Semantic and affective priming as a function of stimulation of the subthalamic nucleus in Parkinson’s disease

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Lexical-semantic and emotional processing deficits have been associated with Parkinson's disease. This study investigated automatic and controlled lexical-semantic processing, the automatic activation of emotional evaluations, and the processing of words conveying negative and neutral emotional connotations in a combined affective and semantic priming paradigm. Eighteen participants with Parkinson's disease who had undergone surgery for deep brain stimulation (DBS) of the subthalamic nucleus (STN) completed a lexical decision task at short and long stimulus onset asynchronies (SOAs), during on and off stimulation conditions. Nineteen non-neurologically impaired participants acted as controls. The results indicated that automatic lexical-semantic and emotional evaluative processes are unimpaired in Parkinson's disease as reflected in the presence of comparable semantic and affective priming effects at the short SOA in on and off stimulation conditions compared with healthy controls. In contrast, participants with Parkinson's disease in the off stimulation condition showed a pattern of aberrant controlled lexical-semantic processing as evidenced by a lack of semantic priming effects at the long SOA condition. Controlled semantic priming was present, however, when the participants with Parkinson's disease were receiving stimulation of the STN, suggesting that STN stimulation modulates non-motor basal ganglia-thalamocortical circuits involved in such processes. Finally, delayed reaction times for negatively valenced targets compared with neutrally valenced targets was evident in participants with Parkinson's disease in the on stimulation condition and control participants, but not for participants with Parkinson's disease in the off stimulation condition, suggesting that the incidental evaluation of negatively versus neutrally valenced words in Parkinson's disease is modulated by basal ganglia-thalamocortical circuits.

Keywords: lexical decision; emotion; deep brain stimulation; semantic priming; language processing

Abbreviations: ACC = anterior cingulate cortex; ANEW = Affective Norms for English Words; DBS = deep brain stimulation; LMM = linear mixed model; RT = reaction time; SOA = stimulus onset asynchrony; STN = subthalamic nucleus.

Introduction

Deficits in emotional processing and lexical-semantic processing have been described in people with Parkinson’s disease and there is emerging evidence that these processes are affected by stimulation of the subthalamic nucleus (STN) in Parkinson’s disease patients who have received surgery for deep brain stimulation (DBS). To date, there have been no studies that have concurrently investigated automatic and controlled lexical-semantic and affective processes, and explored the processing of words with emotional connotations in Parkinson’s disease. This study will explore these processes in Parkinson’s disease and also investigate the degree to which stimulation of the STN modulates these processes via functional changes in non-motor basal ganglia-thalamocortical circuits. Therefore, this study will investigate the incidental processing of
emotional linguistic stimuli via a lexical decision in addition to the automatic activation of emotional evaluations (i.e. the automatic assessment of the emotional valence of stimuli), and the automatic and controlled activation of lexical-semantic representations by utilizing a combined affective and semantic priming paradigm in participants with Parkinson’s disease. Furthermore, the involvement of basal ganglia-thalamocortical circuits on such processes in Parkinson’s disease will be measured via the neuromodulation of the STN.

Lexical-semantic processing in Parkinson’s disease

Investigations into the integrity of lexical-semantic processes in Parkinson’s disease have been largely directed at measures of language processes, such as verbal fluency paradigms, that are confounded by strong executive processes. Deficits in performance on verbal fluency tasks have often been reported in Parkinson’s disease (e.g. Piatt et al., 1999; Zec et al., 1999), suggesting that language processes that have a strong executive component are impaired in Parkinson’s disease. Furthermore, verbal fluency studies have indicated poorer performance with STN stimulation (e.g. Moro et al., 1999; Saint-Cyr et al., 2000; Alegret et al., 2001; Dujardin et al., 2001; Moretti et al., 2002; Daniele et al., 2003; Funkiewiez et al., 2004; De Gaspari et al., 2006); however, studies have also reported no significant change in verbal fluency with STN stimulation (e.g. Limousin et al., 1998; Burchiel et al., 1999; Jahanshahi et al., 2000; Lopiano et al., 2001; Peruzzo et al., 2001; Whelan et al., 2003). Therefore, whilst declines in verbal fluency as a function of STN stimulation have been described, the results of such studies are far from conclusive. Also, the use of paradigms with strong executive components (such as response initiation, set shifting and semantic monitoring) makes it difficult to determine whether specific lexical-semantic processes are impaired in Parkinson’s disease and not just reflective of dysexecutive symptoms typically associated with Parkinson’s disease. There have been a small number of studies that have investigated automatic and/or controlled semantic priming using lexical decision paradigms in Parkinson’s disease (but not as a function of STN stimulation), which enable a more precise mechanism for measuring the integrity of lexical-semantic processes.

