Lexical-semantic inhibitory mechanisms in Parkinson’s disease as a function of subthalamic stimulation

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Abstract

Inhibitory control may be affected by Parkinson’s disease (PD) due to impairment within the non-motor basal ganglia-thalamocortical circuits. The present study aimed to identify the effects of chronic stimulation of the subthalamic nucleus (STN) on lexical-semantic inhibitory control. Eighteen participants with PD who had undergone surgery for deep brain stimulation (DBS) of the STN, completed a picture-word interference (PWI) task and the Hayling test in on and off stimulation conditions. The results of PD participants were compared with 21 non-neurologically impaired control participants. PD participants performed no differently from controls on the PWI task, and no significant differences between on and off stimulation conditions were revealed, therefore suggesting that PD participants are not impaired in lexical-semantic interference control. In contrast, in the off stimulation condition, PD participants had significantly delayed reaction times and increased errors on the inhibition section of the Hayling test compared with the STN stimulation condition and control participants. These results suggest that PD patients are impaired in aspects of inhibitory control that are dependent on behavioural inhibition (such as the suppression of prepotent responses) and selection from competing alternatives without the presence of external cues. Furthermore, STN stimulation acts to restore these behavioural inhibitory processes.

Keywords: Deep brain stimulation; Basal ganglia; Semantic interference; Hayling test; Picture-word interference

1. Introduction

Deficits in inhibitory processes including interference control and behavioural inhibition have commonly been described in participants with Parkinson’s disease (PD). For example, PD participants have exhibited altered patterns of performance on negative priming tasks (Filoteo & Maddox, 1999; Filoteo, Rilling, & Strayer, 2002; Grande et al., 2006), flanker tasks (Seiss & Praamstra, 2006; Wylie, Stout, & Bashore, 2005), and Stroop colour-word interference tasks (e.g., Brown & Marsden, 1988; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Zgaljardic et al., 2006), suggesting that PD affects interference control, and is associated with a disruption in the ability to resolve conflict in the presence of distractors. Studies investigating behavioural inhibition, such as Go no-go (GNG) and stop-signal tasks, have also reported deficits in inhibitory processes in PD (Bokura, Yamaguchi, & Kobayashi, 2005; Franz & Miller, 2002; Gauggel, Rieger, & Feghoff, 2004). Similarly, PD patients perform differently from controls in inhibitory control during the processing of lexical-semantic representations.

Lexical-semantic inhibitory processes have been shown to differ between healthy controls and PD participants in lexical decision semantic priming paradigms. Semantic priming tasks usually entail the presentation of a prime word (e.g., table) followed by either a semantically related target (e.g., chair), semantically unrelated target (e.g., dog), or non-word target (e.g., yope). A lexical decision is then required on the target presentation. For real word targets, reaction times (RTs) are usually significantly faster for related word pairs compared with unrelated word pairs. This effect is referred to as
Mari-Beffa, Hayes, Machado, and Hindle (2005) explored inhibitory control in PD in a semantic priming paradigm where primes and probes were never directly related, but distractor words that were presented around the prime display differed in semantic relatedness. Therefore, for the purpose of this task, inhibitory control was a measure of the ability to inhibit task irrelevant lexical-semantic information. Mari-Beffa et al. reported a lack of lexical-semantic inhibitory control in participants with PD who exhibited significant semantic priming (i.e., a distractor word in the prime display facilitated RTs to a semantically related target in the probe display), whereas controls did not. This study suggests that PD participants may have difficulty inhibiting task irrelevant lexical-semantic information. Mari-Beffa et al. (2005). Similarly, the results of Copland’s (2003) study exploring the semantic priming of ambiguous word pairs in PD participants, suggests that difficulties in meaning frequency-based semantic inhibition may be evident in PD.

Generally, semantic priming is a measure of the automatic spread of activation of lexical-semantic representations (Neely, 1991). However, when the time between the offset of the prime and the onset of the target (i.e., stimulus onset asynchrony; SOA) is extended to around 1000 ms, attentional processes are said to be involved. For example, with increased time between prime and target displays, primes can facilitate RTs via the spread of activation to semantically related targets, however, when primes are semantically unrelated to targets, RTs may be delayed due to the need to overcome the activation of related targets to enable the processing of unrelated targets (i.e., inhibition; Neely, 1991).

While automatic semantic priming effects in PD have generally been comparable with control participants, impaired semantic priming at long SOAs or when attentional semantic processing is invoked, have indicated impaired processing in PD participants compared with controls (Angwin, Cherney, Copland, Murdoch, & Silburn, 2003; Arnott, Cherney, Murdoch, & Silburn, 2001; Spicer, Brown, & Gorell, 1994). These studies provide further support for impaired inhibition of lexical-semantic processes in PD.

