROI. Bar graph indicates relative mean percentage change in BOLD signal in left dorsal striatum as a function of condition (unrelated vs. strategy, each subtracted from the complete baseline). Brackets indicate significant between-group differences in activation ($p < .05$). Error bars indicate standard error mean.

4.3.2.2 Whole brain analysis.

An exploratory whole brain analysis was conducted and results are reported for height threshold of $p < .001$ uncorrected and clusters family wise error (few) corrected ($p < .05$) according to SPM12 (Wellcome Trust Centre for Neuroimaging, 2014). Results were masked to the grey matter. Significant results, including coordinates of peak activations, are detailed in Table 8. Anatomical labels for peak coordinates were obtained using the Neuromorphemetrics atlas associated with SPM12. No main effects of group or condition were detected, nor was a group by condition interaction. An independent t-test identified a significant difference between PD and control groups in those neural regions that were more strongly activated during the strategy condition relative to the unrelated condition. This effect was characterised by greater activation in the right dlPFC, left dlPFC, and right caudate in the PD group during the strategy condition relative to the unrelated condition, in comparison to the control group.

Table 8

Whole-Brain Analysis: Peak Maxima of Clusters Demonstrating Significant Activity as a Function of Condition

Contrast and anatomical label of activation peak	z-score	*k*	Voxel level	MNI coordinates		
			p_{FWE}	x	y	z
Strategy > Unrelated (PD > Control)						
Right dlPFC	4.47	1812	< .001	27	39	4
Left dlPFC	4.23	1233	< .001	-26	42	9
Right Caudate	4.05	508	.028	15	36	10

Note. MNI coordinates of peak activation from whole brain analysis for clusters corrected at the voxel level ($p < .05$). FWE = family wise error. *k* = cluster size (voxels). dlPFC = dorsolateral prefrontal cortex.

4.4 Discussion

The present study aimed to determine whether the deficits observed in the HSCT, when administered to a PD population, result from disrupted verbal suppression or from difficulty in generating and implementing a strategy that can facilitate execution of the task. We further sought to identify the neural substrates recruited for these processes in PD participants relative to healthy controls. We addressed these aims using a variation on the traditional HSCT that incorporated a novel strategy condition in combination with fMRI. While behavioural performance was equivalent in the two groups, the control group showed increased left dlPFC activity and striatal activity during the unrelated condition, and showed decreased activity during the strategy condition. In contrast, the PD group showed increased left dlPFC and striatal activity in the strategy condition relative to the unrelated condition.

While behaviourally it does appear that this PD cohort are able to suppress a prepotent verbal response and generate a task-relevant unrelated alternative (presumably through the implementation of an internally generated strategy) with a degree of proficiency equal to controls, the process is seemingly subserved by an atypical neural network. The control group recruited the left striatum and the left dlPFC to support execution of the unrelated condition. This finding is in line with our hypothesis and previous studies of the HSCT and its analogues in healthy younger adults (Collette et al., 2001; de Zubicaray et al., 2000; Nathaniel-James et al., 1997). Both the dlPFC and the striatum participate in the frontostriatal cognitive loop known to subserve cognitive control processes such as inhibition, working memory, strategy, and attention (for reviews see Hanganu, Provost, & Monchi, 2015; de la Fuente-Fernandez, 2012; Zgaljardic et al., 2006), all of which are

presumably at play during the unrelated component of the HSCT. However, minimal left dlPFC and striatal activity was observed in the PD group during this condition, and the magnitude of this activity differed significantly between groups. The whole brain analyses conducted did not reveal any additional neural recruitment in the PD group during the unrelated condition, and the a priori ROIs also did not appear to participate in this alternative network. It is possible that increased functional connectivity may have compensated for decreased activity in critical frontostriatal structures, as has been observed in previous studies of PD populations (Gorges et al., 2015; Yang et al., 2016), however testing of this hypothesis was beyond the scope of the present study. Thus, further investigation is required to determine how the PD group were able to maintain their behavioural performance during the unrelated condition, in the face of decreased frontostriatal network activity.

In contrast to the unrelated condition, the PD group appeared to rely heavily on the increased recruitment of bilateral striatum and bilateral dlPFC to maintain performance in the strategy condition. This pattern of activity is in contrast to that observed in the control group, who showed significantly decreased activity within these regions, and demonstrated significantly less recruitment of the right hemisphere. The additional neural activity observed in the PD group to maintain behavioural performance in the strategy condition may be explained by closer examination of the cognitive demands associated with the strategy task. Given that similar activity was not observed during the unrelated task, and verbal suppression was expected to be critical to both conditions, it may be assumed that this function was not responsible for the observed increase in activity. In the strategy condition, participants were required to generate members of a given semantic category under strict time constraints, and were asked not to repeat any of their responses. As each category appeared five times throughout the task, it can be assumed that this placed significant demands upon working memory resources, lexical access, and retrieval. In this way, the strategy condition bears close resemblance to a semantic fluency task. Patients with PD consistently demonstrate difficulty in performing these tasks (for meta-analysis see Henry & Crawford, 2004). The PD group in the present study performed at a level commensurate with controls on a measure of semantic fluency. However, given the similarity of this task to the strategy task, this was not unexpected and may strengthen the hypothesis that both are subserved by the same atypical neural network.

Verbal fluency tasks are traditionally complex to analyse, due to the large number of cognitive skills at play during their execution. However, a study conducted by Shao et al. (2014) sought to unpack the semantic fluency task in healthy adults by examining how performance may be predicted by a number of isolated cognitive skills (lexical access speed, vocabulary size, working memory capacity). Their results demonstrated that mean score in a semantic fluency task was better

predicted by the ability to store and update relevant information in working memory, than by lexical access speed or vocabulary size. Interestingly, the PD group in the present study performed at a level commensurate with controls in the Boston Naming Test (a picture-naming assessment; Kaplan, Goodglass, & Weintraub, 2000) and this may broadly suggest that vocabulary and lexical access are relatively intact in this cohort, lending support to the possibility of underlying problems with working memory. This hypothesis is in line with current theories concerning the basal ganglia's secondary role in language processing, as a downstream effect of its involvement in cognitive control functions (Crosson et al., 2003; Frank, 2006).

The possibility of hyperactivation during the strategy condition to support working memory is corroborated by the assumed functions subserved by the regions in question. In the PD group these were the left striatum (putamen and caudate), right caudate, and the left and right dlPFC. The dlPFC and the dorsal caudate nucleus (a component of the striatum) participate in the frontostriatal cognitive loops subserving executive functions (Cole & Schneider, 2007; D'Esposito, 2007; Grahn, Parkinson, & Owen, 2009; Macdonald, Cohen, Andrew Stenger, & Carter, 2000; for meta-analysis see Niendam et al., 2012). Frontostriatal circuitry dysfunction appears responsible for a number of the cognitive deficits associated with PD (for reviews see Owens, 2004; Zgaljardic et al., 2006). More specifically, there exists a growing body of evidence demonstrating a relationship between striatal dopamine uptake, PFC activation, and working memory performance (Gazzaley, Rissman, & D'Esposito, 2004; Landau, Lal, O'Neil, Baker, & Jagust, 2009; Lewis, Dove, Robbins, Barker, & Owen, 2004). Indeed, Frank, Loughry, and O'Reilly (2001) have developed a computational neural network model of working memory based on interactions between the basal ganglia and the frontal cortex. In this model, the selective firing of neurons in the striatum operates as a dynamic gating mechanism, enabling memory representations maintained in the frontal cortex to be rapidly updated according to task-relevant goals. In the PD population, several studies have linked disruptions to working memory capacity, and more specifically the maintenance or manipulation of information in working memory, to reduced striatal uptake of dopamine (Holthoff-Detto et al., 1997; Rinne et al., 2000; van Beilen et al., 2008), and reduced activity in larger-scale frontostriatal networks (Gabrieli, Singh, Stebbins, & Goetz, 1996; Lewis et al., 2003; Owen, 2004). Moustafa, Sherman, and Frank (2008) conducted a study in which medicated and unmedicated PD participants completed several variants of a task that allowed for observation of learning vs. updating vs. attentional aspects of working memory function. Their results showed that medicated participants demonstrated excessive updating of working memory. The authors concluded that this reflected enhanced signalling along relevant pathways as a result of increased striatal dopamine. In the present study it may therefore be inferred that in the strategy condition, the PD group were required to exert increased recruitment of the striatum in order to drive frequent updating of task-relevant

working memory representations. It must, however, be noted that subsequent to Moustafa et al.'s (2008) study, Cools and D'Esposito (2011) demonstrated that the relationship between dopamine and performance is non-linear – following an inverted U-shaped curve. As a result, it must be acknowledged that increased dopamine uptake can also be associated with reduced signalling, and interpretations of the relationship between dopamine and performance based on behavioural observation must therefore be considered with some degree of speculation.

It must be noted that at this point that the present conclusions regarding compensation are largely speculative, and it is acknowledged that labelling atypical activity in clinical populations as evidence of compensation vs. inefficient processing can be difficult to justify. However, while the present study appears to be the first to tentatively identify such compensation during a verbal selection/suppression paradigm, support for the notion may be gained from previous studies that have identified similar patterns of compensation during other cognitively demanding tasks. Tinaz et al. (2008) used fMRI to examine the functional integrity of frontostriatal circuits in non-demented PD participants during a semantic sequencing task. Though this task differs significantly in nature to the HSCT, it is still considered to tap an executive function skill (sequencing) and thus typically recruits cognitive control regions in young healthy controls (Tinaz et al., 2008). While the overall network of brain regions recruited for the task were similar between the PD and control groups, the PD group showed hypoactivation of task-relevant frontal areas, and hyperactivation in both task-relevant and novel regions (Tinaz et al., 2008). Functional connectivity analyses also revealed that the PD group demonstrated stronger correlations in frontostriatal circuits in the right hemisphere, relative to the left hemisphere networks typically recruited by the task. Critically however, this abnormal brain activity was associated with little to no difference in behavioural performance between the groups, in terms of both response time and accuracy. Similarly to the present study, the PD group in the Tinaz et al. (2008) study demonstrated hyperactivity in the left MFG (dlPFC) relative to the control group. This region is considered relevant to the task, and is thought to be involved in the maintenance of information held in working memory. The relative hyperactivation observed in the PD group in this region was therefore considered to reflect compensatory activity that allowed these participants to maintain their behavioural performance. A similar conclusion may be drawn regarding the present study. Presumably the strategy condition places additional demands upon working memory due to the need to recall which category members have already been provided as a response. In the control group, these working memory demands were manageable, however perhaps due to the decreased availability of attentional resources thought to be associated with PD (Dirnberger & Jahanshahi, 2013), this group were required to increase activity in relevant regions in order to maintain performance.

Tinaz et al. (2008) also detected increased activity in the head of the left caudate in the PD

group, where it was not active in the control group, however this was suggested to reflect inefficient processing or ongoing diseases processes rather than compensation. In the present study, increased activity was observed in the left dorsal striatum in parallel with increased recruitment of the left dlPFC, which may in this case reflect compensatory up regulation of working memory related networks.

Tinaz et al. (2008) additionally found greater recruitment of a right hemisphere network in the PD group, relative to both age-matched and younger healthy controls. The authors attributed the activity to additional compensatory mechanisms in right frontostriatal networks. This is line with previous findings of greater recruitment of the contralateral hemisphere both in PD participants during tasks that are hemispherically lateralised in control groups (Carbon & Marié, 2003) and more generally as a mechanism of compensation in healthy ageing (Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013; Cabeza, 2002; Reuter-Lorenz & Cappell, 2008). The present study found significantly increased recruitment of the right dlPFC and caudate in the PD group relative to controls during the demand-heavy strategy condition. Furthermore, the study controlled for handedness and all other conditions revealed activity that was largely focused in left hemisphere networks, which may further support the suggestion that the right-hemisphere activity in this PD group was compensatory in nature.

Recently, Poston et al. (2016) sought to further qualify current hypotheses regarding preservation of cognitive function in early stage PD populations and associated changes in neural activity. Their fMRI paradigm involved performance of a modified Sternberg task, designed to assess working memory capacity. Results demonstrated that in terms of response time and accuracy, the PD group performed at a level commensurate with the control group. However, this occurred in the face of altered underlying neural recruitment in the PD group, characterised by hyperactivation in the putamen and greater load-dependent activation in the left dlPFC. Poston et al. concluded that this hyperactivity represented a robust striatal mechanism active in cognitively unimpaired PD participants that compensated for the loss of nigrostriatal dopamine. Despite the differences in the task assessed, these findings corroborate those of Tinaz et al. (2008), and those of the present study. Similarly, in their fMRI studies of set-switching, Gerrits et al. (2015) identified equivalent performance in PD and control groups, mediated in the PD group by increased activity in task-relevant frontal regions.

Taken together, it would appear that for those processes that necessarily recruit frontostriatal networks, cognitively intact PD participants are able to maintain behavioural performance through the increased recruitment of regions both intrinsic to the task at-hand, and in some cases, in novel regions beyond this network. The regions demonstrating this enhanced activity appear to be dictated by the demands of the given task, however components of the frontostriatal network appear to be

frequently involved in this compensatory network. In the studies analysed here, this may due to the common factor of increased working memory demands, particularly the maintenance of items in working memory, and the dependence of this activity upon nigrostriatal pathways known to be compromised by the pathology of PD. It may be that as nigrostriatal loss progresses, the system is no longer able to compensate sufficiently, and this coincides with the onset of cognitive impairment.

A potential limitation of the present study's design concerns the processing demands associated with each condition of the task. Though the experimental paradigm was designed with the intent of minimizing variations in task demands across conditions (other than response requirements), it must be acknowledged that some inconsistency may be introduced in terms of how response generation was impacted by the preceding sentence stem. It is possible that in the strategy condition, the preceding sentence stem was more readily disregarded during response formulation due to the availability of the category cue. However, as this category cue was only provided *after* presentation of the high cloze probability sentence stem, it may be assumed that the influence of this potential confound was considerably limited.