In a lexical decision task investigating semantic priming, word/non-word judgements are made on target stimuli which are usually preceded by a semantically related or a semantically unrelated prime word. Semantic priming is said to occur when participant responses to real-word targets are faster for related word pair conditions (e.g. *cat*–*dog*) as opposed to the unrelated conditions (e.g. *cat*–*book*). When investigating semantic priming, the primary factor under investigation is the semantic relatedness of the word pairs. The automaticity of semantic priming effects can be manipulated by varying the stimulus onset asynchrony (SOA; i.e. the time between the onset of the prime and the onset of the target). The primary purpose of manipulating the SOA in semantic priming paradigms is to provide a measure of the time course of the activation of lexical-semantic representations and to provide an understanding of the attentional mechanisms involved in semantic priming. If priming is only found when SOAs are brief (e.g. 300 ms or less), priming is thought to involve non-strategic, automatic processing. In contrast, if priming is found at longer SOAs (e.g. 1000 ms), controlled attentional mechanisms are thought to be involved (Neely, 1977, 1991; Fazio, 2001). Semantic priming is usually found at both short SOAs and often to a greater extent at longer SOAs due to the likelihood that inhibition on unrelated word pairs can also contribute to the magnitude of semantic priming effects (see Neely, 1991 for further information regarding facilitation and inhibition effects associated with semantic priming).

Investigations into semantic priming effects in Parkinson’s disease first emerged over a decade ago, where participants with Parkinson’s disease showed differing patterns of priming compared with healthy controls (Spicer et al., 1994; McDonald et al., 1996). These studies focused their attention on expectancy-based strategic processes in semantic priming, and thus it was difficult to establish whether the differing patterns of semantic priming were due to strategic mechanisms or lexical-semantic processing deficits. Arnott et al. (2001) directly investigated the automatic and controlled mechanisms of semantic priming and explored the time course of semantic priming in Parkinson’s disease. Participants with Parkinson’s disease presented with a delayed time course of semantic activation during automatic semantic priming, and impaired inhibitory processes when controlled semantic priming was elicited. Differing patterns of semantic priming as a function of SOA in participants with Parkinson’s disease have also been reported in semantic priming paradigms measuring ambiguity priming (Copland, 2003), and semantic priming via multi-priming paradigms (Angwin et al., 2003, 2005).

Aberrant lexical-semantic processing in Parkinson’s disease has been attributed to the neuromodulatory influence of dopamine depletion resulting in a decreased signal-to-noise ratio in semantic networks or altering the time course of semantic processing (Arnott et al., 2001; Angwin et al., 2005). Research into the specific influence of basal ganglia-thalamocortical circuits in automatic and controlled lexical-semantic processing in Parkinson’s disease via STN stimulation is yet to be explored.

Evidence that STN stimulation may also affect non-motor basal ganglia-thalamocortical circuits (i.e. anterior cingulate, dorsolateral prefrontal and orbitofrontal circuits) is now emerging. The STN is reported to be functionally segregated into sensorimotor, limbic and
associative regions (Parent and Hazrati, 1995; Hamani et al., 2004). The target for STN stimulation, to alleviate Parkinson’s disease motor symptoms, is the dorsolateral (sensorimotor) portion of the STN. Stimulation of this region of the STN, however, is now thought to spread to the more medial limbic and cognitive regions of the STN as well (Baron et al., 2002; Funkiewiez et al., 2003; McIntyre et al., 2004). This study will therefore aim to measure automatic and controlled semantic priming in Parkinson’s disease and to determine the influence of the neuromodulation of basal ganglia-thalamocortical circuits via STN stimulation on these processes.

**Emotional processing in Parkinson’s disease**

Emotional processing deficits have often been reported in patients with Parkinson’s disease. These deficits have ranged from impairments in the recognition of emotional prosody of speech (e.g. Yip et al., 2003; Schroder et al., 2006) and the recognition of affect in facial expressions (e.g. Borod et al., 1990; Jacobs et al., 1995; Yip et al., 2003; Suzuki et al., 2006) to impairments in the production of emotional facial expressions (Borod et al., 1990; Jacobs et al., 1995), affective prosody (e.g. Pell, 1996; Pell and Leonard, 2003), affectively loaded sentences (e.g. Benke et al., 1998) and emotional discourse (e.g. Crucian et al., 2001).

