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Semantic activation in Parkinson’s disease patients on and off levodopa

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Abstract

Research suggests that dopamine may exert a neuromodulatory influence on automatic spreading activation within semantic networks. In order to investigate the influence of dopamine depletion on semantic activation in Parkinson’s disease (PD), nine patients with PD performed a lexical decision task when on and off levodopa medication. Eleven healthy controls matched to the PD patients in terms of sex, age and education also participated in the study. Both directly related word pairs (e.g., tiger – stripe) and indirectly related word pairs (word pairs related via a mediating word, e.g., chalk – black) were used to measure semantic activation across stimulus onset asynchronies (SOAs) of 270 msec, 520 msec and 1020 msec. Analysis of variance statistics revealed that the activation of directly related and indirectly related targets was slower for the PD group relative to the control group. Within group comparisons revealed further changes to semantic activation in PD patients off medication, with no activation of directly or indirectly related target words evident in PD patients off medication. These results further clarify the nature of dopamine’s neuromodulatory influence on semantic activation, and suggest that the nature of altered semantic activation in PD may depend on the magnitude of dopamine depletion.

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1. Introduction

Parkinson’s disease (PD) is characterized by degeneration of the nigrostriatal dopaminergic system (Mink, 1996) and in addition to movement disorders, subtle language processing deficits are a frequently reported feature of the disease. There is currently substantial evidence to suggest that even in the absence of overt dementia, many patients with PD exhibit deficits in lexical-semantic processing (Bayles et al., 1993; Gurd, 1996, 2000; Lewis et al., 1998; Portin et al., 2000; Randolph et al., 1993). While the results of emerging research have indicated that semantic processing deficits in PD may be related to alterations in dopaminergic transmission (Grossman et al., 2002; Watters and Patel, 1999, 2002), the precise nature of dopamine’s influence on semantic processing currently remains unclear. The objective of the present study was to use online semantic priming tasks to delineate the impact of dopamine depletion in PD on semantic activation.

Semantic priming refers to the faster recognition of a target word when it is preceded by a related prime word (tiger – stripe)
compared to an unrelated word (table - stripe). These semantic priming effects have often been attributed to automatic spreading activation (Collins and Loftus, 1975; Neely, 1977; Posner and Snyder, 1975). Spreading activation theories are based on the assumption that concepts form an interconnected semantic network, with semantically/associatively related concepts stored closer together. It is thought that the processing of a prime word induces a temporary spreading of activation that lowers the activation thresholds of related target words. Thus, by varying the stimulus onset asynchrony (SOA) between presentation of a prime and target, it is possible to measure the temporal window over which activation occurs. Spreading activation theories also assume that activation dissipates with increasing distance within the semantic network. Thus, while activation of directly related targets (e.g., tiger – stripe) will typically occur in a semantic priming task, activation may also, to a lesser extent, spread to target words that are only indirectly related to the prime (e.g., lion – stripe, are only related via the mediating word ‘tiger’). Indeed, researchers have revealed significant semantic priming effects for both direct and indirect semantic relations in healthy adults (Angwin et al., 2004; Arnott et al., 2003; Hill et al., 2002; Weisbrod et al., 1999), with some researchers also illustrating faster lexical decisions to directly related compared to indirectly related targets (Hill et al., 2002; Weisbrod et al., 1999).

Accordingly, manipulating both SOA and relatedness (direct/indirect) in semantic priming tasks may represent a comprehensive method of identifying the manner in which dopamine depletion in PD influences semantic processing. Certainly, the potential neuromodulatory influence of dopamine on semantic processing is already well recognized. Kischka et al. (1996) measured direct and indirect semantic priming effects in healthy participants who had ingested either a levodopa or placebo capsule. The results revealed reduced indirect semantic priming in the participants who ingested levodopa, which the researchers suggested was consistent with a dopamine-induced focusing of activation within semantic networks. Similarly, Copland et al. (2003) found that the ingestion of levodopa by healthy participants caused a focusing of activation and a dampening of weaker associations.

In contrast, in another investigation of semantic priming in healthy participants who ingested levodopa, the results were not consistent with a focusing of activation (Angwin et al., 2004). Instead, the results suggested that the onset and decay of activation to both directly and indirectly related targets was occurring more quickly for participants who ingested levodopa. These results suggested that dopamine may also be capable of altering the speed of activation and decay within semantic networks. Specifically, Angwin et al. (2004) suggested that by increasing the signal-to-noise ratio of information processing, dopamine may speed processing of the prime word, leading to a faster onset and decay of semantic activation rather than a focusing of activation. Such findings suggest that a hyperdopaminergic state will result in the presence of both direct and indirect priming at short SOAs, but the absence of such priming effects at longer SOAs.