A number of inconsistencies were noted between the present results and the results of previous studies of the HSCT in PD and healthy populations. The finding of no overall behavioural difference in the PD group relative to the control group is not consistent with previous reports (see section 4.1), where PD participants have recorded slower response times and/or greater number of errors on the suppression component of this task (Bouquet et al., 2003; Castner et al., 2007b; Obeso et al., 2011a). However, it must be noted that several of the studies that found impaired performance in PD recruited participants with greater disease severity and lengthier disease duration relative to our cohort of mild-moderately affected participants. These differences in clinical characteristics may explain the discrepancies present in performance, given the well-established heterogeneity of PD, particularly in terms of the rate of dopaminergic depletion and degree of cognitive impairment (for reviews see de la Fuente-Fernandez, 2012; Monchi et al., 2016; Owen, 2004).

It is also noted that the present investigation was unable to account for the possibility of altered neural recruitment in both the PD and control groups as a result of typical age-related compensatory mechanisms (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008). Though the regions recruited by the control group do reflect those reported in studies of healthy younger adults (as discussed above), the inclusion of such a comparison group in future investigations could allow for greater rigour in labelling activity patterns as typical or atypical.

Importantly**,** the present study does provide evidence to suggest that provision of a strategy improves the accuracy of performance on the HSCT verbal suppression component, in both the

control and PD groups. Assuming that completion of the strategy condition required the suppression of the prepotent response, it may be inferred that it is therefore the process of strategy generation and implementation that accounts for the increased error rate observed in both groups in the unrelated condition. This represents a novel finding, as performance on this task was previously attributed solely to difficulty suppressing a prepotent verbal response (Belleville, Rouleau, & Van der Linden, 2006; Burgess & Shallice, 1996; Chan, Shum, Toulopoulou, & Chen, 2008).

4.5 Conclusions

In conclusion, the present study demonstrated that this cohort of mild-moderate PD participants were able to maintain behavioural performance that was commensurate with controls in our novel variation of the HSCT. However, this performance was achieved in the PD group through the recruitment of compensatory mechanisms that were assumed to bolster working memory function in task-relevant, left hemisphere frontostriatal circuits, and their right hemisphere analogues. In addition, the novel variation on the HSCT employed here determined that the capacity to develop and implement a strategy that supports task execution is a critical component of the suppression task in the HSCT and should therefore be considered when this paradigm in utilised in future investigations.

5 Chapter Five

Investigating the Influence of Contextual Constraint on Verbal Selection Mechanisms and its Neural Correlates in Parkinson's Disease

Chapter 4 examined the nature of verbal suppression and its integrity in PD. The study adopted a novel variation of the HSCT that incorporated a condition designed to isolate strategy generation from the ability to suppress a prepotent response. Behavioural results demonstrated no significant difference in response time or accuracy between groups. Imaging results however, demonstrated that in the PD group, this performance was subserved by atypical neural activity. The control group exhibited an increase in activation in the left dlPFC and left striatum during the unrelated condition, which subsequently decreased in the strategy condition. However, the PD group demonstrated the opposite pattern, with a significant increase in activity in these structures, as well as their right hemisphere analogues, during the strategy condition relative to the unrelated condition. These results were interpreted as suggesting that the strategy condition was considerably harder for the PD participants to execute, possibly due to additional working memory demands. Increased activation of the bilateral dlPFC and striatum was thus postulated to be evidence of compensatory mechanisms, acting to bolster the output of frontostriatal circuits compromised by disease pathology.

Individuals with PD were also observed to perform at a level commensurate with controls during the complete condition of this task (a measure of verbal selection). Desimone and Duncan (1995) have described selection and suppression to be two sides of the same coin. Indeed, both processes have been suggested to recruit regions of the PFC (Badre et al., 2005; Miller & Cohen, 2001), and a small number of studies have described deficits in this process in PD cohorts when selection must occur among a greater number of competing alternatives. However, these studies have largely focused on single-word processing paradigms, such as verb generation. As stated, the HSCT does utilise sentence stems, however traditionally these are designed to carry high contextual constraint, thus inducing low selection demands. The study in Chapter 5 therefore aimed to determine the influence of variable contextual constraint on the selection of a verbal response in PD. This was achieved using an adaption of the HSCT, whereby participants were required to provide a single word to complete a sentence stem with systematically graded selection demands.

5.1 Introduction

Individuals with PD demonstrate impairment across a large catalogue of language tasks including verbal fluency (Auriacombe et al., 1993; Herrera et al., 2012; Piatt et al., 1999; Tröster et al., 1998; for review see Henry & Crawford, 2004), semantic priming (Angwin et al., 2009; Arnott et al., 2001; Copland, 2003; Filoteo et al., 2003; Murdoch et al., 2000), and higher-level language processing (for review see Altmann & Troche, 2011). However, several decades of research in this field have yet to precisely characterise the changes in neurological function or structure that give rise to these deficits.

The primary pathology of PD is the depletion of dopaminergic projections within the substantia nigra, a nucleus of the basal ganglia (Bartels & Leenders, 2009; Kish, Shannak, & Hornykiewicz, 1988). Current understanding holds that while the basal ganglia do not appear to play a primary role in core language functions, these nuclei support language processing via secondary mechanisms (Crosson et al., 2007). In the PD population, this supporting role appears to manifest when the task at hand demands some degree of cognitive control. That is, when a response is required that is not routine or automatic in nature. In the context of spoken language production, cognitive control is thought to be involved in processes of controlled verbal selection; the production of an appropriate response (single word) in the face of increased competition from multiple task-appropriate alternatives or from strongly prepotent but task-irrelevant responses.

The proposal that the basal ganglia participate in the cognitive control of language production is supported by the anatomical properties of this region. Cognitive control is thought to be subserved by the PFC (Braver, Paxton, Locke, Barch, & Smith, 2009; Koechlin, Ody, & Kouneiher, 2003; Macdonald et al., 2000; Miller & Cohen, 2001; Miller, 2000; Norman & Shallice, 1986; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) and this structure has been shown to share reciprocal connections with the basal ganglia (Alexander et al., 1986; Middleton & Strick, 2000). These basal-ganglia-thalamo-cortical loops (or frontostriatal pathways) facilitate communication between regions of the frontal cortex and the basal ganglia, and each subserves a particular behavioural realm. Those loops subserving motor functions have been well studied, and it is widely agreed that their role involves the selection of motor plans for execution from amongst competing alternatives (Jueptner & Weiller, 1998; Mink, 1996; Nambu, 2004; Seiss & Praamstra, 2004). Architectural similarities between these motor loops and their parallel cognitive loops suggest some degree of functional similarity across these behavioural domains, and it has been proposed that they too are involved in selection of cognitive "actions" (Frank, 2006; Redgrave et al., 1999).

Importantly, it has been demonstrated that a number of these frontostriatal pathways terminate in those regions of the PFC thought to participate specifically in verbal selection. Namely,

the ventrolateral prefrontal cortex (vlPFC; Di Martino et al., 2008; Leh et al., 2007; Ullman, 2006). Of note, the anatomical boundaries of the region referred to as the vlPFC are inconsistent across studies, with arbitrary inclusion of Brodmann Areas (BA) 44, 45, and 47. In the following review, included regions will be annotated in parentheses.

The vlPFC has been consistently implicated in semantic retrieval and selection (Poldrack et al., 1999; Thompson-Schill, Amp, Apos, Esposito, & Kan, 1999; Thompson-Schill, D'esposito, Aguirre, & Farah, 1997; Wagner, Maril, Bjork, & Schacter, 2001), and activation of the vlPFC has often been observed in verb generation tasks or paradigms involving words with multiple possible alternatives (Nagel et al., 2008; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Persson et al., 2004). Furthermore, activation of the region increases when subjects are asked to name pictures with lower naming agreement, or generate items from larger categories (Kan & Thompson-Schill, 2004; Tremblay & Gracco, 2006).

Badre et al. (2005) proposed a two-pronged model of the vlPFC's participation in semantic processes. According to this account, the anterior vlPFC (BA 45) meditates controlled semantic retrieval. This mechanism allows for controlled retrieval of semantic knowledge when the cues made available by stimuli are insufficient to drive bottom-up activation. In contrast, the mid vlPFC (BA47) is involved in a domain-general selection mechanism referred to as post-retrieval selection. That is, when a single response must be selected from among several task-relevant representations, each of which was activated in response to the stimulus. Badre et al.'s (2005) account has been widely cited in subsequent literature exploring dissociable mechanisms of controlled retrieval and post-retrieval selection, though some authors have since provided evidence of their being subserved by overlapping or shared regions of the vlPFC (Snyder et al., 2011; Souza, Donohue, & Bunge, 2009).

Indirect evidence for the contribution of the subcortex to verbal selection via its connections with the PFC can be inferred from studies of language production and processing in both healthy populations and in PD. In healthy controls, caudate activity has been identified in studies of word generation (Crosson et al., 2003) and ambiguity resolution (Ketteler et al., 2008), both of which are tasks that inherently involve selection among multiple alternatives. In turn, individuals with PD have demonstrated decreased performance on measures of ambiguity resolution (Copland et al., 2009; Ketteler et al., 2014), verbal fluency (for review see Henry & Crawford, 2004), and verb generation (Boulenger et al., 2008; Colman et al., 2009; Cotelli et al., 2007; Peran et al., 2003; Rodríguez-Ferreiro et al., 2009).

Verb generation is thought to necessitate the recruitment of additional attention and executive resources, due to the increased number of competing alternatives associated with verbs relative to nouns (Silveri et al., 2012). Crescentini et al. (2008) investigated performance on a verb

generation task (generating a verb from a given noun) and a noun generation task (generating a noun from a given noun) in non-demented PD participants and healthy controls. Selection demand (number of alternatives) and stimulus-response association strength (providing a measure of retrieval demands) were manipulated differentially across three conditions. The PD group demonstrated impaired verb production relative to controls as a function of both controlled semantic retrieval demands and post-retrieval selection demands. An effect of association was also detected in noun generation for this group, wherein PD participants responded less accurately when stimulus-response association was weak. The authors suggested that these findings demonstrated a role for the basal ganglia in mediating the processes of controlled semantic retrieval and selection among competing alternatives. It must, however, be noted that an alternative hypothesis suggests the verb generation impairment in PD can be explained via the theory of semantic embodiment. Semantic embodiment theory posits that there is no separation between higher-level cognitive processes such as language and lower-level processes such as action (Jirak, Menz, Buccino, Borghi, & Binkofski, 2010). In the language realm, this suggests that the lexical activation of a word with a strong motor component (i.e. action verbs) will also result in activation of the sensorimotor area subserving the associated action (Kemmerer & Gonzalex-Castillo, 2010). As such, it has been proposed that participants with PD have difficulty generating verbs as a product of the motor impairments that are characteristic of the disease (Boulenger et al., 2008; Cardona et al., 2013; Ibáñez et al., 2013; Peran et al., 2009). While the merits of this account are acknowledged it is noted that for the purposes of the present investigation, analysis and appraisal will focus primarily on the selection deficit account. This is in line with the psycholinguistic theme of the thesis (concerning the lexical-semantic processes of verbal selection and suppression), and is most appropriate given the nature of the data collected (e.g., the methodology of the present study is not explicitly addressing verb generation or relationship to activity in the motor cortex). As such, the selection deficit will serve as the preferred framework for interpretation of data.

Importantly, many of the studies described above have only considered selection mechanisms when generating verbs from single words (either a noun or a verb). However, as Crescentini et al. (2008) demonstrated, noun generation was also impaired in PD when association between response and stimulus was low, regardless of selection demands. It could therefore be suggested that any stimulus that carries low association with its expected response may place greater demands upon controlled retrieval mechanisms. This notion has been largely unexplored in the PD population to date. Furthermore, if the verb generation deficit observed in PD does reflect a deficit in controlled semantic retrieval and post retrieval selection as a result of disrupted frontostriatal signalling, it could be suggested that any condition that places sufficient demands upon these mechanisms will likewise be affected.

In healthy controls, activation of the caudate has been detected in studies of verbal selection that utilise contextually loaded sentences in order to bias meaning selection. For example, Argyropoulos et al. (2013) developed an overt sentence production task that demonstrated strong activation of the caudate in a sentence generation component of the task, in contrast with no activation during sentence repetition, which was interpreted as evidence of the caudate's role in semantic aspects of response selection. Similarly, in studies of word learning in healthy adults, the caudate has been observed to activate in association with the left vlPFC (BA 44 and 45) when new meaning must be derived from sentence context (Mestres-Missé, Camara, Rodriguez-Fornells, Rotte, & Munte, 2008). This is of interest when considering the mechanics of selection, as the selection or retrieval demands imparted by a sentence may not be attributed solely to the characteristic of one word contained within. Rather, they may be derived from the unique interaction of lexical-semantic units at the phrase and clausal level. Furthermore, the word that must be produced may belong to a word class other than verbs, such as nouns, adjectives or adverbs.

Limited studies have explored verbal selection performance in PD beyond the level of single word processing. A small number of authors have administered The Hayling Sentence Completion Task (HSCT; Burgess & Shallice, 1996) to this cohort (Bouquet et al., 2003; O'Callaghan et al., 2013a; O'Callaghan et al., 2013b; Obeso et al., 2011a). The HSCT involves presentation of sentence stems with the final word removed, and participants are asked to either provide a word that completes the sentence correctly (Part A, considered to measure verbal selection) or provide a word that is unrelated to the sentence (Part B, considered to measure verbal suppression). These studies have generally reported minimal differences in performance on Part A between PD and control groups. However, it is noted that the HSCT traditionally involves only sentence stems with a high level of contextual constraint. Contextual constraint refers to the probability that a given word will be provided as the response to complete the stem when the final word of the sentence has been removed. A sentence with high contextual constraint has an extremely limited number of appropriate alternatives, whereas a low contextual constraint sentence has several. It is assumed that sentences with low contextual constraint may carry both greater selection demands (i.e. a larger umber of words that may appropriately complete the sentence) and controlled retrieval demands (insufficient information to support bottom-up activation of a semantic concept), and therefore require increased input from cognitive control facilities. The capacity of individuals with PD to generate an appropriate response for a sentence with low contextual constraint is yet to be explored.