A small number of studies have explored emotional processing in participants with Parkinson’s disease who are receiving stimulation of the STN. Schneider and colleagues (2003) researched mood induction, emotional memory, emotional discrimination and general cognitive, motor and self-reported mood evaluations in 12 participants with Parkinson’s disease in on and off stimulation conditions. STN stimulation was shown to have a positive influence on self-reported mood state, mood induction, emotional story recall and performance on motor tasks, yet STN stimulation had no effect on facial emotion discrimination and cognition. In contrast to Schneider et al. (2003), three studies have revealed a tendency for STN stimulation to cause deficits in facial discrimination of negative emotions such as anger (Dujardin et al., 2004; Schroeder et al., 2004), fear (Biseul et al., 2005), sadness (Dujardin et al., 2004) and disgust (Dujardin et al., 2004). A neuroimaging study has identified that deficits in the processing of facial expressions of negative emotions or emotional situations in Parkinson’s disease patients receiving STN stimulation are associated with a reduction in the activation of the putamen and fusiform gyrus in on stimulation conditions and increased activity in the anterior cingulate cortex (ACC) in the off stimulation condition during emotional processing (Geday et al., 2006). There is also neurophysiological evidence linking the STN to emotional processing. Kuhn et al. (2005) investigated STN field potentials in participants with Parkinson’s disease whilst viewing affectively neutral, negative and positive picture stimuli. A significantly greater decrease in STN alpha activity was noted when participants viewed affective versus neutral stimuli, suggesting an STN role within the basal ganglia-thalamocortical circuitry which mediates the processing of emotional stimuli (Kuhn et al., 2005).

Wieser et al. (2006) recently identified a dissociation between the early processing of emotional stimuli compared with explicit ratings made on emotional stimuli in participants with Parkinson’s disease. Specifically, Wieser and colleagues investigated event-related potentials in participants with Parkinson’s disease and controls whilst viewing emotional pictures in a rapid serial display (i.e. explicit ratings were not required on the stimuli and the rapid nature of the display made attentional processing of the stimuli unlikely). There was no difference in event-related potentials associated with this task in Parkinson’s disease and controls indicating that participants with Parkinson’s disease do not have a deficit in the early evaluation of emotional stimuli. In contrast, when the participants with Parkinson’s disease explicitly rated emotional stimuli, their affective ratings represented an emotional blunting compared with controls.

At present, there have been no studies that have investigated the automatic activation of emotional evaluations or the evaluation of words representing differing emotional connotations in Parkinson’s disease. This study will investigate such processes in Parkinson’s disease and also measure these processes as a function of stimulation of the STN. The automatic activation of emotional evaluations has often been measured in affective priming paradigms (Fazio, 2001; Klauer and Musch, 2003). Theories of affective priming have originated from studies examining semantic priming in lexical decision tasks. In contrast to semantic priming paradigms, the affective priming paradigm involves the manipulation of affective relatedness. That is, if prime and target words are congruent in emotional valence, reaction times (RTs) are faster than when prime and target word pairs represent different emotional valence (i.e. affectively incongruent) (Fazio et al., 1986). For example, the prime *perjury* and target *hazard* are affectively congruent as they both carry negative emotional valence. In contrast, the prime *anxiety* and target *cloth* are considered to be affectively incongruent as *anxiety* represents a negative emotional valence, yet *cloth* is neutral in emotional valence. Responses to affectively congruent word pairs (e.g. *perjury–hazard*) are generally faster than responses to affectively incongruent stimuli (e.g. *anxiety–cloth*). The RT advantage for affectively congruent stimuli compared with affectively incongruent stimuli is referred to as affective priming. Whilst semantic priming is a measure of the activation of lexical-semantic representations, affective priming is a measure of the activation of evaluations (Fazio, 2001; Klauer and Musch, 2003).

Whilst there are numerous similarities in lexical decision tasks measuring semantic association and tasks measuring affective association, there are only a small number of studies that have either controlled for semantic relationship (Hermans et al., 2002) or concurrently manipulated
semantic and affective relationships (Hill and Kemp-Wheeler, 1989). The lack of control for semantic relationship in affective priming paradigms leads to confusion as to the independency of affective priming based on affective/evaluative association and not semantic association. As affectively congruent stimuli are likely to also be semantically related, affective priming could be a reflection of simultaneous semantic priming.

Hermans et al. (2002) investigated affective priming in a valence decision task and a lexical decision task ensuring that word pairs were semantically unrelated. Affective priming was found to occur in both tasks, therefore showing that affective priming can occur irrespective of semantic relationship. In an earlier study, Hill and Kemp-Wheeler (1989) manipulated both semantic and affective relationships to provide further evidence of affective priming occurring independently of semantic association, and the presence of semantic priming regardless of affective association. Hill and Kemp-Wheeler used a lexical decision task with negative emotional valenced targets paired with affectively related and semantically unrelated primes (e.g. drought–muggers), affectively unrelated and semantically related primes (e.g. dream–nightmare), and affectively unrelated and semantically unrelated primes (e.g. tapestry–crisis). Emotionally neutral targets were also included, but were only paired with semantically and affectively related primes (e.g. saucers–cups) and semantically unrelated and affectively related primes (e.g. aerosol–editor). Affective priming occurred when controlled for semantic relatedness (i.e. responses to emotional targets were faster when paired with affectively congruent, semantically unrelated primes as opposed to non-emotional primes that were semantically unrelated) and semantic priming occurred when controlled for affective relatedness (i.e. responses to emotional targets were faster when they were paired with semantically related primes as opposed to semantically unrelated primes when the word pairs were affectively incongruent). There was no difference in the processing of negative valenced targets compared with neutral valenced targets. This study provided support for the independent mechanisms involved in semantic relatedness and emotional relatedness.