Based on this semantic priming research, there is mounting evidence to suggest that dopamine may exert a neuromodulatory influence on semantic activation. Thus, it may be expected that striatal dopamine depletion in PD will result in a pattern of semantic activation opposite to that observed in healthy participants on levodopa. Specifically, dopamine depletion may be expected to slow the spread of activation to both direct and indirect semantic relations, such that direct and indirect priming effects are only evident at longer SOAs. Alternatively, dopamine depletion may also be expected to lead to unfocused activation within semantic networks, such that spreading activation to indirectly related concepts will be increased.

Some researchers have observed delayed semantic activation in patients with PD (Angwin et al., 2005; Arnott et al., 2001), providing support for the influence of dopamine on the speed of semantic activation. More importantly, research has also demonstrated that such delays do not occur in an all-or-none manner, but occur along a continuum. For instance, Grossman et al. (2002) found a normal pattern of semantic activation in a subgroup of PD participants with intact sentence comprehension skills, whilst delayed semantic activation was evident in a subgroup of patients with poor comprehension skills. In contrast, Angwin et al. (2007) found delayed semantic activation both in PD patients with good and poor sentence comprehension skills, but the magnitude of the delay was larger in those patients with poor comprehension skills. Grossman et al. (2002) has suggested that the magnitude of cognitive slowing in PD, which may be manifest as delayed lexical retrieval, could be dependent on the extent of disruption to the dopamine dependent frontal–striatal circuitry. Accordingly, Grossman et al. suggested that delays in semantic activation may only be evident in PD patients with more substantial levels of dopamine depletion. This suggestion is also consistent with other research that has suggested that the striatum plays a key role in the modulation of information processing speed (Harrington et al., 1998; Poldrack et al., 2001; Schubotz et al., 2000).

Since the extent of dopamine depletion may differ markedly across individuals with PD, comparisons of semantic priming in the same group of PD patients when on versus off dopaminergic supplementation may provide additional insight into the influence of dopamine on semantic processing. When on dopaminergic therapy such as levodopa, dopamine deficiency in PD should be temporarily replenished (but see Cools et al., 2003), whilst dopamine levels will decline when patients are off levodopa. To date, only a small number of studies have investigated semantic priming in PD patients both on and off levodopa. Murdoch et al. (2000) and Arnott et al. (2000) observed a negative priming effect (i.e., faster reaction times to unrelated than related target words) in PD patients with mild to moderate PD when off medication, which Arnott et al. (2000) interpreted within the framework of the center-surround theory of inhibition (Carr and Dagenbach, 1990). This theory postulates that when difficulty retrieving semantic information about a prime word is encountered, the activation of semantic concepts closely related to the prime may be inhibited in order to prevent them from blocking the retrieval attempt. Accordingly, Arnott et al. suggested that due to weakened activation of the prime word and/or increased noise within semantic networks in PD patients off levodopa, concepts semantically related to the prime word become inhibited and a negative priming effect is obtained. Angwin
et al. (2006) also investigated semantic priming in people with mild to moderate PD, and whilst they failed to observe negative priming effects in PD patients off levodopa, they did find that semantic priming was more susceptible to disruption when an unrelated word was presented between a related prime and the target word. Angwin et al. suggested that such results could also potentially be explained by weakened activation of the prime word, which makes semantic priming more susceptible to disruption.

Taken together, therefore, the results of semantic priming studies in PD have suggested that dopamine depletion can induce both a slowing of automatic semantic activation as well as weaker or unfocussed activation within semantic networks. Importantly, weaker or unfocussed activation only appears to be evident under conditions of medication withdrawal in PD, suggesting that the nature of altered semantic activation in PD may differ as a function of the magnitude of dopamine depletion. Specifically, whilst dopamine depletion may initially lead to slowed activation, semantic activation may become progressively unfocussed as the magnitude of dopamine depletion increases. Whilst there is evidence to suggest that such unfocussed activation may lead to negative priming effects (Arnott et al., 2000; Murdoch et al., 2000), it is still unclear whether unfocussed activation may also lead to increased spreading activation to distantly related concepts. Increased spreading activation in PD would be predicted based on previous findings of reduced indirect priming effects in healthy adults on levodopa (Kischka et al., 1996).