Such a paradigm however has been administered in healthy adults. Nathaniel-James and Frith (2002) designed a novel variation on the HSCT that manipulated contextual constraint. These authors classified stimuli as either high, medium, or low constraint, and observed the effect of this factor across both selection and suppression components of the task. PET was also utilised in order

to observe associated changes in neural activity. Activation of the left dorsolateral prefrontal cortex (dlPFC) was significantly increased during the suppression component when compared to selection for all levels of constraint, and in fact recruitment increased with increasing contextual constraint. Most intriguingly, the dlPFC was also recruited during the low cloze probability condition of the selection component. In contrast, the initiation component was associated with increased activation in the medial orbital frontal cortex, a region contained within the ventromedial PFC. Based on these results, Nathaniel-James and Frith (2002) concluded that the dlPFC was involved in 'sculpting the response space': that is, generating a set of possible responses from which an alternative can be selected. This description of the dlPFC's role appears to overlap significantly with the aforementioned accounts of the vlPFC's role in controlled retrieval and post-retrieval selection (Badre et al., 2005). Such disagreement or lack of clarity surrounding the putative roles of the dlPFC and vlPFC has been present in the literature for some time and the debate is ongoing (Kerns, Cohen, Stenger, & Carter, 2004b; Nagel et al., 2008; Wagner et al., 2001). Nathaniel-James and Frith (2002) didn't report activation of subcortical nuclei, however it is noted that their study only included six participants, and thus may not have possessed sufficient sensitivity to detect activity in these smaller anatomical regions.

The present study sought to clarify the involvement of frontostriatal circuitry in verbal selection beyond the limitations of a single-word based verb generation task. The task drew upon the design elements of Nathaniel-James and Frith's (2002) sentence completion study combined with fMRI in order to observe the influence of contextual constraint on verbal selection in PD and identify underlying substrates. Results will be considered in the context of current literature, including cortico-subcortical facilitation of cognitive control, Badre et al.'s (2005) two-pronged model of vlPFC function, and the dissociable input of dlPFC vs. vlPFC. Based on converging evidence from studies of word production in PD (see above), it is hypothesised that the PD group will experience greater difficulty selecting items when selection demands are high (i.e. cloze sentences with low contextual constraint) and this will correlate with decreased activity in frontostriatal networks encompassing the subcortex and vlPFC (defined as BA 45 and 47).

5.2 Methods

5.2.1 Participants

Fourteen individuals with diagnosed idiopathic PD were recruited to participate in the study (9 female). All participants in the PD group were required to meet the following inclusion criteria: (1) confirmed diagnosis of idiopathic PD according to the Calne et al. (1992) criteria; (2) right-handed, confirmed with the Annett Hand Preference Questionnaire (Annett, 1970); (3) English as a first language; (4) Hoehn and Yahr (1967/2001) rating of 1-3. Potential applicants were excluded if: (1) they reported a history of substance and/or alcohol abuse, head trauma, stereotaxic surgery

and/or neurological disease other than PD; (2) they achieved a score on the Montreal Cognitive Assessment (MoCA v7.1/7.2, Nasreddine et al., 2005) that was > 1 *SD* below the expected range for their age group and level of education (Rossetti et al., 2011); (3) they presented with moderate-severe dysarthria (in order to minimise variation in response transcription due to poor intelligibility of speech); or (4) they reported an uncorrected hearing or visual impairment that could affect the validity of task performance. Finally, the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was administered to screen for untreated clinical depression. A score greater than 8 was considered indicative of major clinical depression and participants scoring in this range were excluded (Dissanayaka et al., 2011; Dissanayaka et al., 2007). Total years of education (YOE) was calculated for each participant and included years spent in primary, secondary, bachelor, post-graduate, and diploma or certificate studies. Levodopa equivalent daily dosage (LEDD) was calculated for each patient based on the procedures outlined by Tomlinson et al. (2010). One participant was not taking medicinal treatment at the time of testing. Demographic and neurological data for PD participants was collected via self-completed questionnaires and is presented in Table 9.

Table 9

Characteristics of Participants with PD

Participant	Age[a]	Gender	YOE	Disease Duration[a]	H&Y	LEDD	MoCA	GDS
1	57	M	12	8	2	1787.5	30	5[b]
2	49	F	11	2	1	600	24	1
3	62	F	12	8	2	348	28	9[b]
4	56	F	20	3	1	512.5	29	0[b]
5	69	M	17	6	1	349.5	27	0
6	59	F	14	4	1	450	28	1
7	73	M	17	4	2	400	25	5[b]
8	71	F	12	2	2	400	24	1
9	66	F	18	2	1	280	28	0
10[+]	56	M	12	6	2	325	22	1
11	66	F	10	1	2	400	25	0[b]
12	62	F	15	3	2	100	22	3
13	60	M	16	0.5	2	400	27	1
14[+]	63	F	11	3	3	0	26	6
M	**62.14**	NA	**14.07**	**3.75**	**1.6**	**322.72**	**26**	**1.85**
SD	*6.6*		*3.1*	*2.41*	*0.51*	*214.13*	*2.7*	*2.13*

Note. YOE = Years of Education; LEDD = Levodopa Equivalent Daily Dosage (mg/day); HY = Hoehn & Yahr rating. MoCA = Montreal Cognitive Assessment. GDS = Geriatric Depression Scale; M = male; F = female.
[+]Participant subsequently excluded prior to data analysis.
[a]Age and Disease duration are reported in years.
[b]Participant was taking anti-depressant medication at time of testing.

Fifteen neurologically healthy individuals were recruited to serve as a control group (9 females, mean age = 67.7 [5.84], mean YOE = 15.5 [3.9]). Independent t-tests initially confirmed that this group did not differ significantly from the PD participants in terms of gender ($x^2 = 1.0$), or years of education (p = .3), however the mean age of the PD group was significantly older than that of the control group (p = .022). This difference was later eliminated as a result of outlier exclusion during data analysis and was therefore of no further concern. Controls were required to: (1) be right-handed (Annett, 1970); (2) have English as their first language; (3) have no self-reported history of alcohol and/or substance abuse; (4) have no significant neurological disease or history of trauma /surgery; and (5) have normal or corrected-to-normal vision and hearing. Controls were excluded if they achieved a score on the MoCA (v7.1/7.2; Nasreddine et al., 2005) that was > 1 *SD*

below the expected range for their age group (Rossetti et al., 2011). The mean total MoCA score for the control group was 26.5 [1.8].

Participants in both groups completed a battery of neurocognitive and linguistic assessments, comprising the Boston Naming Test 2nd Edition (BNT; Kaplan et al., 2001), selected subtests of the Test of Everyday Attention (TEA; Robertson et al., 1994) including Elevator Counting and Elevator Counting with Distraction, the National Adult Reading Test (NART; Nelson & Willison, 1991), digits forwards and backwards, and verbal fluency (phonemic, semantic, and cued). The study was approved by the Human Research Ethics Committee of the University of Queensland and was therefore in accordance with the ethical standards laid down in the 2007 NHMRC National Statement on Ethical Conduct in Human Research. Participants provided informed written consent and were financially compensated for their participation in the study.

5.2.2 Experimental Design and Stimuli

The study employed a variation on the HSCT (Burgess & Shallice, 1996), similar to that described by Nathaniel-James and Frith (2002), and required participants to provide a single word that correctly completed a given sentence stem. The cloze-probability of the sentence stem was systematically manipulated, in order to allow for observation of verbal response selection as a function of contextual constraint. Sentence stems (120 in total), 6-8 words in length *(M* = 7.2 [0.8]) were selected from a database of 400 sentence completion norms (Block & Baldwin, 2010). This database comprises 400 high cloze probability sentences that expand upon the norms compiled by Bloom and Fischler (1980) and were standardised against an undergraduate student population. N-Watch software (Davis, 2005) was employed to determine the CELEX spoken word frequency of the most probable response for each sentence stem.

Three conditions were constructed based on the level of contextual constraint associated with sentences. Constraint is here defined as the close probability of a particular word being provided to complete a sentence stem. This was calculated based on the frequency with which responses were given in a sampled cohort and may be viewed as relating to the number of competing alternatives that could plausibly complete the sentence accurately. A sentence stem that activates a limited number of possible responses would be described as possessing a high level of constraint (e.g., He loosened the tie around his…"neck"). In contrast, a sentence stem that could be completed by a large number of words would be considered to generate low level constraint (e.g., The boy asked his teacher for extra… "credit" or "help" or "work" or "marks"). Each condition consisted of 30 sentence stems with either (a) high close probability (0.9 or above); (b) medium constraint (0.5 - 0.89); or (c) low constraint (0.49 or less). A baseline condition (read) was also employed in order to control for neural activation related to orthographic and syntactic processing, and motor execution. In this condition, the final word of the sentence was provided, and participants

were required to read this single word aloud. The cloze probabilities of stimuli in the baseline condition were all of a medium constraint level (0.5 - 0.89). Each condition contained 30 trials, which differed in their cloze probability, but did not significantly differ with respect to sentence stem length ($p = .357$), or spoken word frequency of the most probable response ($p = .808$).

The experiment was completed across two runs, each containing 60 trials, with a short break in between. Six pseudorandomisations were created in order to control for trial order effects across these blocks. Baseline read trials were presented in blocks of five, followed by five consecutive complete trials in an A – B – A –B design. Condition (low, medium, high) was varied within the complete blocks.

5.2.3 Procedure

In order to ensure adequate understating of the task requirements, ten practice trials (five read and five complete) were administered prior to testing. Corrective feedback was given as required during practice trials only, in line with the instructions provided in the original HSCT manual (see Burgess & Shallice, 1996).

Behavioural testing was conducted in-scanner. The experiment was created using Cogent 2000 software (Wellcome Department of Imaging Neuroscience, 2013) operating via a Matlab R2011b platform (MathWorks, 2011) with a screen resolution of 1024 x 768, Arial font in size 50. This display was projected onto a large screen visible to the participants via a mirror positioned on the roof of the scanner. Participants were equipped with an MRI-safe microphone to capture overt verbal responses.

Each trial began with a fixation cross which appeared for 250 ms. Sentence stems were then presented visually, one word at a time (500 ms between each word). Once presented, each word remained on screen, such that the sentence stem became visible in its entirety. The final word of the sentence was replaced with a blank line "_____", and a written instruction simultaneously appeared below that informed participants of the nature of the required response (i.e. "read" or "complete"). The entire sentence stems and instruction remained on screen for 5000 ms before automatically progressing to the next trial. During this time, participants were required to overtly provide a single word that completed the preceding sentence stem as accurately as possible (complete condition), or read the final word of the sentence (read baseline condition). Verbal responses were only recorded if they were produced during this 5000 ms temporal window.

5.2.4 Image Acquisition

Images were acquired across two runs using a Siemens Trio (3T; Siemens AG, Germany) with a gradient echo EPI sequence (echo time [TE] = 36 ms, repetition time [TR] = 2500 ms, field of view [FOV] = 210 x 210 mm, flip angle 80, in-plane resolution of 3.6 x 3.6 mm, and 36 slices x 3 mm, with a 0.6 mm gap). During each run, 232 image volumes were acquired. Three-dimensional

T1-weighteed images were also acquired using a magnetization-prepared rapid acquisition with gradient echo sequence (TE = 2.99 ms, TR = 2200 ms, TI = 900 ms, FOV = 256 x 256 x 192 mm, 192 phase encodings in the slice direction, isotropic voxel size of 1 mm^3). A FLAIR sequence was included in the same session in order to remove signal from cerebrospinal fluid from resulting images (FLAIR TE/TR 93/7000 ms, TI [inversion time] = 2500 ms, resolution = 0.86 x 0.86 x 4mm, FOV = 220 mm).

5.2.5 Imaging Data Processing

Raw imaging data was processed using Statistical Parametric Mapping software (SPM v12, Functional Imaging Laboratory Group, 2014) operating via a Matlab R2014b platform (MathWorks, 2014). Pre-processing included realignment and unwarping of the fMRI time series and slice-time correct. Functional images were then co-registered to a within-session, high resolution T1 structural image. A motion-fingerprinting tool was used to automatically assess and correct for the effects of motion within the fMRI time series (as described by Wilke, 2014). A DARTEL template of high-resolution images was created, then normalisation applied to coregistered EPI images (Ashburner, 2007). T1 images were segmented into grey matter, white matter, and cerebrospinal fluid using a tissue classification method. Resulting images were smoothed using an 8mm, full-width, half maximum Gaussian kernel. At the group level, a GLM ANOVA was constructed to model conditions (low, medium, high, read) by group (PD and control). Independent t-tests were also developed to observe group differences in activation between Low and High conditions, and between a general complete condition (collapsed across low, medium, and high) and the read condition.

Mean % BOLD signal change was examined in regions of interest (ROI) that were developed a priori based on the hypotheses outlined above and included seed regions within frontostriatal circuits known to participate in cognitive control functions (Lewis et al., 2003; Owens, 2004; Dirnberger & Jahashini, 2013; Middleton & Strick, 2000). ROIs were developed using the Marsbar ROI toolnox (Brent et al., 2002) in SPM12 (Wellcome Trust Centre for Neuroimaging, 2014). The WFU Pickatalas toolbox (Maldjian et al., 2003) was used to derive anatomical ROIs. These included the left and right vlPFC (built by combining BA 45 and BA 47 as per Nagel et al.'s [2008] findings), and the left dorsal striatum (caudate and putamen nuclei). The left dlPFC was also included as an ROI (-38 30 32) due to its participation in frontostriatal circuitry and implication in previous administrations of the HSCT (Nathaniel-James & Frith, 2002).

5.2.6 Scoring of Behavioural Data

Audio files were digitally filtered in order to reduce interference from scanner noise using Audacity (v2.1.2) software. Response times were manually extracted and measured with millisecond accuracy from the onset of the written instruction indicating required response (e.g.