PD participants have also exhibited deficits in a task which is more reliant on the generation of internal strategies and behavioural inhibition to overcome lexical-semantic conflict. For example, Bouquet, Bonnaud, and Gil (2003) showed that patients with PD display difficulties in response suppression on the Hayling Sentence Completion Test (Burgess & Shallice, 1997). The Hayling task consists of two subtests. In Hayling A, participants are required to complete a series of sentences with the last word missing and respond with a word that adequately completes the sentence. Hayling B requires participants to complete another series of incomplete sentences, but instead to respond with a word that is completely unconnected to the sentence. Hayling A is therefore a measure of response initiation and Hayling B measures response suppression. The Hayling task differs from other inhibitory paradigms described previously as participants are required to internally generate strategies to provide an alternative response. That is, GNG and stop-signal tasks do not require the generation of an alternative response, but rather the ability to withhold a response. Also, whilst stroop paradigms do require the generation of an alternative response, the correct response is provided in the stimulus display and is not required to be internally generated (de Zubicaray, Zelaya, Andrew, Williams, & Bullmore, 2000). The RT delay in Hayling B for PD patients compared with controls in Bouquet et al.’s study, suggest that PD patients are delayed in the suppression of dominant lexical-semantic information in order to internally generate a novel response.

Deficits in inhibitory control in PD may be explained by the neural underpinnings of this disease. PD is caused by the degeneration of dopamine neurons in the substantia nigra pars compacta (Albin, Young, & Penney, 1989; Mink, 1996; Young & Penney, 1998). The degeneration of dopamine impacts upon neural activity within the basal ganglia-thalamocortical circuitry. The basal ganglia-thalamocortical circuits consist of both motor and non-motor circuits with the three non-motor circuits involving the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and the lateral orbitofrontal cortex (LOFC; Alexander, DeLong, & Strick, 1986). The basal ganglia-thalamocortical circuits can be further differentiated into a direct (cortex → striatum → internal segment of the globus pallidus/substantia nigra pars reticulata → thalamus → cortex), and an indirect pathway (cortex → striatum → external segment of the globus pallidus → subthalamic nucleus; STN → internal segment of the globus pallidus/substantia nigra pars reticulata → thalamus → cortex; Alexander et al., 1986). In relation to motor control, the direct pathway is thought to play a role in the execution of movement and the indirect pathway is suggested to be involved in the suppression of unwanted movement (Mink, 1996; Young & Penney, 1998) or the suppression of competing responses (Frank, 2006). Further, it has been suggested that in relation to response selection, the direct pathway is associated with the registration of contexts and the indirect pathway is associated with context negation (Lawrence, Sahakian, & Robbins, 1998). This observation could indicate a potential role of the indirect pathway in the inhibition of dominant or inappropriate responses and the generation of responses in the presence of competing information.

The effects of deep brain stimulation (DBS) of the STN in people with PD on tasks requiring inhibitory control also provide insight into the role of the specific indirect basal ganglia-thalamocortical circuit in inhibitory processing. Stroop tasks provide the largest body of evidence for a deficit in inhibitory processes during STN stimulation in PD. Whilst inconsistencies have been reported in the literature regarding stroop interference performance with STN stimulation, the majority of studies have pointed towards delayed RTs or increased errors during STN stimulation compared with preoperative or off stimulation conditions (Alegret et al., 2001; Dujardin, Defevbre, Krystkowiak, Blond, & Deste, 2001; Jahanshahi et al., 2000; Moretti et al., 2003; Schroeder et al., 2002; Smeding et al., 2005; Smeding et al., 2006; Witt et al., 2004). Other studies have reported no differences in stroop interference performance compared with preoperative or off stimulation performance (Ardouin et al., 1999; Pillon et al., 2000; Romito et al., 2003). Changes in stroop
performance with STN stimulation suggests STN involvement in the regulation of inhibitory response processes via the modulation of basal ganglia-thalamocortical circuits.

Schroeder et al. (2002) investigated neural correlates of the effects of STN stimulation on stroop performance in a PET study. STN stimulation compared with the off stimulation condition was associated with a decline in stroop RTs and a decrease in regional cerebral blood flow (rCBF) in the right ACC and ventral striatum. Further, an increase in rCBF within the left angular gyrus was associated with STN stimulation during the stroop task and interpreted to reflect a difficulty in the suppression of word reading. Therefore, declines in performance on the stroop task as a consequence of STN stimulation, appear to be caused by a disruption of non-motor basal ganglia-thalamocortical circuits (specifically the ACC circuit) and difficulties in suppressing the dominant response (associated with left angular gyrus activity).