Like the semantic priming literature, the time course of affective priming has been investigated in detail. Affective priming is more commonly found at short SOAs (Fazio et al., 1986; Hermans et al., 1994, 2001; Klauer et al., 1997; De Houwer et al., 1998; Fazio, 2001; Klauer and Musch, 2003), providing evidence that affective priming is fast-acting and automatic. The presence of affective priming only at short SOAs is also supported by the more recent electrophysiological data (e.g. Ortigue et al., 2004; Taylor and Fragopanagos, 2005) which has revealed that the evaluation of emotional stimuli occurs in the very early pre-lexical stages of processing.

In summary, there is evidence that emotional processing and lexical-semantic deficits are associated with Parkinson’s disease and that emotional processing deficits are thought to change when participants with Parkinson’s disease receive stimulation of the STN. This study aims to measure the temporal aspects of lexical-semantic and affective processing using a lexical decision task measuring affective and semantic priming at a short and long SOA. Due to the strong evidence reported in the affective priming literature with respect to the automaticity of affective priming, it would be expected that healthy controls will only exhibit affective priming at the short SOA. As automatic affective processing has been reported to be unaffected by Parkinson’s disease (Wieser et al., 2006), the same patterns of affective priming are predicted for the participants with Parkinson’s disease. A combined affective and semantic priming paradigm also allows for the investigation of the incidental evaluation of word stimuli that differ in emotional connotation. That is, whilst an evaluative response (e.g. valence decision) is not required in a lexical decision task, any RT variations for negatively valenced targets compared with neutrally valenced targets, may suggest an implicit variation in the evaluation of emotional connotation. With respect to semantic priming, it is predicted that semantic priming effects may differ as a function of SOA in participants with Parkinson’s disease, in line with the suggestion that participants with Parkinson’s disease are likely to have differing time course of activations within semantic memory, or deficient attentional mechanisms associated with semantic priming at long SOAs. The manipulation of STN stimulation in participants with Parkinson’s disease who have received DBS, will allow for a direct measure of the involvement of basal ganglia-thalamocortical circuits in these processes.

Material and methods
Participants
Eighteen patients (13 males) diagnosed with Parkinson’s disease who had received the implantation of permanent DBS electrodes into the STN were included in the present study (refer to Table 1 for participant information). All participants with Parkinson’s disease had undergone extensive neurological and psychiatric evaluation prior to undergoing surgery for DBS. They met strict inclusion criteria for admission to the DBS program which included no evidence of significant psychiatric symptoms.

Participants with Parkinson’s disease were tested at least 4 months post-surgery 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 lapsed between the two testing sessions. For the off stimulation condition, the stimulators were turned off for at least 1 hour prior to the commencement of assessments. Four participants were no
longer taking levodopa medication; however, the remaining participants were tested whilst taking their usual medication.

Nineteen non-neurologically impaired participants (13 males) were recruited to act as controls. The average age of the control participants was 62.2 (range = 49–74) years and they had received an average of 13.8 (range = 9–21) years of formal education. The age and education levels of the control participants were not significantly different from the participants with Parkinson’s disease (P = 0.812 and P = 0.591, respectively). 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. All participants provided informed consent for participation which was obtained according to the Declaration of Helsinki and this project was approved by the appropriate Institutional Ethics Committees.

**Apparatus**

Experimental stimuli were presented using E-prime v1.1 (Psychology Software Tools). Participants’ responses were made using a PST Serial Response Box model 200a (Psychology Software Tools), allowing the acquisition of RTs with millisecond accuracy. The stimuli were displayed on a high-resolution (1680 x 1050 pixels) colour monitor, with letter strings presented in black text on a white background. Letters were displayed in lowercase bold Helvetica 18 point font.