"complete", "read") to the onset of the participant's response so as to avoid contamination from non-verbal artifacts (e.g., coughing or throat clearing). Two independent markers scored each participant's responses based on predetermined criteria. A correct response was required to consist of a single word (though responses containing two lexical units representing a single semantic concept were accepted e.g., washing machine, swimming pool) that completed the sentence in a way that was conceptually and grammatically correct. Responses containing excessive interjections, false starts, self-corrections, or multiple words were scored as incorrect. Cohen's kappa was run to determine the level of inter-rater agreement, and this was found to be acceptable, $\kappa = .819$ (95% CI 0.803, 0.835), $p < .001$.

5.3 Results

Initial exploration of ROI data (see Section 5.3.2.1) revealed three participants (2 PD, 1 control) who were significant outliers in the included ROIs. Outliers were identified based on interquartile range. Specifically, a data point (representing the mean percentage BOLD signal change) was considered to be an outlier if it fell below the 25th percentile or above the 75th percentile. These three participants were excluded from all subsequent analyses. The final results of the study therefore include 12 PD participants and 14 control participants. There was no significant difference between groups included in this analysis in terms of gender ($x^2 = 1.0$), age ($p = .051$), or YOE ($p = .326$).

Analysis of behavioural data was undertaken using SPSS software (Version 22). Of the total trials administered, 3.1% in the PD group and 2.8% in the control group were recorded as non-responses (no response given) and subsequently discarded from statistical analysis.

5.3.1 Behavioural Results

5.3.1.1 Neurocognitive battery.

A series of independent t-tests were conducted in order to identify group differences in the mean performance of each measure in the neurocognitive battery. Results are presented in Table 9. No significant differences in performance were detected between groups for any measure. Note that participants excluded due to outlying ROI data were also excluded from analysis of neurocognitive battery data. In some cases, participants were unable to complete selected assessment items due to fatigue, reducing the sample size reported in Table 10.

Table 10

Baseline Measurements of Neurocognitive Performance of Participants with PD

Measure	Group	*n*	M_{Score}	*SD*	Significance
Semantic Fluency	PD	12	19.15	3.03	0.292
	Control	14	20.71	4.18	
Phonemic Fluency	PD	12	15.44	2.51	0.739
	Control	14	14.95	4.81	
Cued Fluency	PD	12	24.29	2.33	0.741
	Control	13	23.96	2.61	
BNT	PD	12	55.42	3.63	0.721
	Control	14	55.93	3.58	
TEA - EC	PD	12	7.00	0.00	0.365
	Control	14	6.93	0.27	
TEA - ECD	PD	12	10.25	2.42	0.393
	Control	14	9.36	2.76	
Digits Forward	PD	12	7.42	1.00	0.307
	Control	14	6.93	1.33	
Digits Backward	PD	12	5.50	1.09	0.638
	Control	14	5.71	1.20	
NART_FISQ	PD	12	116.17	8.26	0.96
	Control	13	116.00	8.14	

Note. BNT = Boston Naming Test 2nd Edition; NART_FISQ = National Adult Reading Test Full Scale IQ; TEA – EC = Test of Everyday Attention - Elevator Counting; TEA – ECD = Test of Everyday Attention - Elevator Counting with Distraction.

5.3.1.2 Response time.

Analysis of response time data only considered those responses that were scored as correct. Further, responses were required to be provided within a temporal window of 250 ms to 2500 ms in order to be included. Any responses provided outside this threshold were discarded, resulting in the loss of 8.3% of trials in the PD group, and 7.2% in the control group.

Initial exploration of the distribution of response time data indicated a departure from normality. A log10 transformation was performed and the resulting distribution satisfied requirements for parametric analysis. This transformed data was submitted to a Linear Mixed Model (LMM) analysis with group (PD, control) and the four condition (low, medium, high and read) included as fixed effects and participant as a random effect. Results are presented in Figure 9

in their untransformed state (ms) for ease of interpretation. The analysis revealed a significant effect of condition (F [3, 2575) = 73.2, p < .001) but no effect of group or group by condition interaction. Bonferroni-corrected pairwise comparisons collapsed across group revealed significant differences between all conditions, with the exception of the low versus medium comparison (p = 1.0). Response time increased in a step-wise progression from the high constraint condition, to the read baseline, and to low and medium constraint conditions (slowest response time).

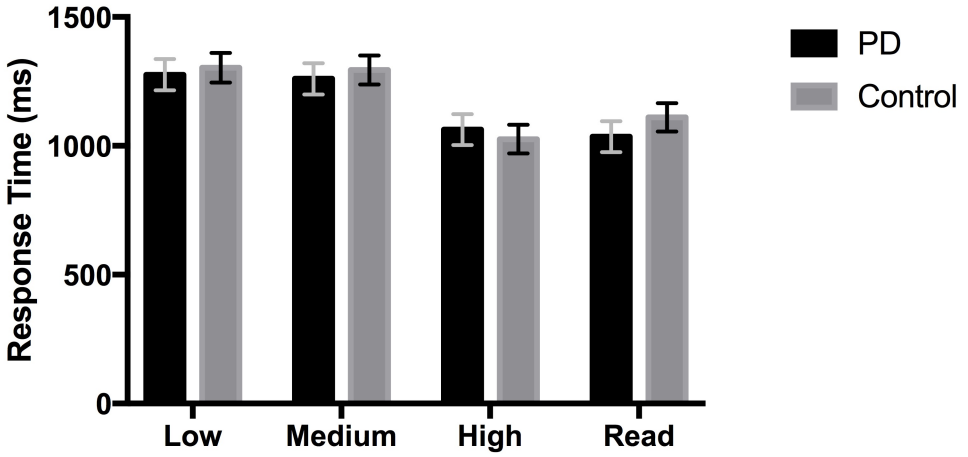

Figure 9. Mean response time (ms) as a function of degree of contextual constraint (high, medium, low). The read condition served as a baseline. Error bars represent mean standard error. A main effect of condition was detected, characterised by significant differences between all conditions (p < .05), with the exception of the low vs. medium constraint comparison, which did not reach significance.

5.3.1.3 Accuracy.

Accuracy data for each participant was extracted in the form of the total percentage correct. Distribution of this data was found to satisfy normality requirements for parametric analysis. A LMM was conducted with group and condition modelled as fixed effects and participant as a random effect. These results are presented in Figure 10. The analysis indicated a significant main effect of condition (F [3, 78] = 91.47, p < .001) that was characterised by a significant difference between all pairwise comparisons of condition, when collapsed for group (with Bonferroni adjustment for multiple comparisons). In addition, the LMM also revealed a significant group by condition interaction (F [3, 78] = 3.17, p = .029). Paired sample t-tests conducted independently within each group revealed the nature of this interaction. In the control group, significant differences were present for all comparisons (consistent with the main effect of condition initially described). However, in the PD group, the difference between scores on the low condition compared to the medium condition did not reach significance (p = .073).

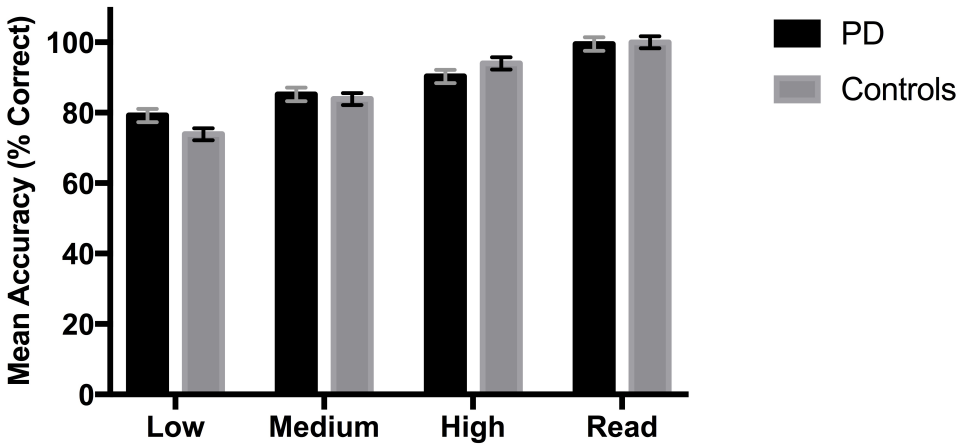

Figure 10. Mean accuracy (percentage correct responses) as a function of degree of contextual constraint (high, medium, low). The read condition served as a baseline. Errors bars represent mean standard error. In the control group, significant differences were present across all pairwise comparisons of condition ($p < .05$). This was also the case in the PD group, with the exception of low vs. medium constraint, which did not reach significance. No main effect of group was detected.

5.3.2 Imaging Results

5.3.2.1 Region of interest analysis.

Mean percentage signal change for the read condition in each ROI was subtracted from each experimental condition (e.g., low minus read), thus controlling for the common processes of sentence comprehension and speech production. These subtraction figures were submitted to independent repeated measures ANOVAs. Independent t-tests were also conducted in order to determine whether read baseline activation was equivalent across groups for each ROI. These tests revealed no significant differences in baseline activation between groups for the left vlPFC and left striatum. Baseline activation was found to be significantly different between groups in the left dlPFC ($t [24] = 2.53$, $p = .018$) and right vlPFC ($t [24] = 2.45$, $p = .022$). Further analysis of ROI data obtained from these regions was therefore not undertaken.

5.3.2.1.1 Left striatum. A main effect of condition was detected in the left striatum ($F [2, 48] = 8.36$, $p = .001$). Paired sample t-tests in the control group revealed significant differences between the medium vs. high conditions ($p = .004$), and low vs. high condition ($p = .005$). In contrast, the PD group did not modulate recruitment of this region as a function of condition, with no significant differences recorded for any pairwise comparison ($p > .1$ for all). These results are plotted in Figure 11.

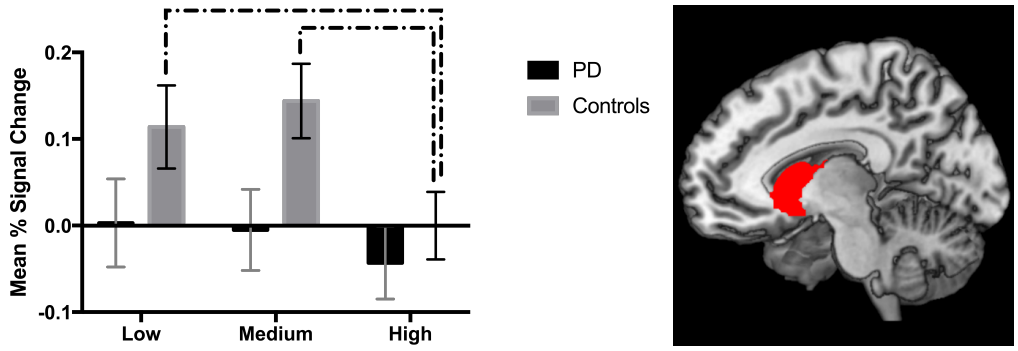

Figure 11. Region of interest analysis for the left striatum. Bar graph indicates relative mean percentage change in BOLD signal in left striatum as a function of degree of contextual constraint (high, medium, low)..Brackets indicate significant within-group differences in activation ($p < .05$). Error bars indicate standard error mean. Figure displays render of a priori defined anatomical ROI for left dorsal striatum (caudate and putamen).

5.3.2.1.2 Left vlPFC. A main effect of condition was detected in the left vlPFC (F [2, 48] = 8.79, p = .001). Paired sample t-tests revealed that this effect of condition was characterised in the control group by significant differences between medium vs. high conditions (p = .006, respectively) and low vs high conditions (p = .001). However, the PD group only recorded a significant change in activation in the medium vs. high comparison (p = .028). These results are plotted in Figure 12.

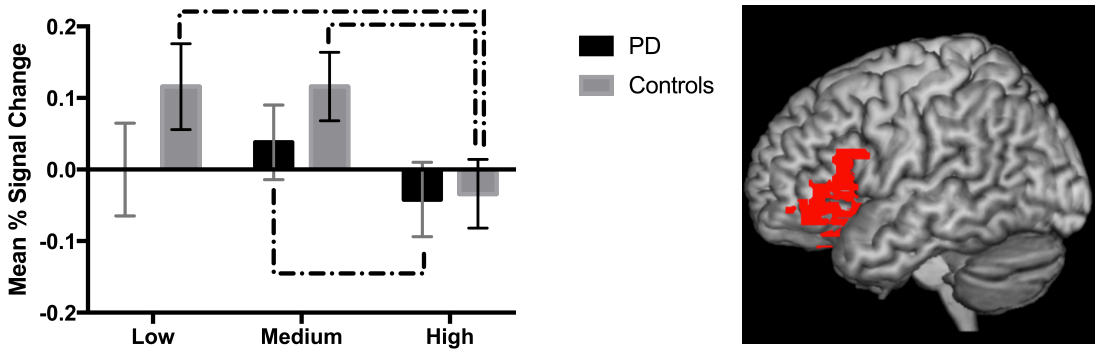

Figure 12. Region of interest analysis for the left vlPFC. Bar graph indicates relative mean percentage change in BOLD signal in left vlPFC as a function of degree of contextual constraint (high, medium, low).Brackets indicate significant within-group differences in activation ($p < .05$). Error bars indicate standard error mean. Figure displays render of a priori defined anatomical ROI for left vlPFC.

5.3.2.2 Whole brain analysis.

An exploratory whole brain analysis was conducted and results acquired using a grey matter mask are reported for a height threshold of $p < .001$ uncorrected and clusters corrected at the voxel level for FWE ($p < .05$). Anatomical labels for significant clusters were retrieved using the Neuromorphometrics software in SPM12 (Wellcome Trust Centre for Neuroimaging, 2014). No main effect of condition or group-by-condition interaction was detected. A main effect of group was detected in the following regions: right triangular portion of the IFG (BA 45, equivalent to right

vlPFC), left caudate, left dlPFC, left angular gyrus, right medial superior frontal gyrus (SFG), right posterior cingulate gyrus (PCgC) and the right superior marginal gyrus (SMG). This effect was characterised by significantly increased activity in these regions in the control group relative to the PD group when collapsed across condition. An independent t-test revealed that the control group showed increased recruitment of the right central operculum relative to the PD group, when all experimental conditions were collapsed into one condition called complete and compared to the baseline read condition. These results are presented in Table 11.