There is also evidence that this modulation of basal ganglia-thalamocortical circuits may impact upon lexical-semantic processes. Specifically, the most commonly reported cognitive sequelae of STN DBS have been declines in verbal fluency performance (e.g., De Gaspari et al., 2006), showing evidence for the involvement of processes requiring the retrieval of lexical-semantic representations with a strong executive component. Executive processes in verbal fluency tasks are proposed to include the initiation of responses as well as the suppression of active representations in order to generate a new word (Burgess & Shallice, 1996; Perrett, 1974; Ruff, Light, Parker, & Levin, 1997). The initiation and suppression mechanisms in verbal fluency tasks are difficult to isolate (Burgess & Shallice, 1996), and it is therefore unknown as to which mechanisms are susceptible to deficit as a result of STN stimulation. More recently, semantic priming with short and long SOAs has been investigated as a function of STN stimulation in PD participants. Castner et al. (2007) found comparable semantic priming effects in PD participants in on and off stimulation conditions and compared with control participants at the short SOA, yet semantic priming effects differed as a function of STN stimulation in the long SOA condition. Specifically, there was an absence of semantic priming effects in the off stimulation condition, but when STN stimulation was applied, semantic priming effects were comparable with control participants. These results suggest that lexical-semantic inhibitory processes may be compromised in PD, yet restored as a consequence of modulation of basal ganglia-thalamocortical circuits via STN stimulation.

The purpose of the current study is to isolate inhibitory lexical-semantic mechanisms in PD and to also investigate the effects of STN stimulation (and therefore the modulation of basal ganglia-thalamocortical circuits) on specific inhibitory lexical-semantic mechanisms.Lexical-semantic inhibitory processes can be measured in the previously described Hayling task, where participants are required to internally generate a novel response. Additionally, picture-word interference (PWI) tasks (a variant of the stroop paradigm), where participants are required to name picture stimuli in the presence of competing distractor words, also require lexical-semantic inhibitory control. PWI tasks, whilst not so dependant on the formation of strategies and the generation of novel responses as required in the Hayling test, allow for the manipulation of the degree of interference at the lexical-semantic/conceptual level. Specifically, the degree of semantic relatedness between the picture stimuli and distractor words can influence the degree of lexical-semantic conflict.

It is predicted that PD participants will show impairment on the Hayling task, consistent with the results of Bouquet et al.'s (2003) study. If STN stimulation acts to modulate impaired non-motor basal ganglia-thalamocortical circuits, then impaired behavioural inhibitory processes in the Hayling task may be restored as a result of STN stimulation. It is less clear as to degree that non-motor basal ganglia-thalamocortical circuits are involved in lexical-semantic interference control as measured by a PWI paradigm, given the varied results of Stroop studies as a function of STN stimulation, and the absence of previous studies investigating PWI in PD.

2. Methods

2.1. Participants

Eighteen patients (13 males) diagnosed with PD who had received the implantation of permanent DBS electrodes into the subthalamic nucleus (see Coyne et al., 2006 for further details regarding the surgical technique), were included in the present study (refer to Table 1 for participant information). PD participants were tested at least four months post-surgically and were considered to have stable stimulator settings by their neurologist. Each participant was tested with their stimulators turned on and again with their stimulators turned off. The order of test condition was counterbalanced, and at least 6 weeks separated the two testing sessions. For the off stimulation condition, the stimulators were turned off for at least one hour prior to the commencement of assessments. Each participant was tested whilst taking their usual medication.

Twenty-one non-neurologically impaired participants (13 males) were recruited to act as controls. The average age and years of education for the controls was 62.3 (range = 49–74) and 13.3 (range = 8–21) years respectively, and these were not significantly different from the PD participants (p = .79 and .82). All control participants were right handed, had no history of neurological impairment, were not taking any medication deemed to affect neurological functioning, had no self-reported hearing loss, and had self-reported normal or corrected-to-normal vision.

This study was approved by the appropriate ethics committees and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants gave informed consent prior to their inclusion in this study.

2.2. Picture-word interference task

2.2.1. Apparatus

Experimental stimuli were presented on a computer using E-prime v1.1 (Psychology Software Tools, 2002). Participants’ response latencies were recorded with millisecond accuracy, using the voice key from PST Serial Response Box model 200a (Psychology Software Tools). The stimuli were displayed on a computer monitor set to 640 × 480 bit-depth resolution. Black line drawings were presented on a white square of 283 × 283 pixels in the centre of the screen. Black text was presented in Helvetica 36 point font.

2.2.2. Design and stimulus materials

A picture-word interference task was designed, where participants were required to name a series of pictures with distractor words being presented simultaneously. Naming latency was the dependent variable, with the type of distractor word (unrelated, high association and low association) acting as a within-subject factor.