The present study seeks to provide further insight into the dopaminergic changes to automatic semantic activation in PD, by combining measures of direct and indirect semantic activation across time with the testing of PD patients both on and off levodopa. Attempts to measure automatic semantic activation, however, are often confounded by the influence of conscious or attention-based processes. For instance, pre-lexical expectancies and/or post-lexical semantic matching strategies may influence semantic priming effects, particularly under experimental conditions where longer SOAs are used and/or when a high proportion of nonwords or related word pairs are used (Neely, 1991; Neely et al., 1989). To facilitate automatic semantic activation and to reduce the influence of attentional confounds on semantic priming, the use of a pattern mask after the prime word will be implemented in the present study. By presenting a prime word only briefly (e.g., 80 msec) with a pattern mask presented (e.g., a random series of letters) after the prime, a participant’s awareness of the prime may be lowered and the impact of conscious or attention-based processing on the lexical decision may be reduced. Recently, significant semantic priming effects have been successfully obtained with the use of masking techniques (Deacon et al., 2000; Ruz et al., 2003). The use of a neutral priming condition will also be implemented in the present study. It has been well established that while automatic semantic priming results in facilitation (defined as significantly faster RTs to related target words relative to neutral target words), strategic or controlled processing can result in both facilitation as well as inhibition (defined as significantly slower RTs to unrelated target words relative to neutral target words) (Neely, 1977). Hence, the inclusion of a neutral prime to measure facilitation and inhibition is necessary in order to determine whether priming effects reflect automatic or controlled processes.

The aim of the present research was to measure automatic semantic activation across time in PD patients (both on and off levodopa medication) and healthy controls using a semantic priming task with three SOAs (270 msec, 520 msec and 1020 msec) and four prime conditions (directly related, indirectly related, neutral and unrelated). Although strategic processing is typically observed at longer SOAs, the three SOAs from 270 msec to 1020 msec were chosen in order to explore the temporal aspects of semantic activation similar to that implemented in previous research (Angwin et al., 2005, 2007). Further, a masked prime word was utilised in order to minimise the potential influence of such strategic processes.

For healthy controls subjects, it was predicted that activation of directly and indirectly related concepts would be evident at both the 270 msec and 520 msec SOAs. It was further predicted that no activation would be evident at 1020 msec SOA for the healthy control group, consistent with the decay in automatic semantic activation for healthy adults (Stern et al., 1991). In contrast, it was hypothesized that dopamine depletion would result in alterations to automatic semantic activation for the PD group. For the PD group on medication, it was predicted that the activation of directly and indirectly related concepts would not emerge until the 520 msec SOA, and that this activation would persist across the 1020 msec SOA, consistent with suggestions of a delayed time course of semantic activation in PD (Angwin et al., 2007; Arnott et al., 2001; Grossman et al., 2002). For PD patients tested whilst off medication, it was predicted that the increased magnitude of dopamine depletion would lead to further disruptions to semantic priming due to an unfocussed or weaker activation of the prime word. Specifically, it was predicted that testing PD patients off levodopa would result in either increased activation of indirectly related concepts (as evidenced by an increased magnitude of indirect priming) or that negative priming effects would emerge.

2. Method

2.1. Participants

Nine participants with idiopathic PD (diagnosis confirmed by a neurologist using Calne et al.’s (1992) criteria for diagnosing PD) and 11 non-neurologically impaired control participants comprised the study’s two participant groups. All participants were right-handed, native speakers of English with no history of neurological surgery, drug or alcohol abuse, or dementia, and were not taking any anti-depressive or anti-cholinergic medications. The PD group had a mean age of 66.89 years [Standard deviation (SD) 7.08] and mean education of 13.44 years (SD 5.18), whilst the control group had a mean age of 66.45 years (SD 9.74) and mean education of 11.82 years (SD 5.18). Prior to the commencement of testing, the cognitive status of all participants was assessed using the Dementia Rating Scale (DRS) (Mattis, 1988). The mean DRS score was 140.11 (SD 3.33) for the PD group and 141.36 (SD 2.16) for the control group. Mann–Whitney U tests revealed that the mean...
The PD group had a mean disease duration of 3.67 years (SD 2.06, range 1–8) and a mean age at onset of 63.33 years (SD 7.66, range 45–68). Hoehn and Yahr scores (Hoehn and Yahr, 1967) were used to classify the disease severity of the PD patients, with a mean score of 2.22 (SD 3.1). The predominant symptom was tremor for 4 patients and bradykinesia for 1 patient, while the remaining 4 patients experienced predominant symptoms of both tremor and bradykinesia. All PD patients were taking levodopa (i.e., Madopar/Sinemet) with a mean daily dosage of 423.61 mg (SD 185.03), while two patients were also taking the dopamine agonist cabergoline (Cabaser) (range 1–2 mg). Two of the PD patients also experienced a predictable ‘wearing off’ effect associated with their levodopa medication, such that motor symptoms typically increased approximately 3–4 h after dosage.