Table 11

Whole Brain Analysis: Peak Maxima of Clusters Demonstrating Significant Activity as a Function of Group and Condition

Contrast and anatomical label of activation peak	z-score	*k*	Voxel level	MNI coordinates		
			p_{FWE}	x	y	z
Main Effect of Group						
Right Triangular IFG	6.91	5825	<.001	54	27	16
Left Caudate	6.08	4621	<.001	-24	10	21
Left dlPFC	5.46	474	.017	-36	50	16
Left Angular Gyrus	4.81	487	.015	-32	-64	27
Right mSFG	4.68	507	.012	4	52	18
Right PCgC	4.57	592	.005	8	-42	28
Right SMG	4.33	384	.041	56	-33	44
Complete > Read (Control > PD)						
Right Central Operculum	4.17	655	.005	39	3	20

Note. MNI coordinates of peak activation from whole brain analysis for clusters corrected at the voxel level ($p < .05$). FWE = family wise error. *k* = cluster size (voxels). IFG = inferior frontal gyrus; dlPFC = dorsolateral prefrontal cortex; mSFG = medial superior frontal gyrus; PCgC = posterior cingulate gyrus; SMG = superior marginal gyrus.

5.4 Discussion

The present study aimed to determine the influence of contextual constraint on verbal selection and identify its underlying neural substrates in a PD cohort. A sentence completion task was employed that manipulated the contextual constraint of the sentence stem across three conditions (low, medium, and high constraint). The primary finding of the study was largely commensurate behavioural performance in the PD and control groups in terms of response time and accuracy (with the exception of no significant difference between low and medium constraint accuracy in the PD group), accompanied by significant group differences in underlying neural activity. Such differences were characterised by increased overall activity across a distributed network of frontal and subcortical regions in the control group relative to the PD group. Several key regions were identified in line with the aforementioned hypotheses, including the left caudate and bilateral vlPFC. The control group relied heavily upon recruitment of these regions during the low and medium constraint conditions relative to the high constraint condition, while the PD group demonstrated minimal modulation of activity as a function of condition.

Relative to controls, the PD group demonstrated significantly decreased overall activity in a number of regions across the frontal cortex and subcortex, including the right vlPFC, left dlPFC, and the caudate nucleus. Numerous imaging studies of PD have demonstrated that decreased signalling in these networks accompanies impairments in cognitive and linguistic function (Dirnberger & Jahashini, 2013; Grossman et al., 2003; Hanganu et al., 2015; Ketteler et al., 2008; Lewis et al., 2003; Owens, 2004; Zgaljardic et al., 2006). In the present study it was therefore hypothesised that decreased activation would be observed within these regions in the PD group. However, unexpectedly, although this difference in neural activity was indeed observed, it was not accompanied by impaired behavioural performance. Rather, the PD group was able to maintain their behavioural output at a level commensurate with the control group, despite this significant decrease in frontostriatal activity.

Possible explanations for the discrepancy between the findings of the present study and pre-existing evidence will be discussed further below. The results for the healthy control group will be considered first, providing the contextual framework necessary to support subsequent inferences regarding the performance of the PD group.

5.4.1 Involvement of the Lateral Prefrontal Cortex

ROI analysis revealed increased activation of the left vlPFC during conditions with increased selection demands (i.e. low contextual constraint). A recent meta-analysis conducted by Noonan, Jefferies, Visser, and Lambon Ralph (2013) examined neuroimaging data from 53 studies of semantic control in healthy adults and semantically-impaired stroke patients, as a means of confirming the neural substrates of this process. The analysis identified a bilateral network

extending beyond the left and right lateral PFC (dorsal and ventral), to include the left posterior MTG, angular gyrus, and ACC. In particular, the left PFC and angular gyrus were significantly activated as a function of semantic control across a variety of tasks (e.g., categorization, comparison, and ambiguity processing), irrespective of expressive versus receptive processes. In contrast, though the present study identified increased activity in both the right vlPFC (triangular portion of IFG or BA 45) and left vlPFC (BA 45/47) during conditions of low and medium constraint, whole brain analysis did not reveal evidence of activation in the MTG.

Given Badre et al.'s (2005) distinction between controlled retrieval and post-retrieval demands in the vlPFC, this lack of MTG activation may be inferred as indirect evidence of limited controlled retrieval demands in this task. Instead, the observed vlPFC activation may be more representative of post-retrieval selection demands, which may not necessitate the recruitment of the MTG. This may be conceivable considering the design of the task. Low and medium constraint sentences can be completed by a large number of alternatives presumed to be activated by the contextual information. For example, the low constraint sentence stem "The two opposing families had an ongoing ____" may be reasonably completed by a number of words including "feud", "argument", "disagreement", etc. The semantic similarity of these linguistic units suggests that sufficient information is provided by the sentence to drive bottom-up activation of relevant concepts. However, a large number of equally appropriate words are activated. In this way, it could be surmised that post-retrieval selection mechanisms are of greater importance when completing this task than controlled retrieval mechanisms.

Irrespective of the specific mechanisms, the present study does provide evidence to substantiate prior claims of a role for the vlPFC in the controlled selection of contextually appropriate words. Interestingly, the Nathaniel-James and Frith (2002) study upon which the present study is based did not find evidence of vlPFC activity during the completion component of their task. However a number of factors may account for this discrepancy, as the study only assessed six healthy males (aged 32 to 63), and did not include a baseline measure. These limitations may have masked any effects in the vlPFC from reaching significance.

Nathaniel-James and Frith (2002) did identify significant dlPFC activity across all levels of constraint during the suppression condition (generation of an unrelated word) as well as during the low constraint condition of the completion task, and attributed this to 'sculpting of the response space'. As described previously, this refers to the process of generating a set of possible responses (when no single response is prepotently appropriate) and appears to overlap somewhat with the concept of selection among competing alternatives. In the present study, a significant difference between groups in activation of the left dlPFC was also identified at the whole brain level, characterised by increased recruitment in the control group relative to the PD group. However, this

effect could not be examined further with ROI analysis due to group differences in the baseline condition. Activation of the dlPFC during a selection task does appear to raise the question of whether these regions have unique, overlapping, or shared roles.

Kerns et al. (2004b) had previously noted this contention surrounding the differential roles of the dlPFC and vlPFC, and suggested that both may contribute to a similar goal via complementary mechanisms. They framed their investigation in the context of guided activation theory (Miller & Cohen, 2001); a widely endorsed model of how the PFC performs its role as the instigator of cognitive control. It proposes that the PFC exerts top-down influence over more posterior regions of the cortex responsible for task execution in order to bias task-relevant responses. Such guidance is particularly necessary when a task introduces the need for novel responses, selection among competing alternatives, or selection of a task-relevant response in the face of a strongly prepotent but task-irrelevant response. Previous applications of the model in language-processing paradigms have suggested that the PFC represents and maintains the contextual information conveyed by a syntactic structure and uses this information to bias the selection of a context-appropriate response in posterior language regions (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992). In this way, selection of the most appropriate response can occur. The model therefore posits that context maintenance and selection of a response are the same mechanism.

Kerns et al. (2004b) interprets this notion as suggesting that maintenance and selection would be subserved by the same region of the PFC, and tested this assumption with a missing letter paradigm. In this task, participants were asked to fill in the blank in order to create a complete word, and this took place following presentation of sentences designed to provide contextual priming for the probing words. Whole brain analysis found that activity in both the dlPFC and the vlPFC during encoding and maintenance phases was associated with the provision of context-appropriate verbal response. Such a relationship was not observed elsewhere. Furthermore, these same regions demonstrated increased activation during the provision of a verbal response that was context-inappropriate. Kerns et al. (2004b) interpreted their findings as evidence for guided activation theory. They inferred that both the dlPFC and vlPFC were involved in representing and maintaining contextual information derived from sentence processing in order to bias the selection of an appropriate response. When this process failed, the selective activation of the appropriate response did not occur, and as a result participants were required to generate a response presumably from multiple competing alternatives. At this point a selection mechanism (likened to Badre's et al.'s [2005] post-retrieval selection mechanisms) was required to choose one response from among these alternatives. Kerns et al. (2004b) suggested that this accounted for the increased activity observed in the dlPFC and vlPFC during the response phase and conclude that maintenance of

context and selection of a response during language processing are subserved by a unitary mechanism, presumably involving both dlPFC and vlPFC. This account does not functionally segregate these two regions (BA 9/46 and BA45). The present study appears to provide support for Kern's et al.'s (2004) conclusions, as activity in both the vlPFC and dlPFC was detected.

Importantly, it is noted that the present study identified prefrontal activity in both left and right hemispheres. Noonan et al. (2013) similarly identified a bilateral network hypothesised to subserve semantic control. This is a departure from earlier findings that have largely implicated left hemisphere structures (Badre et al., 2005; Nagel et al., 2008; Snyder et al., 2011; Souza et al., 2009) however it is possible that the bilateral activity noted in our cohort and Noonan et al.'s cohort relate to the older age of these participants relative to previously studied cohorts and reflect typical age-related hemispheric compensation (Berlingeri et al., 2013; Cabeza, 2002; Reuter-Lorenz & Cappell, 2008). Indeed, this phenomenon has been specifically reported in studies of age-related changes in semantic processes (Diaz, Johnson, Burke, & Madden, 2014; Wierenga et al., 2008).

5.4.2 Involvement of the Striatum in Verbal Selection

In the present study, whole brain analysis also identified significantly increased activation in the left caudate for the control group, relative to the PD group. ROI analysis of the left striatum further revealed that this effect was characterised by increased recruitment during low and medium constraint conditions, and a decrease during the high constraint condition. This pattern of recruitment suggests that striatal participation in verbal selection is necessitated when either selection and/or controlled retrieval demands are increased. As hypothesised, this pattern of engagement mirrors that observed bilaterally in the lateral PFC, suggesting the existence of a frontostriatal network recruited to mediate processing when selection demands are increased. This is in line with previous studies that have identified activity in the caudate during the execution of tasks with a verbal selection component (Argyropoulos et al., 2013; Crosson et al., 2003; Ketteler et al., 2008; Mestres-Missé et al., 2008).

Taken together with the parallel activation in the lateral prefrontal cortex, this finding corroborates and extends the proposals of Chatham et al. (2014), who noted that cognitive control requires achieving a balance between the need to flexibly update goals and the need to maintain them over time. Consistent with guided activation theory (Miller & Cohen, 2001), they suggest that in order to maintain task-relevant representations in the PFC, selective updating of these representations must occur in response to dynamic changes in the contextual environment. This, they claim, must be supported by two distinct mechanisms. The PFC is responsible for the maintenance of contextual information in working memory, while the basal ganglia provides an input gating mechanism, reliant upon dopamine-driven frontostriatal networks, that exercises selective control over the updating of this information, in line with internal goals. This maintained

information is then available to exert top-down control over activity in more posterior regions of the cortex, in order to bias task-relevant responding. Furthermore, Chatham et al. (2014) also propose an output gating system that acts to allow only selected representations to exert this top-down bias. This output mechanism is likewise thought to be controlled by structures within the basal ganglia which amplify selected representations received from the PFC via frontostriatal pathways.

This model may be extrapolated and applied to the results of the present study. Previous accounts have demonstrated that reciprocal connections exist between the head of the caudate and the vlPFC (di Martino et al., 2008; Leh et al., 2007). In the present study, these structures appear to be co-activated under conditions of increased selection demand, suggesting the presence of a distributed network. It may be hypothesised that the lateral PFC structures were responsible for maintaining the contextual representations during sentence stem processing, and the caudate selectively updated these representations as contextual information dynamically altered with the addition of each word in the string. Output gating co-ordinated by the caudate then amplified specific representations in order to bias selection from among the multiple competing alternatives activated by the maintained contextual information. These selected representations in the PFC were then able to exert top-down influence over posterior language regions, allowing for production of a single, relevant response.

Returning to our findings in the PD cohort, despite the differences in activation detected between the groups in frontostriatal networks thought to be critical to verbal selection processes, the present study did not identify any difference in behavioural performance between groups. The question of how the PD group were able to maintain response times and accuracy commensurate with controls, in the face of significantly decreased recruitment in these networks, must therefore be addressed. Given that whole brain and ROI analysis did not identify possible compensatory activity, any hypotheses here can only be speculative in nature. One explanation may be that compensatory mechanisms were at play in regions where there was not sufficient power to detect significant activity in the whole brain analysis, or that were not included in our set of pre-determined ROIs. Previous studies have described equivalent behavioural performance in PD participants in the face of altered neural recruitment during cognitively-loaded tasks including set-shifting (Gerrits et al., 2015; Poston et al., 2016) or semantic event sequencing (Tinaz et al., 2008). However unlike the present study, the compensatory activity observed in these cohorts has been largely characterised by the presence of hyperactivity in task relevant areas, or their right hemispheres analogues.

Alternatively, behavioural performance in this group may have been maintained via increased functional connectivity between task-relevant regions. Though the present study was unable to address this possibility, emerging evidence of this phenomenon has been identified in the realm of cognition. Gorges et al. (2015) recently demonstrated hyperconnectivity in cortical, limbic,

and basal-thalamic areas in individuals with PD who were cognitively intact relative to healthy controls. Further, individuals with PD who were cognitively impaired were observed to have decreased connectivity between these regions relative to controls in these regions. Gorges et al. suggest that this increase in connectivity in the cognitively intact PD cohort may represent a compensatory mechanism. In addition, Yang et al. (2016) demonstrated that levodopa medication can alter resting-state functional connectivity in the striatum, with differential effects upon dorsal and ventral pathways. Given that the participants recruited for the present study were considered to be in a mild-moderate stage of the disease and were medicated at the time of testing, this may also have played some role in bolstering behavioural performance.