Forty pictures were selected from The International Picture Naming Project (IPNP, see Szekely et al., 2004 for more information) with the majority of pictures originating from Snodgrass and Vanderwart (1980). Pictures belonged
<table>
<thead>
<tr>
<th>Participant</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Education (years)</th>
<th>Handedness</th>
<th>Disease duration (years)</th>
<th>Severity (H and Y)</th>
<th>UPDRS III on score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Levodopa medication (mg/day)</th>
<th>Stimulator settings</th>
<th>Pulse width L/R (μs)</th>
<th>Frequency L/R (Hz)</th>
<th>Amplitude L/R (V)</th>
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<td>1</td>
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<td>M</td>
<td>15</td>
<td>R</td>
<td>15</td>
<td>3</td>
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<td>60/60</td>
<td>160/160</td>
<td>3.0/3.2</td>
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<td>2</td>
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<td>7</td>
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<td>0</td>
<td>60/90</td>
<td>130/160</td>
<td>2.3/3.6</td>
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<tr>
<td>3</td>
<td>51</td>
<td>F</td>
<td>10</td>
<td>R</td>
<td>5</td>
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<td>6</td>
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<td>4</td>
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<td>R</td>
<td>17</td>
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<sup>a</sup> On stimulation and on medication.

<sup>Note</sup>: H and Y, Hoehn and Yahr; UPDRS, unified Parkinson’s disease rating scale; L, left; R, right.
to the following semantic categories: musical instruments, vehicles, clothing, animals, body parts, furniture, fruits and vegetables, insects, weapons, and tools.

Each picture was paired with a semantically unrelated distractor word and half of the pictures were re-paired with a categorically related, highly associated (HA) distractor word (e.g., “dog” as a distractor for a picture of a cat) and the remaining half were re-paired with a categorically related, low association (LA) distractor word (e.g., “tuba” as a distractor for a picture of a violin). Thus there were 40 unrelated distractor items, 20 HA and 20 LA distractor items. The degree of association between the distractors and the picture stimuli was derived from word association norms (Kiss, Armstrong, Milroy, & Piper, 1973; Moss & Older, 1996). In these normative studies, participants were asked to respond to stimulus words with the first word that came to mind. Word association values for the distractors were therefore recorded as a percentage value of participants who responded to stimuli with a particular item. HA distractors had a mean association value of 17% (S.D. = 11.89) and LA distractors had a mean association value of 1% (S.D. = .44). The degree of relatedness between distractor words and picture stimuli was manipulated to assess the degree of semantic interference (delayed RTs in the presence of related distractor stimuli) or semantic facilitation (speeded reactions times in the presence of unrelated distractor stimuli) that is occurring at the lexical-semantic level as opposed to response level conflict. That is, if there is greater interference for HA compared with LA, then it can be assumed that the degree of relatedness at the lexical-semantic level is impacting upon inhibitory processes.

Distractor words were either superimposed within the picture stimuli, or presented in a random location around the picture stimuli. As each picture stimulus was presented with an unrelated distractor as well as a related distractor, the location of the distractor remained constant for each specific picture.

Naming latency and name agreement norms for the picture stimuli were obtained from the IPNP. The picture stimuli that were paired with HA distractors were not significantly different from the picture stimuli that were paired with LA distractors with respect to naming latency (t(58) = −1.54, p = .13) and name agreement (t(58) = −0.39, p = .70). Imageability, concreteness, and frequency norms for all distractors were obtained from the MRC Psycholinguistic Database (The University of Western Australia, 1987). The unrelated, HA, and LA distractors did not significantly differ in imageability (F(2,60) = 1.54, p = .22), concreteness (F(2,59) = 0.39, p = .68), or frequency (F(2,70) = 1.34, p = .27). Additionally, the unrelated, HA, and LA distractors did not significantly differ in written word length (F(2,77) =0.88, p = .42). All distractor words were phonologically dissimilar to target words. Finally, an additional eight pictures (paired with either unrelated, HA, or LA distractors) were included in the stimulus set to act as non-experimental buffers.

2.2.3. Procedure

Prior to the commencement of the PWI task, all participants completed a familiarisation phase, where stimulus pictures were presented without the presence of distractors. Participants were required to name the pictures and were corrected if an incorrect name was produced. Although the picture stimuli were considered to have a high percentage of name agreement (M=94, S.D. = 8.33), participants occasionally produced names that were synonymous with the required targets (e.g., “sofa” for a picture of a couch), or visually similar to the required targets (e.g., “mouth” for a picture of teeth). If this occurred, they were advised of the required target name for the purpose of this task. Each picture was presented to the participant on one occasion and if a participant produced target names with at least 90% accuracy, they proceeded to the experimental phase of the task. If less than 90% accuracy was achieved, all pictures were presented for a second time.