The experimental tasks were administered to all participants as a subcomponent of a larger battery of tests. Specifically, during each testing session, all participants performed an additional two semantic priming tasks that were unrelated to the present study and which utilized different stimuli and conditions to those used in the present study. PD participants were tested at their homes in both an on and an off medication state. During the on medication testing sessions, care was taken to ensure that PD participants were achieving maximum clinical benefit from their medication at the time of testing. Therefore, testing of the PD group was conducted approximately 45 min after dosage. In order to avoid testing during a person’s ‘wearing off’ phase, all participants were requested to report to the researcher if they felt that their medication was wearing off, so that testing could be ceased. In addition, the PD group performed the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al., 1987) finger tap subtest at 30 min intervals throughout each testing session. This short test required participants to tap their index finger and thumb together as rapidly as possible for 5 sec, each hand being assessed separately. A score between 0 (normal performance) and 4 (barely able to perform task) was then calculated. Since the effects of medication ‘wearing off’ are associated with reduced mobility, testing could be ceased if a participant’s UPDRS score increased during any one testing session. During the course of data collection, however, no testing session was ceased. The off medication sessions were conducted before patients had taken their first morning dose of medication, such that they had been without dopaminergic medication for at least 12 h.

### 2.2. Stimuli

A stimulus set consisting of 96 prime – target pairs was assembled, with the same stimulus set used for each SOA. Whilst the prime word was always a real English word, half the target words were real words and half the target words were pronounceable nonwords. Four different types of prime preceded the real word targets, with 12 items in each of these prime conditions. Examples of each condition were as follows:

1. **Direct Semantic Relation** (e.g., tiger – stripes)
2. **Indirect Semantic Relation** (e.g., chalk – black; via the mediating word white)
3. **Neutral relation** (e.g., blank – pills)
4. **Unrelated** (e.g., organ–swamp).

The directly related and indirectly related word pairs were derived mainly from stimulus materials used by Balota and Lorch (1986) and DeGroot (1983), which were derived from association norms. All related stimulus materials held an obvious semantic relationship (e.g., tiger – stripes), and did not form compound words (e.g., maple – syrup, bus – stop) or reflect associatively related words without semantic relatedness (e.g., cottage – cheese). In addition to these stimulus materials, an additional 3 directly related word pairs and 4 indirectly related word pairs were created. To validate these additional word pairs, 20 undergraduate students (13 females, 7 males) were asked to produce associates to the direct and indirect prime words. The results from this task indicated that participants produced the target word as an associate to the direct primes but did not produce the target word as an associate to the indirect primes. The majority of words used were nouns, however, some verbs and adjectives were also used. Specifically, of the 48 critical stimuli, 46 of the prime words were nouns, with 1 adjective and 1 verb also used. The neutral prime word was always the word ‘blank’. Target word stimuli consisted of 37 nouns, with 4 adjectives and 7 verbs also used. All prime words for the unrelated and nonword targets were matched to the average frequency and syllable length of the related word primes.

To avoid repetition of target words, different targets were used for each prime condition. In order to achieve this, different target words were chosen for the neutral and unrelated conditions, matched to the frequency (Kucera and Francis, 1967) and syllable length of the target words in the related conditions. To validate the use of these different target words, mean lexical decision reaction times (RTs) for each target word were obtained from the database of the English Lexicon Project (Balota et al., 2002). ANOVA statistics revealed no significant main effect of target word type (i.e., direct, indirect, neutral, unrelated) on RT \( (p = .238) \). Finally, all nonword targets were developed by changing one to three phonemes in an existing English word, which was matched in frequency and syllable length to the real target words. Twelve of the nonwords were preceded by the neutral prime ‘blank’ and 36 by a standard word prime.

The same stimulus list was used for each SOA, but the order of presentation of word pairs was randomised for each SOA and participant. The order in which participants performed the experiments (i.e., 270 msec, 520 msec or 1020 msec SOA) was counterbalanced, and each experiment was completed during a different testing session held at least two weeks apart to reduce the influence of repeated exposure to the same stimuli. However, repetition of stimuli (i.e., first, second or third exposure to the stimuli) was also factored into statistical analyses in order to determine whether this influenced priming or facilitation effects. Testing sessions for PD patients off levodopa did not commence until at least 4 weeks after completion of the on levodopa testing sessions. All stimuli were presented using Superlab experimental software (Version 2.0) (Cedrus, 1996), which measured participant’s RTs via a Cedrus RB-420 response pad (accurate to within 1 msec) and collected all errors and RT data automatically. Button 2 on
a 4-button response pad was marked with the word ‘Yes’ and button 3 was marked with the word ‘No’.