Another alternative explanation may also be drawn from consideration of medication effects in this cohort. A number of authors have suggested that dopamine has a modulatory effect upon activation in semantic networks. In their placebo-controlled study of semantic priming in healthy adults, Kischka et al. (1996) concluded that dopamine exerted a "focusing effect" over the automatic spread of lexical activation through semantic networks, limiting this activation to only those concepts closely related to the target word. Subsequent studies have furthered this notion with several finding evidence of decreased indirect priming (reduced activation of distantly related concepts) and decreased activation of weaker representations when participants had ingested levodopa versus a placebo (Copland, Chenery, Murdoch, Arnott, & Silburn, 2003; Roesch-Ely et al., 2006). However, alternative findings suggest that dopamine may act to modulate the speed with which the spread and decay of semantic activation occurs (Angwin et al., 2004). Specifically, Angwin et al. suggest that increased levels of dopamine will result in the absence of direct or indirect priming at long SOAs (i.e. when controlled processing is invoked). Subsequent investigations in a PD population described a relationship between the increasing magnitude of the semantic processing impairment, and the degree of dopaminergic depletion (Angwin et al., 2009).

It is well established that the depletion of dopaminergic projections progresses through the striatum in a dorsal to ventral pattern (Kish et al., 1988). Cools (2006) has further demonstrated that those structures that receive output from the dorsal striatum are therefore affected earlier in the course of the disease, relative to those that receive output from the ventral striatum. The pre-SMA and premotor cortex are therefore the earliest affected, and this can account for the earlier onset of motor symptoms relative to manifestation of cognitive impairment. Prefrontal regions, including the vlPFC and dlPFC, are affected later in the course of the disease. As a result, levodopa medication can induce a hyperdopaminergic state in these as yet unaffected areas in the early stages of the disease.

With respect to the present study, decreased activation of critical selection substrates was observed in the medicated PD group because activation of possible responses during sentence

processing resulted in limited spreading activation or faster decay of activated concepts. As a result, fewer competing alternatives were available for selection to this group, reducing the need for frontostriatal mechanisms of controlled retrieval and selection. This tentative suggestion may offer some support in the results of the whole brain analysis, which detected significant group differences in the pars triangularis. According to Badre et al.'s (2005) model, this is the region of the vlPFC associated with post-retrieval selection (choosing among multiple competing alternatives). The fact that activation in this region was reduced in PD participants relevant to controls may therefore further demonstrate that the PD group did not require engagement of post-retrieval selection mechanisms to the same degree, as a result of more focused activation within the semantic network. In addition to greater sample sizes, future investigations in this field should strive to include on and off medication testing of PD participants, in order to observe the differential effects of dopaminergic medication upon controlled semantic retrieval and selection mechanisms and resulting influence on underlying neural recruitment.

5.5 Conclusions

In conclusion, the results of the present study suggest that in older adults, the capacity to select a contextually appropriate linguistic unit under conditions of increased contextual constraint is subserved by a number of frontal and subcortical regions related to cognitive control. These primarily include the left dlPFC and bilateral vlPFC, and the left striatum. The coordinated nature of these parallel activations is yet to be determined.

Furthermore, in the early stages of PD the behavioural efficiency of this linguistic process appears to be maintained, despite underlying decreases in frontostriatal activity. While this behavioural performance does not appear to be facilitated by up-regulation of activity in task-relevant regions, it may be hypothesised that increased functional connectivity between critical structures, or an over-medication effect in frontal networks act to compensate for disease-driven loss of signalling along cortico-subcortical pathways.

6 Chapter Six

Conclusion

Language disturbances in PD have been widely documented though the precise nature and severity of these impairments remain unclear. In particular, the manner in which the basal ganglia mediate the cognitive control of language and the nature of its disruption in PD is yet to be clearly discerned. A primary aim of this thesis was therefore to address the question of whether a deficit in the control of spoken language production (i.e. verbal selection and/or suppression) underlies the language impairments observed in individuals with PD. These studies involved a combination of behavioural and fMRI techniques, in order to elucidate how this hypothesised impairment related to changes in neural activity in frontostriatal circuitry. All studies recruited a group of individuals with mild-moderate PD and a group of age-matched healthy older adults to serve as controls. Findings were considered within the context of existing models of cognitive control and cortico-subcortical interaction. This chapter will summarise the primary findings of each study (Section 6.1), identify the key themes emerging from their integration with reference to overarching aims and relevant theoretical and mechanistic models (Section 6.2), discuss the limitations in study design and proffer recommendations for future investigations (Section 6.2 and 6.3), and finally, offer concluding remarks (6.4)

6.1 Summary of Study Aims and Primary Findings

The Hayling Sentence Completion Task (HSCT; Burgess & Shallice, 1996) was identified as a widely used measure in the study of verbal selection and suppression, and critical evaluation of elements of this paradigm served as scaffolding for the present investigations. Identification of the potential limitations of the HSCT's design, in addition to consideration of the aspects of selection and suppression that it does not address, drove the development of four complementary studies. Firstly, the algorithm by which verbal suppression ability was determined did not account for the need to generate and implement a strategy as a step in producing an unrelated word. This was considered important in PD, as strategy generation is a cognitive skill that has been noted to be impaired in this population (Taylor et al., 1986). Thus, conclusions regarding not only the capacity of people with PD to perform the task, but also the functional role designated to neural mechanisms involved in the suppression condition in previous studies could be underspecified. Though limited in number, studies that have administered the HSCT to a PD population have consistently observed decreased performance on the suppression component of the task, relative to healthy controls (Bouquet et al., 2003; Copland et al., 2012; O'Callaghan et al., 2013b; Obeso et al., 2011a). This has generally been interpreted as an indication of impaired semantic inhibition in this population. However, authors employing other measures of semantic inhibition in PD cohorts have found

differential results, with some reflecting similar deficits (Arnott et al., 2010; Copland et al., 2009; Filoteo et al., 2002; Marí-Beffa et al., 2005), while others have not identified any significant difference between the PD group and controls, for example in picture-word interference (Castner et al., 2007b) and object-based negative priming (Possin et al., 2009). A critical difference between these studies was identified as relating to aspects of paradigm design, including input and output modality (i.e. visual-semantic vs. orthographic vs. visuospatial input, word production vs. lexical decision) and temporal parameters.

Chapter 2 therefore examined inhibition of irrelevant semantic information using a visual-semantic negative priming task, originally described by Tipper (1985), as a means of addressing some of the inconsistencies in the literature concerning inhibition of representations in individuals with PD. The study employed a task design that eliminated the need for strategy generation, thus avoiding the confounds of the HSCT's measure of inhibition. The exclusive use of visual-semantic stimuli also allowed for uniformity across input modality. It was hypothesised that PD participants would record faster response times for probe items that were semantically related or identical to a preceding distractor item, as a result of difficulty inhibiting irrelevant information.

The results of the study demonstrated no main effect of group or significant group-by-condition interaction in terms of response time or accuracy. A negative priming effect was present in both groups, with probe stimuli named fastest when they were unrelated to the distractor stimuli, relative to distractor stimuli that were related or identical to the probe. This result suggested that the ability to ignore a distractor image and its related semantic concepts was intact in this PD cohort. These findings were interpreted as evidence for the possible existence of multiple, specialised inhibitory mechanisms that may be differentially affected as a result of PD. Drawing on previous findings of difficulty inhibiting the automatic processing of written words during the Stroop paradigm in PD (Henik et al., 1993), it was suggested that the orthographic pathway may be more vulnerable to disrupted inhibitory processing, while the visual-semantic pathway is largely intact (at least in a mild-moderate cohort). Alternatively, it was also suggested that the availability of external cues may be a critical factor in facilitating inhibition processes in this cohort (Brown & Marsden, 1988). For example, when the correct response is available externally, the need for internal generation of a response is eliminated, lessening the cognitive loading of the task. These theories could account for intact object-based negative based negative priming, despite documented deficits in lexical decision paradigms and the HSCT.

The study in Chapter 2 only observed inhibition across a brief temporal window, where the item to be inhibited was presented immediately prior to production of it or its semantic relative. Beyond semantic priming paradigms, little exploration of the time-course of semantic inhibition has taken place, and less still in the PD population. A number of authors have demonstrated the

emergence of altered semantic priming in individuals with PD when ISI is lengthened beyond the parameters of automatic processing (Angwin et al., 2009; Angwin et al., 2004; Arnott et al., 2001; Grossman et al., 2002). Indeed, Angwin et al. (2009) suggested that the time-course of spreading lexical activation may be delayed in this population. However, few studies have considered inhibitory processing beyond a temporal window of 1-2 seconds. Copland et al. (2009) demonstrated that PD patients had difficulty inhibiting incongruent meanings across several intervening trials in a lexical ambiguity task. However, Copland et al. only examined processing during comprehension (lexical decision making) and there is a lack of research examining the time-course of inhibitory processing elicited during spoken language production tasks (including the HSCT) in PD. The study in Chapter 3 was therefore designed with the intention of examining the time-course of semantic inhibition and its integrity in PD through use of a verbal production task. It was hypothesised that the PD group would not record a difference in response time for previously suppressed items or their semantic relations, relative to unrelated items, as a result of difficulty maintaining inhibition over time. This behavioural study employed a novel hybridisation of the HSCT (Burgess & Shallice, 1996) and a competitor priming paradigm (Wheeldon & Monsell, 1994). Participants were presented with high cloze probability sentence stems with the final word removed and required to produce an unrelated single word response (as per the suppression component of the HSCT). This was alternated with trials requiring the naming of a pictured object. The semantic relationship between the prepotent response associated with the sentence stem (presumed to be suppressed) and the picture to-be-named was manipulated to include conditions where the two were identical, semantically related, or unrelated. Finally, the interval between presentation of the priming sentence stem and presentation of the associated picture naming trial was manipulated in order to study inhibition mechanisms over time.

Due to methodological limitations, response time data was unable to be analysed for picture naming trials. Non-parametric analysis of picture naming accuracy data (as function of lag and sentence completion accuracy) revealed that across most measures the PD group performed at a level commensurate with controls, suggesting the ability to suppress a strongly prepotent response and maintain this suppression across intervening trials was largely intact in this PD cohort. However, a significant difference between groups was identified when the sentence trial was completed incorrectly and lag = 0. That is, when participants with PD were unsuccessful in suppressing a prepotent response on a sentence completion trial, they were more likely to make an error in the picture naming trial that immediately followed. Further analysis revealed that this error pattern did not vary as a function of the relationship between the picture and the suppressed prepotent response. This effect was no longer present after two intervening trials had elapsed. Additionally, no significant group differences in response time or accuracy were detected when the

sentence completion component was analysed independently, demonstrating that the ability of the PD cohort to generate an unrelated word in the face of a strongly prepotent response was intact.

It was speculated that these findings may reflect a conditional disruption to cognitive flexibility facilities, such that the ability to move between two different "sets" (i.e. picture naming vs. generation of an unrelated word in a sentence completion task) was only impaired when the system was placed under additional demands. In this case, the additional demand was presumed to arise from error processing. This account was found to be consistent with widely reported deficits in cognitive flexibility in PD (Kopp, 2016; Kudlicka et al., 2011; Monchi et al., 2004; Woodward et al., 2002), as well as with the multiple hit hypothesis, which suggests that impaired executive functioning in PD manifests only when more than one process is in demand simultaneously (Lange et al., 2016). An alternative account related to hypothesised changes in underlying neural substrates. It has been well established that the anterior cingulate cortex (ACC) participates in error monitoring and resolution by mediating the subsequent re-focusing of cognitive control resources (Botvinick et al., 2004; Carter et al., 1998; Carter & van Veen, 2007). Furthermore, the ACC is implicated in a frontostriatal pathway (Cohen et al., 2000; Middleton & Strick, 2000) and thus its function can be disrupted as a result of aberrant signalling in the basal ganglia (Baggio et al., 2014; Rosenberg-Katz et al., 2016). It was therefore postulated that when the PD participants failed to successfully suppress a prepotent response during the sentence completion component of the task, this error-induced state of conflict was insufficiently resolved by the ACC and thus further errors were not prevented. However, this conflict was able to be resolved (or passively decayed) after a longer interval. It must be noted that conclusions drawn in Chapter 3 were highly speculative in nature. The inherent complexity of the task design appeared to give rise to a high rate of error and non-response in both groups, and as such, a limited number of trials were considered valid for analysis. For this reason, as was communicated in Chapter 3, interpretation of findings must be treated with considerable caution.

The finding of no group difference in accuracy or response time for the sentence completion component of the task was inconsistent with previous reports of impaired performance on Part B of the HSCT in PD cohorts (Bouquet et al., 2003; Copland et al., 2012; O'Callaghan et al., 2013b; Obeso et al., 2011a). In fact, in the studies described in both Chapter 2 and Chapter 3, the PD cohort demonstrated little departure from the control group in terms of behavioural performance, contrary to the documented impairments in language processing present in PD (discussed above). However, as these studies were only behavioural in their design, any conclusions regarding how underlying neural activity may have facilitated this performance could only be speculative. The studies in Chapter 4 and Chapter 5 therefore employed a combined behavioural and fMRI design, in order to elucidate the neural activity underlying the cognitive control of spoken language production.

Chapter 4 returned to an earlier question raised by the design of the traditional HSCT (Burgess & Shallice, 1996), seeking to determine the influence of strategy generation upon the ability to generate an unrelated word in the face of a strongly prepotent response. Employment of an fMRI design also allowed for comparison of neural activity between PD and control groups. A novel variation on the HSCT was employed which introduced an additional condition referred to as strategy. In this condition, participants were required to produce a word that was unrelated to the given sentence stem, however a cue was provided to assist in this process. Cues were high-frequency semantic categories. In this way, the participant could produce an unrelated word by naming a member of the prompted category. It was hypothesised that the PD group would demonstrate increased response times and decreased accuracy on the suppression component of the task, as a result of disrupted frontostriatal pathways. Furthermore, this performance would improve during the novel strategy condition if the underlying deficit related to strategy generation and implementation, and not to disrupted verbal inhibition.