For the experimental phase of this task, participants were informed that they would see the same stimulus pictures as seen in the familiarisation phase, but that they would now appear with a distractor word presented around the picture. They were asked to name the pictures as quickly and accurately as possible, whilst ignoring the distractor. Participants were reminded to use the same target names used in the familiarisation phase.

Each trial commenced when the participant pressed a mouse button. A fixation cross was then presented for 700 ms followed by a blank screen for 300 ms. The picture stimuli, along with the distractor word would then appear on the screen simultaneously (i.e., the stimulus onset asynchrony was 0 ms) until the voice key triggered a response. Incorrect responses and voice key recording errors were manually scored throughout the duration of the experiment.

The order of experimental trials was randomised on each presentation; however, as each picture stimulus was repeated for the two distractor conditions, the order of each distractor condition was counterbalanced. Therefore, on each occasion, half of the participants were presented with a picture paired with an unrelated distractor first and then saw the same picture paired with a related distractor, and the remaining half would see the related condition followed by the unrelated condition. At least 22 trials separated the first and second presentation of the picture stimuli.

Experimental trials were divided into four blocks of 20 trials, separated by three short breaks. Two non-experimental buffers were presented prior to the commencement of each of the four blocks. Completion of the entire experiment (including the familiarisation phase) took a total of approximately 20 min to complete.

2.3. The Hayling test

The Hayling test (Burgess & Shallice, 1997) consists of 30 sentences with the last word omitted from each sentence. In Hayling A (response initiation), the participants were required to respond to half of the incomplete sentences with a word that accurately completed the sentence (e.g., the old house will be torn... “down”). Participants were encouraged to respond as fast as they could. The time between the offset of the last word presented by the test administrator and the onset of the participant’s response was manually recorded with a stopwatch along with the participant’s response. RTs were measured as stated in the Hayling test manual, where whole second RTs were recorded and not rounded up. For example, RTs between 0 and 0.99 s were recorded as 0 and RTs between 1 and 1.99 were recorded as 1, and so on.

In the second section of the Hayling test (Hayling B), the participants were presented with the remaining 15 incomplete sentences that were matched to the Hayling A sentences with respect to completion norms (Bloom & Fischer, 1980). In response to the incomplete sentences in Hayling B, participants were required to produce a word that was completely unconnected to the sentence in every possible way (e.g., the captain wanted to stay with the sinking... “newspaper”). Again, RTs and participant’s responses were recorded.

Responses in Hayling B were also scored in relation to the compatibility of the response with each sentence. For example, if a participant responded with a word that adequately completed the sentence or was closely related, this was scored as a category A error. During the administration of Hayling B test items, if a participant responded with a category A error, they were informed of the relatedness of their response and reminded of the task instructions. Alternatively, if the response was loosely connected (e.g., the captain wanted to stay with the sinking... “helicopter”), this was scored as a category B error. A combined error score (Hayling C) was then derived based on category A and B errors.

Finally, to determine the degree in which correct responses in Hayling B were reliant on the internal generation of strategies, all correct Hayling B responses were scored in relation to strategy use. Specifically, responses that were semantically related to responses in the previous trial, responses that consisted of the naming of objects located around the room (e.g., if the testing location was in a hospital setting, responses such as bed and nurse, would fall under this strategy), and responses that consisted of a combination of semantically related and object naming, were all classed as strategic responses. The remaining correct responses were considered to be non-strategic.

Prior to the commencement of Hayling A and Hayling B, participants received two practice trials. The total time to complete both sections of the Hayling test was approximately 7 min.

3. Results

3.1. Picture-word interference task

3.1.1. RT analyses

RT data was excluded from RT analyses if the participant’s response resulted in an error (2.89% of data), if RTs were less than 100 ms or greater than 3000 ms (.55% of data), or if the
Voice key was incorrectly activated (6.82% of data). Furthermore, RTs that were greater or less than two standard deviations from the distractor relatedness condition mean for each participant were removed from data analyses (4.9% of data). The mean RT data for each distractor condition and semantic interference/facilitation effects are presented in Table 2.

Linear Mixed Model (LMM) analyses were conducted on RT data with differences in session, namely PD versus controls and on and off stimulation for PD participants, as between and within-subject terms respectively. Distractor relatedness (HA, LA, and unrelated distractors) was also a within-subjects fixed factor. As the picture stimuli were repeated for related and unrelated conditions, the order of presentation for each picture acted as a covariate. RT subject variations, in addition to subject variation across sessions for PD participants, were treated as random factors.