2.3 Procedure

Participants were informed that a word would appear very quickly in the centre of the screen, which they may or may not recognise, followed by a second word. They were asked to make a lexical decision to the second word as quickly as possible, by pressing the ‘Yes’ button if it was a real word and pressing the ‘No’ button if it was a nonword. Experimental stimuli were presented to participants via 3 blocks of 32 trials, with an opportunity to rest provided to participants following the completion of each block. Participants were also reminded during rest breaks, that they should make lexical decisions to the target words as quickly as possible. A practice block, consisting of 12 word pair trials similar to those in the experimental proper, was given to each participant to allow familiarisation with the procedure prior to the commencement of testing. The practice set given always featured the same SOA as the experiment it preceded, and participants were told that they were free to repeat the practice block until they felt comfortable with the testing procedure. All testing was conducted using a portable laptop computer, with the participant seated approximately 50 cm from the computer monitor.

All stimuli were written in lower case letters of 75 point Arial font. The sequence of events during both the practice trials and experimental trials was as follows: (a) a blank screen was presented for 2000 msec; (b) the prime word was presented in the center of the screen for 80 msec; (c) a backward mask consisting of 5 letters (hsibk) was then presented in the center of the screen for 190 msec; (d) the target word would then be presented either immediately following the mask (SOA 1 = 270 msec), or would follow a 250 msec presentation of a blank screen (SOA 2 = 520 msec) or a 750 msec presentation of a blank screen (SOA 3 = 1020 msec). This target word was presented in the centre of the screen until the participant either gave a response, or until 3000 msec had passed with no response. The following trial then began automatically. Figure 1 illustrates the procedure used for a typical trial.

3. Results

Only RTs for the critical trials were analysed. All participant errors and all RTs less than 200 msec or greater than 1500 msec were removed from analyses. Following the removal of this data, individual and group outliers (defined as any RT more than two SDs above or below the mean) were also excluded from analyses. This process resulted in the exclusion of more than 25% of the data for one of the control participants, whose data was subsequently excluded from all remaining analyses. With this participant’s data excluded, the removal of errors and all RT outliers resulted in the removal of 10.66% of the remaining data set. Table 1 displays the percentage accuracy for each group and for each prime condition. Due to the low percentage of errors, no analyses were conducted on the error data. Table 2 displays the mean RTs for each group and for each condition. Separate analyses were conducted on the RT data to compare the control group to the PD group on medication, and to compare the PD group on and off medication.

3.1 Controls versus PD on medication

Individual participant RTs were entered into a mixed linear model analysis with subject as a random factor, group (control, PD) as a between subjects factor, and SOA (270 msec, 520 msec, 1020 msec) prime (direct, indirect, neutral, unrelated) and repetition (first, second or third exposure to stimuli) as within subject factors. The results revealed significant main effects of SOA and prime [F(2,2376) = 12.81, p < .001 and F(3,2359) = 8.76, p < .001, respectively] and an interaction effect of group x SOA [F(2,2376) = 31.97, p < .001]. Although there was also a significant main effect of repetition [F(2,2376) = 20.22, p < .001], together with interaction effects of group x repetition, SOA x repetition, and group x SOA x repetition [F(2,2376) = 7.10, p < .001; F(4,1687) = 30.00, p < .001; and F(4,1687) = 7.69, p < .001, respectively], there were no interactions between repetition and prime, illustrating that repeated exposure to stimuli did not have an influence on the magnitude of priming/facilitation effects for either group.

While the main and interaction effects are provided for descriptive purposes, the data provided therein do not test explicitly the hypotheses being considered (i.e., whether there was a differential pattern of activation between the two groups for directly and indirectly related concepts across time). Consequently, of particular interest in this experiment were the priming/facilitation effects for the direct and indirect conditions at each SOA. Overall priming effects were analysed separately for each group and SOA, therefore, by way of planned pairwise comparisons between the related prime conditions (direct, indirect) and the unrelated condition. Pairwise comparisons were also made between related and neutral prime conditions for the analysis of direct and indirect facilitation effects, and between unrelated and neutral prime conditions for the analysis of inhibition effects. These
The results revealed significant main effects of group and SOA (on, off), SOA, prime and repetition as within subject factors. Individual participant RTs were entered into a mixed linear model analyses. Whilst an interaction effect of group × prime was just outside significance \( F(3,2221) = 2.35, p = .071 \). There was also a significant main effect of repetition \( F(2,221) = 9.00, p < .001 \), together with interaction effects of group × repetition, SOA × repetition, and group × SOA × repetition \( F(2,2221) = 10.37, p < .001; F(4,2216) = 3.04, p = .017; \) and \( F(4,2176) = 5.21, p < .001, \) respectively. No interactions between repetition and prime were significant.