The PD group performed at a level commensurate with controls in terms of response time and accuracy. The pattern of performance reflected an improvement in accuracy in both groups when presented with a strategy, though response times in this condition were the slowest. This finding contradicted previous accounts of impaired performance on the HSCT in PD populations (discussed above). The imaging results provide some explanation as to how this PD cohort maintained performance. During the unrelated condition, the control group showed increased activity in the left dlPFC and striatum relative to the strategy condition. The opposite pattern of activity was observed in the PD group. Thus while it does appear that the PD group were able to suppress a strongly prepotent response in favour of a contextually unrelated alternative, the process was subserved by an atypical neural network. In the strategy condition, the PD group appeared to rely on increased recruitment of bilateral striatum and dlPFC relative to the unrelated condition in order to maintain their performance, where the controls showed significant decreases and less recruitment of right hemisphere analogues. This was taken to suggest that the strategy condition was quite difficult for PD participants to execute, possibly as a result of its similarity to a verbal fluency task (performance of which is known to be impaired in PD - see Henry and Crawford, 2004). The presence of increased activity in task-relevant regions (dlPFC and striatum) was interpreted as evidence for compensatory mechanisms working to bolster behavioural performance. This was consistent with previous reports of compensatory hyperactivity in PD populations when executing cognitive or semantic processing task (Grossman et al., 2003; Poston et al., 2016; Tinaz et al., 2008). In this case, the excess activity in the striatum was hypothesised to reflect increased dependence upon working memory networks, consistent with current computational network models proposing cortico-subcortical maintenance of working memory (Frank et al., 2001).

Studies in the first three chapters addressed the process of verbal suppression in the PD population. A second line of investigation considered the complementary process of verbal selection, particularly, the process of selecting among multiple competing alternatives or the selection of an appropriate response in the face of limited contextual information. Similarly to verbal suppression, verbal selection processes are thought to be mediated by regions of the prefrontal cortex, though some debate exists as to whether this includes the vlPFC, dlPFC, or both (Badre et al., 2005; Snyder et al., 2011; Souza et al., 2009). An emerging line of evidence also implicates subcortical structures (Argyropoulos et al., 2013; Crosson et al., 2003; Ketteler et al., 2008). In the PD literature, verbal selection processes have been primarily studied in the context of verb generation paradigms, where documented verb-specific impairments are assumed to arise as a result of the fact that verbs inherently tend to be associated with a greater number of competing alternatives (Boulenger et al., 2008; Crescentini et al., 2008). However, this conclusion may be premature, given that if individuals with PD have difficulty generating verbs due to disrupted ability to select among competing alternatives, a similar deficit should presumably be manifest for any stimuli with similarly increased selection demands. Furthermore, few studies have considered the process of selection in PD beyond the level of single-word processing, as occurs in the HSCT. In this instance, a response must be selected based on contextual information conveyed by a cloze probability sentence stem. Chapter 5 therefore aimed to determine the capacity of individuals with PD to select and produce a task-appropriate response as a function of increased selection demands associated with contextually constrained sentence stems.

The design of this fMRI study was based on Nathaniel-James and Frith (2002) and required participants to provide a single word to complete a given sentence stem. The contextual constraint of the sentence stem was varied across three conditions (low, medium, high) in order to manipulate selection demands (i.e. low constraint sentences placed increased demands upon selection due to the greater number of alternatives that could appropriately complete the sentence). A control condition was also incorporated in which the final word of the sentence was provided (in addition to the sentence stem as per experimental conditions) and participants were simply required to read this word aloud. It was hypothesised that the PD group would record lengthier response times and decreased accuracy when selection demands were increased, as a result of disruption to frontostriatal networks including the vlPFC and striatum.

The results of the study revealed no main effect of group in terms of response time or accuracy, though a group-by-condition interaction in accuracy was noted. This was characterised by a significant difference in scores between low and medium levels of constraint for control participants, while the difference in scores for the PD group did not reach significance. Marked differences in underlying neural activity were detected. The control group showed increased

recruitment of the dorsal striatum and the vlPFC under conditions that placed greater demands upon selection (i.e. low and medium constraint), and greater activity overall in the left dlPFC and right vlPFC (collapsed for condition). This was consistent with previous findings in the literature regarding the participation of the PFC in controlled selection (Badre et al., 2005; Kerns et al., 2004b; Snyder et al., 2011). These results were also in line with models of cortico-subcortical interaction in cognitive processing and were extrapolated to describe their participation in verbal selection (Chatham et al., 2014).

Given the near equivocal performance of the two experimental groups, it was expected that the participants with PD would present with a similar profile of activation to the controls. However the PD group demonstrated significantly reduced activity relative to controls in those regions considered critical to selection during conditions of increased demand (i.e. the vlPFC, dlPFC, and striatum). As mentioned, the finding of intact behavioural performance in the face of altered neural activity reflects the findings of the study in Chapter 4. However in that case, hyperactivity was detected in task-relevant regions, suggestive of compensatory mechanisms. In contrast, no hyperactivity was detected in whole brain or ROI analysis of the PD group's data in the study in Chapter 5, raising the question of how these participants managed to maintain their behavioural performance. As described in Chapter 5, it is possible that compensatory hyperactivity may have been present in regions beyond those investigated as a priori seeds in the ROI analysis, or that variation in the regions recruited by individual participants prevented detection of activity at the group level. Increased functional connectivity between critical substrates may also have served as a compensatory mechanism (Gorges et al., 2015; Yang et al., 2016).

Alternatively, it was suggested that as all participants were in the mild-moderate stage of the degree, and were taking dopamine replacement medication at the time of testing, it was possible that an overmedication effect could account for the observed brain-behaviour discrepancy. This possibility is discussed in detail in Chapter 5, however, it was speculated that dopamine replacement medication may have induced a hyperdopaminergic state in frontostriatal pathways as yet unaffected by dopaminergic depletion (see Cools, 2006). A small number of studies investigating the influence of dopamine on semantic networks have demonstrated that it can either limit the spread of activation to related concepts, thus providing a focusing of activation, or it can increase the speed with which activation spreads and decays (Angwin et al., 2009; Angwin et al., 2004; Copland et al., 2003; Roesch-Ely et al., 2006). Both of these actions could have the effect of reducing the number of possible alternative concepts activated in response to a low or medium constraint sentence stem, thus reducing the associated selection demands and prefrontal activity.

6.2 Emerging Themes

A number of themes emerged across the results of Chapters 2 - 5 that will now be discussed in addition to associated limitations and suggested future directions.

6.2.1 Modelling the Neural Correlates of Verbal Selection and Suppression

Taken together, the results from healthy control participants in studies described in Chapter 4 and Chapter 5 provide converging evidence for the participation of subcortical structures in the cognitive control of language processing. With regard to the primary aim of determining the underlying source of language processing impairment in PD, it was found that the PD cohorts studied here performed at a level commensurate with controls across the majority of behavioural measures in all four studies. Thus, this thesis is unable to make robust claims concerning the possibility of a core deficit in verbal selection and suppression in this population. However, this behavioural performance was accompanied by atypical activation in those networks identified in control participants as task-relevant, and in Chapter 4 and Chapter 5 it was suggested that this output was maintained by either compensatory neural mechanisms (as in Chapter 4), medication effects, or compensatory changes in functional connectivity (though this was not investigated). It may therefore be speculated that as the disease progresses, and this compensatory capacity is degraded, deficits in verbal selection and suppression processes may begin to manifest as impaired spoken language production in tasks that require cognitive control.

Further discussion of these compensatory mechanisms will be discussed below (Section 6.2.2). The remainder of Section 6.2.1 will be dedicated to synthesis of imaging findings and application of this information to current models of cognitive control and cortico-subcortical integration.

In healthy controls, activation of lateral regions of the prefrontal cortex (both ventral and dorsal) was observed under conditions of increased cognitive demand, in association with increased striatal activity. For example, when required to generate a novel, alternative response in the face of a strongly prepotent response (as in Chapter 4), and when required to select a single word from among multiple competing alternatives as a result of low contextual constraint (as in Chapter 5). In contrast, activity in these regions was relatively decreased under conditions that alleviated demands on controlled processing, such as the completion of highly contextually constrained sentences, as observed in Chapter 4 and Chapter 5.

Converging evidence drawn from the present studies concerning the neural organization of verbal selection and suppression can be applied to current models of cortico-subcortical interaction and cognitive control in order to derive a speculative account of their relevance in language processing. The popular guided activation theory of cognitive control, outlined by Miller and Cohen (2001) describes the role of the PFC in biasing activity in more posterior regions of the cortex in

order to favour task-relevant responses. In line with this model, the present studies have identified increased activity in dlPFC and vlPFC as a function of cognitive control during spoken language production tasks. Chatham et al. (2014) elaborated further upon this hypothesis, and described an interactive cortico-subcortical model that posited a role for the striatum as an input gating mechanism responsible for selectively updating representations held in the PFC. They further suggested a complementary output gating mechanism, also subserved by the striatum, that allowed specific representations in the PFC to be selected to bias activity in more posterior cortical regions. This account is consistent with the increase in striatal activity identified in healthy controls in Chapter 4 and Chapter 5 (described above), occurring in parallel with increased activity in the dlPFC and/or vlPFC and, behaviourally, with increasing cognitive control demands.

This thesis proposes a unification and extension of these two aforementioned models, to accommodate the processes of verbal selection and suppression. Contextual information such as task goals, rule sets, or information derived from the processing of individual words in a sentence stem, is assumed to be represented in the ventral and dorsal lateral PFC. Input gating mechanisms subserved by the striatum provide signals to the PFC to allow for selective updating of these representations as contextual information is changed or modified e.g., as subsequent words in the sentence are processed and meaning is refined. When a response needs to be made, the striatum releases the output gating mechanism, allowing selected representations in the PFC to provide a top-down signal to posterior language regions in the cortex. This biasing action drives the production of a contextually appropriate verbal response. Though speculative, it can be noted that aspects of this proposal are consistent with previous models of subcortical language processing. For example, Wallesch and Papagno (1988) and Crosson (1985) both theorise a role for the subcortex in the selection and/or release of linguistic units, via interactions with anterior and posterior language regions.

This proposal accounts for how a response is selected. In Chapter 4 and Chapter 5, the dlPFC was observed to be active during both selection and suppression driven tasks. Indeed, Mostofsky and Simmonds (2008) and Desimone and Duncan (1995) have commented that selection and suppression may be two sides of the same coin in the context of cortico-subcortical processes. The striatum only provides output to the cortex via direct and indirect pathways that travel via other nuclei in the basal ganglia (DeLong & Wichmann, 2009). A direct pathway provides facilitatory "go" signals, while the indirect pathway provides inhibiting "no-go" signals (though see Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo [2014] for updates to this model). It may therefore be speculated that suppression of task-irrelevant information occurs as a by-product of the system's capacity to only update and maintain information relevant to the task's goals and rules, or it could

be possible that the striatum's input gating mechanism provides both "go" and "no-go" signals, based on the feedback it receives from the cortex.

Elucidating the specifics of internal basal ganglia function is beyond the scope of this study, however it does represent an avenue for future investigations. A growing number of studies have employed DBS paradigms in order to study subcortical language processing (Castner, Chenery, Copland, & Silburn, 2004; Castner et al., 2007a; Castner et al., 2008; Cilia et al., 2007; Marshall et al., 2012; Phillips et al., 2012; Silveri et al., 2012). This methodology offers increased sensitivity and specificity over fMRI in terms of its ability to manipulate the engagement of individual nuclei within the basal ganglia during administration of language tasks. This technology can be utilised in two approaches: Online testing during surgical placement of electrodes can allow for greater flexibility in terms of the location and degree of stimulation, or alternatively, post-surgical testing both with stimulators switched on and with stimulators switched off. This can potentially be paired with pre-surgical data to assist in delineating premorbid capacity, from surgical micro-lesioning and effects of stimulation. In the context of the present investigations, utilisation of on/off DBS stimulation in subthalamic nucleus (STN) could assist in mapping the nature of the striatal activity observed in Chapter 4 and Chapter 5 to activity within the direct and indirect subcortical pathways, as distinct from activity related to increased cortical input.

An additional limitation of the present study is the inability to demonstrate a causative relationship between activity in the striatum and activity in PFC regions, as opposed to concurrent but functionally isolated activity. This information is critical if the interactive model described above is to be verified. Advances in imaging technology now allow for the manipulation of stimulation parameters while patients undergo PET scanning. Such a design could be utilised to observe changes in frontostriatal activity as a function of STN stimulation, and hence striatal output. For example, in their study of verbal fluency in PD participants with bilateral STN implants, Schroeder et al. (2003) observed increased activity in task-relevant frontotemporal networks when stimulation was present, relative to when stimulation was ceased.

This information could also be obtained using effective connectivity analysis, which allows for study of the causal relationship between activation of different neuronal populations. Dynamic Causal Modeling (DCM) is an example of such a tool that additionally allows for observation of how this effective connectivity is modulated by experimental conditions (Friston, Harrison, & Penny, 2003), and its use in PD is emerging (Rowe, Hughes, Barker, & Owen, 2010). More recently, Stephan et al. (2008) developed a modified method of DCM, referred to as nonlinear DCM, which models how the connection between two neuronal regions is gated by activity in other regions. This technique could offer a valuable insight in the study of interaction between the

striatum, PFC, and posterior language regions, and may be able to address the hypothesised striatal gating mechanisms described above.

Another non-invasive neuromodulatory technique that has been gaining popularity in the study of neurocognitive processing is transcranial direct current stimulation (tDCS). Previous studies utilising tDCS in PD have demonstrated improvements in working memory when applied to the dlPFC (Boggio et al., 2006), and have even been linked to improved performance on Part B (verbal suppression) of the HSCT in healthy adults (Metzuyanim-Gorlick & Mashal, 2016). Utilisation of this technology in PD may assist in further elucidating the mechanics of frontostriatal networks and could represent a possible avenue for the development of intervention approaches. For example, Pereira et al. (2013) applied tDCS to the dlPFC in a PD cohort and observed increased functional connectivity in posterior verbal fluency networks. As described elsewhere (see Chapter 1), verbal fluency tasks require the interaction of linguistic processes with a number of cognitive control functions including verbal selection and suppression. If the Pereira et al. (2013) findings are the result of increased activity in the cognitive-linguistic control network outlined above (striatum → PFC → posterior language regions) then a similarly facilitative effect may be achieved for other language tasks with underlying verbal selection and suppression demands.