**Design and stimulus materials**

The stimuli set consisted of words classed as carrying negative emotional valence (e.g. venom) and words classed as being neutral in emotional valence (e.g. table). The level of emotional valence for most words was derived from affective norms (Toglia and Battig, 1978; Bradley and Lang, 1999). Due to the limited number of affective word norms available to enable a sufficient number of word pairings for the present study, it was necessary to collect an additional set of affective norms. Affective word norms were collected from 66 Australian university students with an average age of 22.3 (SD = 4.3) years and with an average of 16 (SD = 1.6) years of formal education. The university students rated 118 words according to the normative data collection methodology outlined by Bradley and Lang’s (1999) Affective Norms for English Words (ANEW), where words were rated on a scale from 1 to 9 for emotional valence (1 representing the most emotionally negative and 9 representing the most emotionally positive) and emotional arousal (1 representing the least emotionally arousing and 9 representing the most emotionally arousing). As a reliability measure, the 118 words that were rated in the present study consisted of 52 words that were previously rated in Bradley and Lang’s (1999) normative study, and the remaining 66 words were previously un-normed.

**Table 1** Parkinson’s disease participant information

<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 &amp; Y)</th>
<th>UPDRS III on Score</th>
<th>L-Dopa medication (mg/day)</th>
<th>Stimulator settings</th>
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H & Y = Hoehn and Yahr; UPDRS = Unified Parkinson’s Disease Rating Scale; ‘on’ refers to on stimulation and on medication; L = Left, R = Right.
Pearson correlations performed on the 52 mean emotional valence and arousal ratings obtained in the present study and the respective mean emotional valence and arousal ratings obtained in Bradley and Lang’s (1999) study, indicated that the emotional valence and arousal ratings were highly correlated across the two ratings ($r = 0.927, P < 0.001$; $r = 0.496, P < 0.001$, respectively).

The ratings obtained from the present normative study and the ANEW ratings were then classed as negative or neutrally valenced words as per Crosson et al.’s (2002) study. Words with valence ratings less than 3.5 ($M = 2.351, SD = 0.618$) and arousal ratings greater than 5 ($M = 6.472, SD = 0.795$) were classed as carrying negative emotional connotation. Words were considered to not carry any emotional connotation (i.e. neutral words) if they were rated on average between 4 and 6 for emotional valence ($M = 5.144, SD = 0.391$) and less than 5 for arousal ($M = 4.227, SD = 0.360$). Finally, additional valence norms were derived from Toglia and Battig (1978) where words were ranked on a seven point scale with respect to emotional pleasantness (1 representing the most unpleasant and 7 representing the most pleasant). Negative valenced stimuli included in the present study had an average ranking of 2.478 ($SD = 0.298$) and neutral valenced stimuli had an average ranking of 4.191 ($SD = 0.457$).

The stimuli set consisted of a total of 320 prime-target pairs which were divided into two separate lists (List A and List B). Lists A and B real-word targets were matched for imagability [$t(140) = 0.74, P = 0.458$, frequency [$t(156) = -0.526, P = 0.600$] and number of letters [$t(158) = -0.21, P = 0.832$]. Normative data for imagability and frequency were obtained from The MRC Psycholinguistic Database (The University of Western Australia, 1987). In addition, RT and accuracy data was obtained from The English Lexicon Project (Balota et al., 2002) and Lists A and B real-word targets were matched for RT [$t(158) = -0.2, P = 0.790$] and accuracy [$t(158) = -0.374, P = 0.709$]. The lists were presented in two SOA conditions in a counterbalanced manner, in that nine participants with Parkinson’s disease and nine control participants were presented with List A for the short SOA and List B for the long SOA and nine participants with Parkinson’s disease and 10 control participants were presented with List A for the long SOA and List B for the short SOA.

Each list consisted of 80 real-word target pairs and 80 non-word target pairs. Of the 80 real-word pairs, 40 were semantically related and 40 were semantically unrelated word pairs as determined by word association norms (Kiss et al., 1973; Moss and Older, 1996). Using the relatedness values obtained, List A and List B related word pairs were matched for degree of relatedness [Moss and Older, $t(45) = 0.688, P = 0.495$; Kiss et al., $t(73) = 0.504, P = 0.616$].

Within each related and unrelated condition, half of the real-word pairs were affectively congruent (i.e. the prime and targets were both of negative valence or the primes and targets were both affectively neutral) and the remaining half consisted of affectively incongruent word pairs (i.e. one neutral and one negative word). See Table 2 for examples of real-word target pairings.

Within Lists A and B, all related and unrelated targets were matched for imageability, frequency, number of letters, RT and accuracy ($P > 0.1$). All congruent and incongruent targets were also matched for imageability, frequency, number of letters, RT and accuracy ($P > 0.1$).

The 80 non-word target pairs comprised either a unique negative or neutrally valenced prime word, selected from the same norms and criteria described earlier, and were paired with orthographically legal and pronounceable non-word targets which were not homophonic with real English words. Non-words were selected from the ARC Nonword Database (Rastle et al., 2002) and were matched with the real-word targets for number of letters [$t(318) = 0.040, P = 0.968$].