Comparisons were conducted using additional mixed linear model analyses.

Analysis of the control group’s data revealed significant direct and indirect priming effects at the 270 msec SOA \( t(2407) = -2.38, p = .017; \) and \( t(2407) = -2.04, p = .042, \) respectively, together with significant direct and indirect facilitation effects at 270 msec SOA \( t(2407) = -2.34, p = .019; \) and \( t(2407) = -2.00, p = .046, \) respectively. Similarly, analyses revealed significant direct and indirect priming effects for the control group at 520 msec SOA \( t(2407) = -2.86, p = .004; \) and \( t(2407) = -2.08, p = .037, \) respectively, and significant direct facilitation effects \( t(2407) = -2.51, p = .012 \). No priming or facilitation effects were significant for the control group at 1020 msec SOA.

In contrast, analysis of the PD on group’s data revealed significant direct and indirect facilitation effects at 520 msec SOA \( t(2407) = -2.59, p = .010; \) and \( t(2407) = -2.83, p = .005, \) respectively and significant indirect priming and facilitation effects at 1020 msec SOA \( t(2407) = -2.20, p = .028; \) and \( t(2407) = -2.24, p = .025, \) respectively. Comparisons between RTs for the unrelated and neutral prime conditions for the analysis of inhibition effects were not significant for either group at any SOA.

### 3.2 PD on versus off medication

Individual participant RTs were entered into a mixed linear model analyses with subject as a random factor and medication (on, off), SOA, prime and repetition as within subject factors. The results revealed significant main effects of group and SOA \( F(1,2221) = 6.29, p = .012; F(2,2221) = 33.05, p < .001, \) respectively}

<table>
<thead>
<tr>
<th>Prime condition</th>
<th>Control SOA</th>
<th>PD on SOA</th>
<th>PD off SOA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>270 520 1020</td>
<td>270 520 1020</td>
<td>270 520 1020</td>
</tr>
<tr>
<td><strong>Direct</strong></td>
<td>627 (75) 661 (99) 646 (104)</td>
<td>735 (131) 684 (120) 706 (109)</td>
<td>759 (148) 715 (127) 707 (139)</td>
</tr>
<tr>
<td><strong>Indirect</strong></td>
<td>631 (81) 670 (90) 638 (102)</td>
<td>743 (128) 685 (132) 700 (120)</td>
<td>752 (133) 705 (127) 705 (131)</td>
</tr>
<tr>
<td><strong>Neutral</strong></td>
<td>661 (97) 689 (107) 648 (91)</td>
<td>756 (154) 723 (145) 729 (139)</td>
<td>757 (138) 718 (126) 700 (143)</td>
</tr>
<tr>
<td><strong>Unrelated</strong></td>
<td>660 (80) 698 (105) 653 (94)</td>
<td>745 (134) 698 (114) 725 (132)</td>
<td>753 (130) 691 (125) 710 (129)</td>
</tr>
</tbody>
</table>

Note. Standard deviations in brackets.

### 4. Discussion

Using measures of both direct and indirect priming across multiple SOAs, the present study investigated semantic activation in PD patients on and off levodopa and in healthy control participants. It was hypothesised that dopamine depletion in PD would modulate spreading activation within semantic networks, altering patterns of activation for directly
and indirectly related concepts over time. As anticipated, a differential pattern of direct and indirect priming/facilitation was observed across time for the PD group on levodopa compared to controls. In particular, semantic activation of direct and indirect targets emerged later in the PD group. Such findings may be consistent with suggestions that dopamine alters the speed of semantic activation (Angwin et al., 2004; Grossman et al., 2002). Within group comparisons also revealed an absence of any priming effects in the PD group off medication, although a negative direct priming effect was almost significant. The findings of the present study are discussed in terms of the potential neuromodulatory influences of dopamine on semantic activation.