6.2.2 Compensatory Mechanisms in the Control of Language Production in Parkinson's Disease

In Chapter 2 and Chapter 3 it was predicted, based on converging evidence in the literature, that the PD cohort would experience difficulty in the execution of the studied task, as a result of disrupted signalling in task-relevant frontostriatal circuitry. However, both studies failed to identify significant differences between the PD and control groups in the measured aspect of semantic inhibition (with the exception of a minor disruption to error-processing in the PD group, evidenced in Chapter 3). As described above, we initially speculated that this discrepancy between our findings and those documented in the literature may relate to: (a) differences in the integrity of mechanisms subserving each task (this hypothesis, as discussed above, was dependent upon the notion of multiple, specialised inhibitory mechanisms); or (b) generalised heterogeneity of the PD population (for example, 8.5% of individuals with PD present with cognitive impairment in the first year of diagnosis, progressing to 47.4% after six years [Pigott et al., 2015]). This is particularly relevant given the mild-moderate level of disease severity and medicated status of the cohort included in the present series of studies. Given that the studies in Chapter 2 and Chapter 3 investigated behavioural performance only it was not possible to comment on underlying neural activity. However, subsequent analysis of behavioural and imaging data obtained in Chapter 4 and Chapter 5 revealed not only a similar lack of difference in behavioural performance between PD and control groups, but also provided a possible neural explanation for this finding.

As discussed above, contextually constrained verbal selection and effortful verbal suppression appeared to be maintained in these PD cohorts via underlying changes in neural activity. In Chapter 4, this was characterised by increased activity in task-relevant regions within frontostriatal pathways. In Chapter 5 the mechanisms of compensation were less apparent, though we speculated that hyperdopaminergic effects in regions as yet unaffected by disease pathology may have acted to focus neural activity (Cools, 2006). A compensatory increase in functional connectivity between task relevant regions may also have served to bolster behavioural performance in these cohorts. Indeed, hyperconnectivity has been observed in the PD population during the execution of cognitive-linguistic tasks, and presumed to be a means of facilitating function in regions subject to disease pathology (Gorges et al., 2015; Yang et al, 2016). Though confirmation of this possibility was beyond the scope of these investigations, it nevertheless bears consideration and represents a viable basis for future investigations.

Given that the cohort studied across all four chapters largely overlapped, with a large majority of the individuals in each study having participated in one or more investigations, it is suggested that the performance observed in Chapter 2 and, to a lesser extent (given the limited trials available for analysis), Chapter 3 may also have been maintained by underlying compensatory mechanisms. Furthermore, the disease severity of included participants across studies was, on average, Stage 1-2 on the Hoehn and Yahr (1967/2001) rating scale and maximum of Stage 3. In addition, all but one participant was taking dopamine-replacement medication at the time of testing. It is therefore proposed that, in the mild-moderate stages of the disease, individuals with PD are able to maintain age-appropriate cognitive-linguistic function as a product of compensatory neural mechanisms. These could include increased recruitment of task-relevant or novel regions (particularly in the contralateral hemisphere, as seen in Chapter 4), increased functional connectivity within task-relevant networks, or alternatively, preservation of function as a by-product of overmedication effects in pathologically unaffected regions.

This proposal may offer some explanation as to the degree of inconsistency present in literature concerning cognitive function and language production in PD (Monchi et al., 2016). It is argued that as the disease progresses, the capacity of the system to compensate for pathological loss of function decreases, and deficits in behavioural performance manifest when this capacity is lost, fatigued, or overloaded. Studies that have recruited cohorts with greater disease severity or increased disease duration may therefore be more likely to identify impairment, as neural compensation is no longer present or as effective in these individuals. In Chapter 3, though PD participants appeared to perform in a manner that was largely commensurate with controls, a decrease in task accuracy was observed when an error had been made on a previous trial. This finding may represent an example of compromised compensatory mechanisms, as a result of

additional cognitive loading associated with error processing (however note the highly speculative nature of this hypothesis, as outlined in Section 3.5).

Evidence of compensatory mechanisms similar to those described above have been documented in the motor realm (Appel-Cresswell, de la Fuente-Fernandez, Galley, & McKeown, 2010; Palmer, Li, Wang, & McKeown, 2010; Yu, Sternad, Corcos, & Vaillancourt, 2007), with some authors suggesting these processes are initiated even prior to clinical manifestation of the disease (Bezard, Gross, & Brotchie, 2003; Obeso, Rodriguez-Oroz, Lanciego, & Diaz, 2004). In the cognitive-linguistic literature, an increasing body of evidence also describes compensatory neural mechanisms facilitating cognitive performance in individuals with mild-moderate PD (Gerrits et al., 2015; Poston et al., 2016; Tinaz et al., 2008). In terms of language processing, limited studies have utilised both behavioural and imaging data and thus evidence of compensated performance is minimal (though see Grossman et al. [2003]), particularly as regards the processes of verbal selection and suppression. Our findings therefore represent a novel contribution to current understanding of the nature and time course of linguistic impairment in PD.

If the hypothesis regarding compensatory neural mechanisms supporting cognitive-linguistic processing in early stage PD is to be advanced, future investigation must consider the integrity and nature of these mechanisms over time. Such investigation is particularly critical given the burden of mild cognitive impairment (MCI) in this population. MCI occurs in PD with a prevalence of approximately 17-30%, and can be detected even within one to two years of initial disease diagnosis (Aarsland, Brønnick, & Fladby, 2011). Furthermore, the presence of significant cognitive impairment is linked to increased experience of disability and functional impairment of day-to-day activities (Leroi et al., 2012), and greater likelihood of eventual dementia (Janvin, Larsen, Aarsland, & Hugdahl, 2006). It may be that those individuals who present with MCI, particularly at diagnosis or in the early stages of the disease, may do so as a result of inadequate or absent compensatory mechanisms. Future investigations should therefore consider mapping the onset of neural compensation and associated pathological or neurological triggers, longitudinal stability or effectiveness of the mechanism, capacity to adapt and reconfigure as the disease progresses, and factors associated with the failure or declining efficiency of compensation. Such data could be collected in longitudinal cohort studies or cross-sectional studies of individuals sampled across early to advanced stages of the disease. An additional line of investigation could also identify predictors of compensatory capacity such as age of disease onset, rate of progression, pre-morbid structural and functional neuroanatomical profiles, premorbid linguistic and cognitive skill, and lifestyle factors such as substance use and physical health (similar to studies investigating predictors of successful cognitive ageing e.g., see Depp & Jeste, [2006] and Yaffe et al. [2009]).

6.2.3 Specialised vs. Unitary Mechanisms of Inhibition

In Chapter 1 it was postulated that inhibitory processes may be subserved by a number of domain-specific mechanisms, and an example was proffered whereby the inhibitory processing of visual-semantic information was suggested to be intact in PD relative to impaired inhibition of lexical-orthographic information. As an alternative, the possibility of endogenous vs. exogenous specialisation was considered, making a distinction between those mechanisms subserving the processing of internally generated representations and those subserving the processing of externally available stimuli. However, both of these accounts were not able to adequately account for the results of Chapter 2 and Chapter 3. The unrelated sentence completion condition that featured in both of these tasks was assumed to require the inhibition of an internally represented prepotent response, and internal generation of an alternative, unrelated response. The specialised-mechanisms hypothesis, both in terms of impaired lexical-orthographic processing or impaired endogenous processing, would therefore predict deficits on this task in the PD group. However, results of both studies demonstrated comparative performance with controls in terms of the ability to suppress the strongly prepotent response in favour of an unrelated alternative, disproving both accounts. It is noted that the small cohort studied here was mildly-moderately affected by the disease, and that imaging results appeared to suggest that compensatory mechanisms were at play. Future investigations may therefore consider returning to these hypotheses, utilising larger sample sizes and a number of inhibitory measures across behavioural domains, in order to establish whether such differentiation may occur as the disease progresses.

6.3 Additional Limitations and Future Directions

A significant limitation of the present series of studies has been the inability to differentiate between observations related to the disease process, and those related to the effects of dopaminergic medication. This issue has been discussed in greater detail in Chapters 2 - 5 with reference to the specific mechanisms implicated by their unique study design. Broadly however, a large body of evidence demonstrates the modulatory effect of dopamine upon semantic processing (Angwin et al., 2009; Angwin et al., 2006; Arnott et al., 2011; Pederzolli et al., 2008; Peran et al., 2013), and its differential effect upon cognitive functions (Cools, 2006; Cools et al., 2001; Rinne et al., 2000; Rowe et al., 2008). As discussed in Chapter 5, in the earlier stages of disease progression dopaminergic medication can induce a hyperdopaminergic state in frontostriatal pathways that are as yet unaffected by disease processes (Cools, 2006; Cools & D'Esposito, 2011). In Chapter 5 it was suggested that the interaction of this hyperdopaminergic state together with the neuromodulatory effect of dopamine in the semantic system could account for the altered neural activity observed in the PD group in this study. It is apparent that testing of participants both on and off dopaminergic medication is critical to understanding both the mechanisms of verbal selection

and suppression, as well as their disruption and potential treatment in disorders such as PD. Future investigations may also seek to administer a simple measure of reaction time, such as a finger-tapping test, before and after completion of the language task in order to provide an indirect indication of response to medication (similar to Angwin, Chenery, Copland, Murdoch, & Silburn, 2007).

It is also noted that the PD cohort included in the present study were only generally defined in terms of their neurological characteristics. Severity was only described based on subjective Hoehn and Yahr (1967/2001) rating and self-reported disease duration, and specific symptomatology was not described. In future investigations it may be of value to develop a more detailed profile of each individual's disease characteristics including sub-typing by primary motor symptom (e.g., bradykinesia, tremor, rigidity) or side-of-onset. This approach has been employed by previous authors and some have demonstrated an association between such features and altered disease progression or onset of cognitive impairment (De Letter, Van Borsel, & Santens, 2011; Katzen, Levin, & Weiner, 2006; Reijnders, Ehrt, Lousberg, Aarsland, & Leentjens, 2009; Tremblay, Achim, Macoir, & Monetta, 2013). Such information may provide some insight as to which individuals may be more likely to develop and or/compensate for cognitive-linguistic impairment, and reveal possible links with pathophysiology. Inclusion of a measurement indicating degree of motor impairment would also aid in indirectly establishing the relationship between cognitive impairment, utilisation of compensatory mechanisms, and degree of dopaminergic depletion.

Finally, with reference to the aim of elucidating the role of the subcortex in spoken language production, it must be said that PD does not represent an idealistic model for investigation. Disease-related changes in neurovascular coupling may be present in this population, which can confound interpretation of the BOLD signal when fMRI analysis is employed (D'Esposito, Deouell, & Gazzaley, 2003). Furthermore, though the primary characteristic of PD is the depletion of dopaminergic projection within nigrostriatal and, to a lesser extent, mesocortical pathways (Jellinger, 1991), numerous peripheral pathologies are also associated with the disease. These can include widespread neurochemical deficiencies and Lewy-related pathologies (Bartels & Leenders, 2009; Braak & Del Tredici, 2008; Braak et al., 2004), all of which may contribute to cognitive symptoms (Biundo, Weis, & Antonini, 2016). Furthermore, structural atrophy of the frontal cortex and subcortical structures is documented with disease progression (Burton, McKeith, Burn, Williams, & O'Brien, 2004; Morgen et al., 2011; Sterling, Lewis, Du, & Huang, 2016) and has also been linked to cognitive decline (Hanganu & Monchi, 2016). More specifically, a recent VBM study identified a link between decreased grey matter density in the frontal lobes and performance on the suppression component of the HSCT in individuals with PD (O'Callaghan et al., 2013a).

Future investigation of subcortical language processing mechanisms should therefore strive to amass converging evidence from a variety of healthy and clinical populations with varying pathological profiles including Huntington's disease, Tourette's syndrome, Binswanger's disease and subcortical stroke or lesion. Furthermore, given the older age of onset of many of these conditions and the research principle of utilising age-matched controls for such studies, investigations in younger populations may provide additional insight into age-related changes versus PD-related deficits. This may be particularly valuable in delineating normal function from normal-ageing function, as changes in hemispheric organisation and utilisation of neural circuits have been widely correlated with neurotypical ageing (Berlingeri et al., 2013; Cabeza, 2002; Reuter-Lorenz & Cappell, 2008).

6.4 Concluding Remarks

The present series of studies has demonstrated that the control of spoken language production, through verbal selection and suppression, appears to be subserved by basal ganglia and PFC structures. It has been proposed that language control may be best accounted for by integrating current models of cortical-subcortical control (namely, Miller & Cohen [2001], and Chatham et al. [2014]) in which striatal activity acts to gate both the updating of contextual representations held in the PFC and the subsequent selection of specific representations to bias activity in posterior language regions, facilitating the production of a task-relevant response. Future investigations should endeavour to employ advanced imaging and non-invasive neuromodulation techniques in larger PD cohorts, as a means of further refining this model and confirming the causal relationship between striatum, PFC, and posterior language regions. Testing of participants on and off levodopa medication will further advance understanding of how this critical neurotransmitter acts to modulate the interaction between elements of this model in different stages of the disease. It has also been demonstrated that in the early stages of the PD, compensatory neural mechanisms may act to preserve behavioural performance in the face of declining frontostriatal function. This finding may go some way toward explaining the considerable heterogeneity identified in the literature concerning the onset, nature, and severity of cognitive decline in this population. Determining the neurobehavioural predictors of neural compensation, and mapping the action of these mechanisms over time will inform prognosis and management of patients.

Ultimately, this thesis has contributed to greater understanding of subcortical language processing and has provided evidence of this system's capacity to temporarily offset the behavioural effects of neurodegenerative pathology. This information will be critical to the development of effective cognitive-behavioural or neurological interventions not only in PD, but other clinical populations with associated subcortical pathology.

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