The LMM results revealed a significant main effect for PD versus control participants ($F(1,37) = 8.07, p < .005$), which reflected an average RT delay for PD participants (in both on and off stimulation conditions) compared with controls. The effect of stimulation (corrected for session order) was significant ($F(1,1020) = 5.61, p < .05$) reflecting an overall delay in naming latencies for PD participants in the off stimulation condition compared with the on stimulation condition. The main effect for distractor relatedness was highly significant ($F(2,2820) = 9.68, p < .001$). Pairwise comparisons were made between the estimated marginal means for HA and unrelated distractors, and LA and unrelated distractors in order to measure semantic interference (i.e., slower RTs in the presence of a related distractor word) or semantic facilitation (i.e., faster RTs in the presence of a related distractor word) at each distractor level. A highly significant semantic interference effect (an average 36.98 ms) was evident for HA distractors ($p < .001$), and the semantic interference effect for LA distractors (an average of 1.34 ms) failed to reach statistical significance ($p = .87$). There was no interaction between session and distractor relatedness ($F(4,1016) = .87, p > .05$), indicating RTs for controls and PD participants in off and on stimulation conditions, did not differ as a function of distractor relatedness.

In summary, RT analyses for the PWI task revealed significant semantic interference under the HA distractor condition, but not the LA distractor condition compared with unrelated distractors. The magnitude of semantic interference effects was no different for PD participants (on and off stimulation sessions) and controls. RTs for PD participants however, were overall slower compared with control participant RTs.

### 3.1.2. Error analyses

Errors were classed as responses that differed from the target in any way. These included responses that consisted of distractor word reading errors, or responses that deviated from both the picture stimuli and distractor words. The percentage of errors across each distractor condition for PD and control participants is presented in Fig. 1.

LMM analysis on the error data was comparable to above-described RT data. Specifically, a main effect for relatedness reached significance ($p < .001$) where pairwise comparisons revealed significantly greater number of errors under the HA condition when compared with the unrelated condition (an average difference of 3.7%). The main effect for session and interaction between session and relatedness ($p > .05$) failed to reach significance.

### 3.2. The Hayling test

Analyses for normality and homogeneity of variance revealed that the RT and error data for the Hayling test were significantly

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1. The effect of distractor relatedness was also confirmed with separate repeated measures analysis of variance on the subject means for control participants ($p = .016$) and there was a marginal condition effect for PD participants ($p = .051$).
2. This semantic interference effect for HA distractors compared with unrelated distractors was also confirmed with separate repeated measures analysis of variance on the item means for PD participants ($p = .044$) and there was a marginal interference effect for HA distractors compared with unrelated distractors for control participants ($p = .057$).
positively skewed. All further analyses were therefore conducted using non-parametric statistics.

3.2.1. RT analyses

Hayling RT and error data for the PD participants was analysed separately from controls using Wilcoxon Signed Ranks Test, with session (on versus off stimulation) as a within subjects factor. RT dependent variables were Hayling A RT (as a measure of speed of response initiation), Hayling B RT (as a measure of speed of response inhibition), and Hayling B minus Hayling A RTs (Hayling B–A) to account for the impact of response initiation delays on response inhibition times. The average RTs for Hayling A, Hayling B, and Hayling B–A for PD participants and controls are presented in Table 3.

The Hayling RT data revealed speeded RTs in on stimulation conditions for Hayling B (an average difference of 21 s) and Hayling B–A (an average difference of 23.23 s) compared with the off stimulation condition, suggesting that response inhibition was improved with STN stimulation. This was reflected in statistical analyses where significant differences were found in overall Hayling C error scores \( (p < .05) \) and Hayling B RT (as a measure of speed of response initiation) delays on response inhibition times. The isolation of category A and category B errors identified a marginally significant difference in category A errors \( (p = .052) \), but no difference in category B errors \( (p > .05) \) suggesting that response initiation times were significantly faster for controls than PD participants (by an average of 5.46 s). There was no difference in Hayling B RT \( (p > .05) \) or Hayling B–A RTs \( (p > .05) \) between controls and PD participants when comparing PD off stimulation with controls, Hayling B and Hayling B–A RTs were significantly slower for PD participants \( (p < .05) \). Therefore, STN stimulation appears to improve response inhibition times in PD participants to a similar level as controls.

3.2.2. Error analyses

Hayling C converted error scores were calculated by totalling the number of category A and category B errors, with category A errors receiving more weighting than category B errors (refer to Burgess & Shallice, 1997 for further information). The breakdown of category A and category B errors are presented in Table 3.