4.1. Semantic activation in controls

The control group showed direct semantic priming/facilitation effects at both the 270 and 520 msec SOAs, with no priming/facilitation evident at 1020 msec SOA. It has been shown that automatic semantic activation typically decays in healthy older adults approximately 1000 msec following presentation of the prime word (Stern et al., 1991). Therefore, this pattern of direct facilitation that only persists until 520 msec, together with the absence of inhibition effects, is consistent with the notion of automatic semantic activation and suggests that the masked priming paradigm implemented in the present study successfully reduced the influence of conscious processing on semantic priming. In contrast to the pattern of direct facilitation, indirect priming/facilitation effects were evident at the 270 msec SOA, but indirect facilitation effects were absent at both the 520 msec and 1020 msec SOAs suggesting that automatic activation of indirectly related concepts had decayed by 520 msec. Although this absence of indirect facilitation at 520 msec SOA was unexpected, it has been suggested that while direct semantic priming effects are robust, indirect semantic priming is sensitive to both the experimental condition (Hill et al., 2002) as well as individual differences in language abilities (Moritz et al., 1999). Hence, factors such as the use of a masked priming paradigm and/or the older age of participants in the present study may have contributed to the finding of no indirect facilitation at 520 msec SOA. Overall, the pattern of facilitation for the control group appears consistent with automatic semantic activation at each SOA, providing a valid baseline against which to compare semantic priming in the PD group.

4.2. Semantic activation in PD patients on levodopa

For PD patients on levodopa, it was predicted that the activation of directly and indirectly related concepts would first emerge at the 520 msec SOA, and that this activation would persist across the 1020 msec SOA. This hypothesis was supported by the results, with the absence of any priming/facilitation effects at 270 msec SOA, but significant direct and indirect facilitation effects at 520 msec SOA and significant indirect facilitation effects at the 1020 msec SOA. These results suggest that directly and indirectly related targets were activated more slowly for the PD group relative to the control group, and so are in keeping with previous findings of a delayed time course of semantic activation in PD (Angwin et al., 2007; Arnott et al., 2001; Grossman et al., 2002).

Given the striatal dopamine depletion evident in PD, these results provide direct support for proposals that dopamine exerts a neuromodulatory influence on the speed of semantic activation (Angwin et al., 2004) and that the functioning of the dopamine dependent frontal–striatal–thalamic system influences such processes (Grossman et al., 2002). The fact that delayed semantic activation was evident even in patients tested while on medication is consistent with suggestions that cognitive slowing in PD is not ameliorated by dopaminergic treatment (Johnson et al., 2004). Further, such changes to the speed of activation may also contribute to PD patients’ poor performance on other tests of semantic processing such as verbal fluency, which researchers have suggested may be related to deficits in semantic retrieval (Randolph et al., 1993; Raskin et al., 1992).

Recent findings have indicated that delayed semantic activation may only be evident in a subset of PD patients (Angwin et al., 2005; Grossman et al., 2002), and that delays to semantic activation may be more severe in some PD patients relative to others (Angwin et al., 2007). Such findings have been attributed to the magnitude of endogenous dopamine depletion and subsequent disruption to the frontal–striatal–thalamic system in PD (Grossman et al., 2002). Hence, the results of the present study indicate that even in mild to moderate PD, the magnitude of frontal–striatal dysfunction may be sufficient to slow the speed of semantic activation. It may also be expected that delays to semantic activation will become longer for an individual with PD as the magnitude of dopamine depletion increases.

Research has also demonstrated that the profile of cognitive dysfunction in PD may be a function of a complex relationship between the side of disease onset and the initial motor symptom (Katzen et al., 2006). Accordingly, future studies with a larger number of participants might consider exploring whether variable patterns of direct and indirect activation are evident in different subgroups of PD patients, and whether these patterns can be linked to disease related variables such as side of onset and initial motor symptom.

Also worthy of note is that whilst indirect facilitation was only evident for the control group at 270 msec SOA, indirect facilitation effects were significant at both the 520 msec and 1020 msec SOAs for the PD group. This result suggests that the activation of indirectly related target words was maintained for a longer period of time in PD participants relative to healthy controls. The finding of significant indirect facilitation at 1020 msec SOA in the PD group also highlights the potential value of investigating semantic activation in neurologically impaired populations using both directly and indirectly related stimuli. If measures of only direct priming had been used, the results would have given the false impression that semantic activation was only present for the PD group at 520 msec SOA (as evidenced by the significant direct facilitation effect). Instead, the use of indirectly related stimuli in the present study revealed further alterations to semantic activation at the longest SOA. Hence, indirectly related stimuli may be a useful and sensitive measure of automatic semantic activation, and researchers should consider measuring both...
direct and indirect semantic priming in future studies within this field. The following discussion will now focus upon the pattern of semantic priming observed in PD patients off levodopa.

4.3. Semantic activation in PD patients off levodopa

Within group comparisons did reveal a different pattern of priming/facilitation for PD patients off, relative to on, levodopa. While on levodopa, the PD group demonstrated significant direct and indirect facilitation at 520 msec SOA, followed by the emergence of indirect facilitation at the longest SOA. In contrast, no significant priming or facilitation effects were evident for the PD group off medication at any SOA.