Within each list, the 160 real word and non-word pairs were pseudo-randomly divided into four different blocks consisting of 20 real-word pairs and 20 non-word target pairs. All items within each block were pseudo-randomly organized, so that neither a word or non-word condition was presented more than three times consecutively. For each participant on each occasion, the four blocks were presented in a random order. Two non-experimental buffers were presented prior to the commencement of each block.

### Procedure

Participants were advised of the process of making a lexical decision using the yes/no method (i.e. respond by pressing one button if the target was a real word and pressing an alternate button if the target was a non-word). Participants were also advised to respond as quickly as possible, without compromising accuracy.

For the short SOA condition, a fixation cross appeared centrally for 750 ms followed by the prime for 150 ms and an inter-stimulus interval of 50 ms, making the short SOA equal to 200 ms. The target was then presented for 3000 ms.
or until a response was made. The following trial commenced 1500 ms after the completion of the previous trial. The long SOA condition consisted of the fixation cross also appearing centrally for 750 ms; however, the prime was presented for 750 ms and with an inter-stimulus interval of 250 ms. The target was also presented for 3000 ms or until the participant responded. Therefore, the long SOA condition consisted of an SOA of 1000 ms.

Before the commencement of each experiment, participants were shown a demonstration of the task containing two items. Following this, they participated in a practice session containing 20 unique items. Each experiment took ~25 min to complete.

Results

Statistical analyses were performed on RT data pertaining to real-word responses only. RT data was excluded from analyses if the participant’s response resulted in an error (3.29% of data for participants with Parkinson’s disease and 1.41% of data for control participants), if RTs were <100 or >2000 ms (1.7% of data), and if RTs deviated more than two standard deviations from the condition means for each participant (4.7% of data). Statistical analyses were not conducted on the error data due to the overall low number of errors in the present study. Visual inspection of the RT distribution revealed that the data was positively skewed and violation of distribution normality was confirmed with the Kolmogorov–Smirnov Test of Normality ($P < 0.001$). Therefore, statistical analyses were conducted on the logarithmic transformation of the RT data. For ease of interpretation, raw RT data will be presented for descriptive purposes only.

Affective and semantic priming on negative and neutral targets

Linear Mixed Model (LMM) analyses were conducted on RT data with session (Parkinson’s disease on versus off stimulation, and controls) as within and between-subjects fixed factors. Affective congruency (congruent and incongruent), semantic relatedness (related and unrelated), target valence (negative and neutral) and SOA (short and long) were included as within-subjects fixed factors. RT subject variations, in addition to subject variation across sessions for participants with Parkinson’s disease, were treated as random factors. Refer to Tables 3 and 4 for mean (SD) RTs for Parkinson’s disease and control participants.

Initial analyses revealed a significant main effect for session [$F(2, 25.057) = 4.660$, $P < 0.05$], and highly significant main effects for affective congruency [$F(1, 7967.072) = 14.722$, $P < 0.001$], semantic relatedness [$F(1, 7967.116) = 163.169$, $P < 0.001$], target valence [$F(1, 7967.108) = 19.051$, $P < 0.001$] and SOA [$F(1, 7967.249) = 17.702$, $P < 0.001$].

An interaction between session and target valence reached significance [$F(2, 7967.148) = 4.438$, $P < 0.05$]. Planned contrasts on the parameter estimates revealed that RTs for control participants were significantly slower on negatively valenced targets ($M = 710$ ms, $SD = 163$ ms) compared with RTs on neutral targets ($M = 695$ ms, $SD = 156$ ms; $P < 0.005$). Similarly, participants with Parkinson’s disease in the on stimulation condition were also significantly slower on negative targets ($M = 854$ ms, $SD = 278$ ms) in comparison to neutral targets ($M = 830$ ms, $SD = 268$ ms; $P < 0.001$); however this was not the case during off stimulation where an average 5 ms RT advantage for neutral targets was not statistically significant ($P > 0.05$).

Therefore, regardless of the semantic relatedness or affective congruency of word pairs, RTs in the Parkinson’s disease on stimulation condition and control participant RTs were significantly slower on negatively valenced targets compared with neutrally valenced targets.

A two-way interaction between affective congruency and semantic relatedness was significant [$F(1, 7967.089) = 13.135$, $P < 0.001$]. A three-way interaction between affective congruency, semantic relatedness and SOA was highly significant [$F(1, 7967.154) = 14.102$, $P < 0.001$], and a four-way interaction between session, affective congruency, semantic relatedness and SOA was also significant [$F(2, 7967.187) = 7.402$, $P = 0.001$]. Affective priming was therefore analysed separately on semantically unrelated word pairs, and semantic priming on affectively incongruent word pairs, to further isolate the effects