To summarise, STN stimulation in PD participants improved Hayling response inhibition RTs and errors to a level which was comparable with age and education matched non-neurologically impaired controls. With respect to response initiation times, STN stimulation resulted in a reduction in the number of category B errors \( (p < .05) \), but not category A errors \( (p > .05) \). The Kruskal–Wallis test was applied to the error data comparing control participants with the different PD stimulator conditions separately. When comparing controls with the on stimulation condition, a mean difference of .06 in the number of Hayling C errors was not significant \( (p > .05) \). However, when compared with the PD off stimulation condition, significant differences were found in overall Hayling C error scores \( (p < .05) \), reflecting a larger number of errors in PD participants when off stimulation \( (p > .05) \) compared with controls \( (p = .052) \). The isolation of category A and category B errors, identified a marginally significant difference in category A errors \( (p < .05) \), but no difference in category B errors \( (p > .05) \). Therefore, in comparison to control participants, PD participants without STN stimulation produced a larger number of category A errors.

3.2.3. Hayling strategy use

Finally, correct responses on Hayling B were separated into responses that were generated based on internally generated strategies (e.g., responses that were semantically related to responses in the previous trial, or responses where participants named items located around the room) versus non-strategic responses. PD participants in the on stimulation condition, generated an average of 5.67 (S.D. = 3.66) strategic responses compared with 4.94 (S.D. = 4.02) in the off stimulation condition. Control participants produced an average of 5.33 (S.D. = 3.53) responses that were considered to be the result of internally generated strategies. Statistical analyses revealed no significant differences in the number of strategic responses for PD on stimulation versus off stimulation conditions \( (p > .05) \). PD on stimulation compared with controls \( (p > .05) \), and PD off stimulation compared with controls \( (p > .05) \). To summarise, STN stimulation in PD participants improved Hayling response inhibition RTs and errors to a level which was comparable with age and education matched non-neurologically impaired controls. With respect to response initiation times, STN stimulation resulted in a significant improvement \( (z = 2.07, p < .05) \) revealing that less errors were made when PD participants were receiving STN stimulation \( (M = 2.94, S.D. = 3.57) \) compared with the off stimulation condition \( (M = 6.39, S.D. = 7.95) \). Further analyses on the number of category A versus category B errors revealed that STN stimulation resulted in a reduction in the number of category B errors \( (z = 2.11, p < .05) \), but not category A errors \( (z = 1.27, p > .05) \).
stimulation in PD participants resulted in significantly slower RTs than controls in contrast to the off stimulation condition, where no differences in initiation RTs were found. PD participants (in on and off stimulation conditions) and controls did not differ in the number of correct responses that were generated based on the use of strategies.

4. Discussion

One major finding of the present study was that PD participants performed similarly to controls on a PWI task, revealing that inhibitory lexical-semantic mechanisms under these conditions are not impaired in PD. Furthermore, inhibitory lexical-semantic processes, as assessed by the PWI task, did not differ as a function of STN stimulation, suggesting that basal ganglia-thalamocortical circuits are not involved in such processes. In contrast, the results of the Hayling task indicated that PD participants who were not receiving STN stimulation were impaired in the suppression of dominant responses and the generation of a novel response, yet when STN stimulation was applied, this impairment was resolved to a level which was comparable with healthy controls. The variable results yielded from the PWI task and Hayling task will be discussed in relation to the differing inhibitory mechanisms required for each task and the potential involvement of the basal ganglia-thalamocortical circuits in specific inhibitory lexical-semantic mechanisms.

Whilst the PWI task and Hayling test both involve the recruitment of inhibitory lexical-semantic processes, there are some distinct differences between the two tasks. Nigg (2000) identified several component processes associated with effortful inhibition of cognitive responses. Interference control refers to the ability to prevent interference in the presence of competing information, yet behavioural inhibition is more applicable to tasks which require the suppression of prepotent responses. The PWI task, requiring the ability to name picture stimuli in the presence of semantically related distractors, is more reliant on interference control, whereas the Hayling task, involving the suppression of straightforward sentence completion and the subsequent generation of a novel response, is more reliant on behavioural inhibition. It is possible that the differential behaviour patterns seen in the PWI and Hayling task in PD participants may be in part due to the different inhibitory subcomponents measured. People with PD may be more susceptible to deficits in behavioural inhibition rather than interference control.

Variable performance on the PWI and Hayling task may also be attributed to the different response level mechanisms involved in each task. As discussed by de Zubicaray et al. (2000), in contrast to many tasks measuring inhibitory control, the Hayling task places large demands on the generation and selection of alternative responses from a large array of competing alternatives. Specifically, Hayling B does not just require the suppression of a habitual response, but also the internal generation of a novel response from a wide array of possibilities. As the novel response must be completely unrelated to the presented sentence, the response subsequently needs to be monitored for compatibility. The PWI task also requires the suppression of a habitual response and the generation of a response, however, the response is provided in an external cue; being the picture to be named. The response selection constraints are therefore considerably different for the two tasks, where a response in the Hayling task requires the selection of a response from many competing alternatives, and in the PWI task, the alternative response is externally provided. In the present study, the delayed RTs in Hayling B for PD participants in the off stimulation condition may be reflective of a delay in the selection of responses from competing alternatives. STN stimulation then acts to facilitate response selection. This interpretation is consistent Frank’s (2006) computational model which proposes that the STN plays a role in response selection, particularly under conditions where there are multiple competing alternatives.