It should be noted, however, that a negative direct priming effect almost reached significance at 520 msec SOA, which is in keeping with our hypotheses and with the findings of previous research measuring semantic priming in PD patients off medication at similar SOAs (Arnott et al., 2000; Murdock et al., 2000). Also worthy of note is that this negative priming effect is not associated with decreased task accuracy (Table 1). Hence, the mechanism responsible for negative priming effects in PD does not influence the ability to make a correct lexical decision, but rather distracts or slows participants’ task performance. As suggested by Arnott et al. (2000), such results may potentially be interpreted within the context of the centre-surround theory of inhibition (Carr and Dagenbach, 1990). Carr and Dagenbach (1990) proposed that when difficulty retrieving semantic information about a prime word is encountered (e.g., during masked priming), participants might direct attention towards the meaning of the prime. It was further proposed that this attention causes an automatic activation of a center-surround mechanism, which acts to dampen semantic representations closely related to the prime in order to prevent them from blocking the retrieval attempt. Applying this mechanism to negative priming in PD, Arnott et al. (2000) suggested that dopamine depletion during medication withdrawal may result in prime signals becoming obscured by noise, such that activation of the prime must occur at the expense of spreading activation. Specifically, to produce a more salient prime signal, attentional resources must be directed to the suppression of related nodes whilst unrelated words remain unaffected. This suppression consequently delays RTs to related target words, which take longer to be retrieved than unrelated words, leading to a negative priming effect.

The notion of weakened prime activation due to increased noise is consistent with the potential neuromodulatory influence of dopamine on information processing. Cepeda and Levine (1998) suggested that dopamine is able to increase the signal-to-noise ratio in neural networks by integrating relevant information and screening out less relevant information. Thus, dopamine depletion in PD will be expected to decrease the signal-to-noise ratio of relevant and irrelevant signals. Indeed, it has been suggested that reduced dopamine input in schizophrenia results in a smaller difference in activity between relevant and irrelevant lexical nodes in semantic networks (Spitzer et al., 1993). Similarly, increased noise within semantic networks during medication withdrawal in PD may be conceptualized as an increase in background activity within the semantic network, such that activation of the prime word may be obscured by increased activation of other semantic concepts. As a result, suppression of related nodes may help stabilize activation of the prime word in the presence of increased background semantic activity, leading to negative priming effects. It should be noted, however, that there was no evidence of negative priming effects for the indirect condition (Table 2), suggesting that inhibition within semantic networks in PD may be spatially constrained to concepts closely related to the prime word.

Based on findings of more focused semantic activation in healthy adults on levodopa (Kischka et al., 1996), it was also hypothesized that dopamine depletion in PD would lead to an increased spread of activation to indirectly related concepts. However, there was no evidence of increased indirect priming effects in PD patients on or off levodopa in the present study. These findings suggest that unfocussed activation during dopamine depletion does not lead to increased spreading activation in semantic networks, but rather leads to a weakening of the prime signal and the subsequent emergence of negative priming effects.

As discussed earlier, Katzen et al. (2006) have suggested that there is an intricate relationship between side of disease onset and type of motor symptom, which may subsequently influence the extent of cognitive dysfunction in PD. Similarly, it is possible that the extent of cognitive dysfunction during medication withdrawal will also be influenced by such variables. Hence, the nature and extent of any alterations to semantic activation during medication withdrawal in PD may depend on specific symptomatic variables and the subsequent profiles of cognitive deterioration. This issue needs to be investigated in future research by using a larger sample size, and by comparing the pattern of semantic priming between subgroups of PD participants with different symptomatic profiles.

Another limitation to our study is that the on and off medication testing conditions utilised the same stimuli for the experimental task. Hence, it is possible that the repeated exposure to stimuli may have influenced the pattern of priming effects obtained in the off medication condition. Further research using different stimuli across the on and off medication conditions should be conducted in order to further confirm the emergence of negative priming in PD patients off levodopa.

5. Conclusions

The current study investigated automatic semantic activation in PD patients on and off levodopa and healthy adults. Although the results of the present study appeared to support a neuromodulatory influence of dopamine on semantic activation, the results also suggested that the precise nature of this influence varies in PD, depending on the extent of dopamine depletion. Specifically, it is proposed that striatal dopamine depletion in PD initially leads to a slower time course of semantic activation and decay, but that increased levels of dopamine depletion may lead to unfocussed or weaker
activation of prime words and, subsequently, to additional disruptions in semantic activation. One caveat of the present study that must be considered is that only a small number of PD patients were able to participate in the research whilst off levodopa. Therefore, the results of this research need to be validated using a larger cohort of PD patients.

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