<table>
<thead>
<tr>
<th>Table 3 Mean (SD) RTs for participants with Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>On stimulation</td>
</tr>
<tr>
<td>Short SOA</td>
</tr>
<tr>
<td>Related and congruent RTs (ms)</td>
</tr>
<tr>
<td>Negative         Neutral                                    Negative         Neutral</td>
</tr>
<tr>
<td>860 (285)         824 (282)                                 817 (284)         810 (285)</td>
</tr>
<tr>
<td>828 (258)         813 (246)                                 862 (290)         804 (266)</td>
</tr>
<tr>
<td>845 (229)         824 (269)                                 851 (302)         848 (300)</td>
</tr>
<tr>
<td>898 (257)         865 (251)                                 895 (307)         852 (249)</td>
</tr>
</tbody>
</table>

SOA = stimulus onset asynchrony; RT = reaction time; negative and neutral refers to the valence of the target stimuli; related and unrelated refers to the semantic relatedness of word pairs and congruent and incongruent refers to the affective congruency of word pairs.
of affective priming and semantic priming as a function of session and SOA.

**Affective priming on semantically unrelated word pairs**

To gain an understanding of affective priming effects as a function of session and SOA, LMM analysis was conducted on semantically unrelated targets only. The main effects for session, congruency and SOA were consistent with the preliminary analysis.

In relation to affective priming effects, there was a significant interaction between affective congruency and SOA \([F(1,3921.449) = 6.549, P < 0.05]\). Mean RTs for affectively congruent and incongruent word pairs at each SOA are presented in Fig. 1. Planned contrasts on the parameter estimates revealed that affective priming effects were evident at the short SOA condition \((P < 0.001)\), but not the long SOA condition \((P > 0.05)\). There was no interaction between session, affective congruency and SOA \([F(2,3921.032) = 2.028, P > 0.05]\), suggesting that the presence of affective priming at short SOAs was consistent for control participants and participants with Parkinson’s disease in on and off stimulation conditions.

**Semantic priming on affectively incongruent word pairs**

In order to isolate semantic priming effects, LMM analyses were conducted on the RTs for affectively incongruent word pairs. Again, the main effects of session, semantic relatedness and SOA were consistent with the initial analysis.

With respect to semantic priming, there was a significant interaction between semantic relatedness and SOA \([F(1,3945.475) = 5.116, P < 0.05]\). Interestingly, the interaction between session, semantic relatedness and SOA also reached statistical significance \([F(2,3945.688) = 4.172, P < 0.05]\), suggesting that the magnitude of semantic priming at the short and long SOAs differed as a function of session. The means (SD) for this interaction are presented in Table 5.

Planned contrasts on the parameter estimates were performed to isolate semantic priming effects for each session at short and long SOAs. Significant semantic priming was evident for all testing sessions at the short SOA \((P < 0.001)\). In contrast, at the long SOA, significant priming was only found amongst controls and participants with Parkinson’s disease in the on stimulation condition \((P < 0.001)\). The mean priming effect of 6 ms failed to reach

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**Table 4 Mean (SD) RTs for control participants**

<table>
<thead>
<tr>
<th></th>
<th>Short SOA (ms)</th>
<th>Long SOA (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related and congruent RTs (ms)</td>
<td>714 (166)</td>
<td>653 (109)</td>
</tr>
<tr>
<td>Related and incongruent RTs (ms)</td>
<td>717 (175)</td>
<td>662 (132)</td>
</tr>
<tr>
<td>Unrelated and congruent RTs (ms)</td>
<td>750 (209)</td>
<td>702 (132)</td>
</tr>
<tr>
<td>Unrelated and incongruent RTs (ms)</td>
<td>761 (180)</td>
<td>733 (150)</td>
</tr>
</tbody>
</table>

SOA = stimulus onset asynchrony; RT = reaction time; negative and neutral refers to the valence of the target stimuli; related and unrelated refers to the semantic relatedness of word pairs and congruent and incongruent refers to the affective congruency of word pairs.

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Fig. 1 Affective priming as a function of SOA condition. *P < 0.001.
The present study investigated automatic and controlled processing of lexical-semantic representations via a semantic priming paradigm, the automatic activation of emotional evaluations via an affective priming paradigm, and the incidental processing of stimuli representing differing emotional connotations. The following discussion will address each of these processes in relation to theoretical models of semantic priming, affective priming and the processing of emotional words and the potential involvement of basal ganglia-thalamocortical circuits in these processes.