Furthermore, the lack of external cues provided in the Hayling task increases the need for the participant to internally generate strategies. To successfully overcome the suppression of prepotent responses in the Hayling task, a number of internally generated strategies can be utilised. For example, participants may use strategies such as responding with names of objects located around the room or responses that are semantically related to their response to a previous item (Burgess & Shallice, 1996). Such use of strategies is not possible in the PWI task. In order to identify the extent to which correct responses on Hayling B were reliant on the internal generation of strategies, Hayling B responses were separated into strategic and non-strategic responses. Considering that there were no differences in the number of strategic responses provided by PD participants (on and off stimulation) and controls, suggests that delayed RTs and increased errors in the PD off stimulation condition were not a result of an inability to internally generate strategies.

The differential inhibitory lexical-semantic processes involved in PWI and the Hayling test are also evident in neuroimaging studies investigating the various brain regions activated during the inhibitory components of the respective tasks. Two studies investigating changes in rCBF during the Hayling task, have identified regions of the DLPFC that have been linked to performance on Hayling B (Collette et al., 2001; Nathaniel-James & Frith, 2002). Nathaniel-James and Frith suggest that DLPFC activity in this task is associated with the selection of a response amongst competing alternatives, and Collette et al. suggest that this region is involved in the manipulation of information and the use of strategy to generate a novel response. Alternatively, an fMRI study investigating active brain regions during a PWI task, has identified greater activity in regions of the ACC during semantic interference (de Zubicaray, Wilson, McMahon, & Muthiah, 2001). The ACC is a region which is believed to be involved in the detection of conflict and the alerting of other regions to exert attentional control (Botvinick, Cohen, & Carter, 2004; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). DLPFC activity is therefore more strongly linked with the ability to generate responses in the Hayling task compared with greater ACC activity during the detection of conflict in the PWI task. Potentially, the results of the present study indicate that the basal ganglia-thalamocortical circuit related to the DLPFC is more affected in this cohort of PD participants and that STN stimulation acts to restore activ-
bition in PD participants (Bokura et al., 2005; Bouquet et al.,
of other studies that have found deficits in behavioural inhi-
stimulation in PD participants. Therefore, the greater interference
single semantic category in the stroop paradigm induces greater
possibly, the presence of the more relevant and highly related
always evident in the stroop colour-word task (Henik,
category of “colour” versus several semantic categories in the
the suppression of prepotent lexical-semantic responses and
impaired processing evident in the Hayling task (without
present study. Furthermore, in the present study, there was no difference in performance on
the RTs of non-neurologically impaired controls, whereas there
was no difference in response initiation times when STN stimu-
result in excessive inhibition of unwanted movements, and dif-
ficulties in stopping one motor program and switching to anther.
Perhaps the difficulties in response inhibition in Hayling B evid-
ent when PD participants did not receive STN stimulation, is reflective of a difficulty in the suppression of a prepotent response, and the cognitive switching required to generate a novel response. These deficits may be caused by hyperactivity of the STN and decreased inhibition of the indirect pathway. The absence of response inhibition deficit when STN hyperactivity is modulated by high frequency stimulation supports the notion that indirect basal ganglia-thalamocortical circuits are involved in the suppression of prepotent lexical-semantic responses and the switching to another lexical-semantic concept to generate a novel response. Theories relating to the initiation and suppression of motor programs in relation to the interplay of direct and indirect pathways of the basal ganglia-thalamocortical circuit may therefore be extended to cognitive processes, as suggested by the current results.

In conclusion, the current study provides evidence for differential susceptibility of lexical-semantic inhibitory mechanisms in PD and the subsequent involvement of basal ganglia-thalamocortical circuits as a result of STN stimulation. PD participants were only impaired on the Hayling task which is reliant on the suppression of habitual responses and the generation of a novel response from many competing alternatives. STN
stimulation acted to restore this performance to a level which was comparable to non-neurologically impaired individuals, implying that indirect basal ganglia-thalamocortical circuits are involved in the modulation of such inhibitory processes. In contrast, the ability to overcome conflict in the PWI paradigm was not impaired in PD participants and no changes were identified subsequent to STN stimulation, suggesting that interference control mechanisms invoked in the PWI paradigm are not affected by PD or the neuromodulation of basal ganglia-thalamocortical circuits via the STN.

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