**Semantic priming**

In the present study, semantic priming was evident at the short SOA for both control and participants with Parkinson’s disease in on and off stimulation conditions. The purpose of investigating semantic priming at short SOAs is to study access to lexical-semantic representations which is due to automatic spread of activation, rather than being confounded by pre-lexical or post-lexical attentional mechanisms (Neely, 1991). The comparable semantic priming effects at the short SOA for both control and participants with Parkinson’s disease (on stimulation and off stimulation) suggests that the automatic spread of activation of lexical-semantic representations is unimpaired in Parkinson’s disease and is not influenced by the modulation of basal ganglia-thalamocortical circuits via stimulation of the STN. Unimpaired automatic semantic priming in the present study is consistent with Copland’s (2003) study where comparable priming of ambiguous meanings was found in participants with Parkinson’s disease and controls when a short inter-stimulus interval was employed. Also, a lack of interaction between priming effects in control and participants with Parkinson’s disease at short SOAs has also been presented in studies utilising multi-priming paradigms (Angwin et al., 2003, 2005), further supporting the notion that automatic semantic priming is unaffected by Parkinson’s disease.

Whilst similar semantic priming effects at the short SOA were evident in Parkinson’s disease (both on and off stimulation) and control participants in the present study, this was not the case at the long SOA. Specifically, participants with Parkinson’s disease in the off stimulation condition displayed an absence of semantic priming at the long SOA in contrast to the presence of semantic priming in the Parkinson’s disease on stimulation condition and control participants. The absence of semantic priming at long SOAs in the off stimulation condition is consistent with Angwin et al.’s (2005) study which found no significant priming effects for participants with Parkinson’s disease at a long SOA (1200 ms) compared with the presence of semantic priming effects in control participants.

Semantic priming effects at long SOAs are more likely to elicit controlled semantic priming, which are influenced by attentional mechanisms (Neely, 1991). For example, semantic priming at long SOAs can be influenced by facilitatory spread of activation for related word pairs in comparison to neutral conditions (e.g. if a prime display consists of a series of x’s or the word blank), or when attentional mechanisms are in play, inhibitory processing of unrelated word pairs compared with neutral conditions can occur. Also, the investigation of semantic priming effects at various SOAs allows for the charting of the time course of activation within semantic memory. For example, the Gain/Decay hypothesis proposed by Milberg and colleagues, to explain patterns of semantic priming in Alzheimer’s disease, suggests that pathological semantic priming can be influenced by the speed of initial activation, the level of activation and the subsequent decay of activations within semantic memory (Milberg et al., 1999).

The lack of semantic priming at the long SOA for participants with Parkinson’s disease in the off stimulation condition could reflect reduced attentional mechanisms (thereby reducing inhibitory effects for the semantically unrelated condition) and/or decay in the activation of lexical-semantic representations of prime words with time (i.e. degradation of spread of activation effects) resulting in reduced facilitation on related word pairs. Reduced inhibition on semantically unrelated word pairs and

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**Table 5** Mean (SD) semantic priming effects in Parkinson’s disease and control participants as a function of SOA

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease participants</th>
<th>Control participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On stimulation</td>
<td>Off stimulation</td>
</tr>
<tr>
<td></td>
<td>Short SOA</td>
<td>Long SOA</td>
</tr>
<tr>
<td>Semantically related RTs (ms)</td>
<td>818 (250)</td>
<td>824 (276)</td>
</tr>
<tr>
<td>Semantically unrelated RTs (ms)</td>
<td>876 (253)</td>
<td>867 (271)</td>
</tr>
<tr>
<td>Semantic priming effect (ms)</td>
<td>58*</td>
<td>43*</td>
</tr>
</tbody>
</table>

*P < 0.001. SOA = stimulus onset asynchrony.

Significance for the participants with Parkinson’s disease in the off stimulation condition (P > 0.05).
reduced facilitation on semantically related words pairs may have resulted in reduced semantic priming effects in the present study. However, determining the degree to which facilitatory and inhibitory effects influence semantic priming in the present study would require the use of a neutral prime condition to serve as a baseline for such effects.

Regardless of the facilitatory and inhibitory mechanisms that are affected in participants with Parkinson’s disease at the long SOA, STN stimulation in the present study resulted in the restoration of semantic priming. The dissociation between semantic priming effects at the long SOA as a function of STN stimulation condition is suggestive of a role of basal ganglia-thalamocortical circuits in either the attentional mechanisms involved in semantic priming or in the prolongation of facilitatory effects of semantic priming at a long SOA.

The recent emergence of fMRI studies investigating the regions of neural activation associated with semantic priming provide an insight into potential regions within the basal ganglia-thalamocortical circuitry associated with semantic priming at long SOAs. For example, Rossell et al. (2001) reported activity within the striatum associated with semantic priming at long SOAs. Furthermore, whilst ACC activity was associated with semantic priming at short and long SOAs, the region activated was generally more caudal in the long SOA condition. More recently, Gold et al. (2006) found greater activation bilaterally in the ACC during semantic priming at long SOAs compared with semantic priming at short SOAs. Generally, ACC activity associated with semantic priming at long SOAs has been attributed to inhibitory mechanisms in semantic priming (Gold et al., 2006).

To summarize, the semantic priming effects observed in the present study suggest that automatic access to lexical-semantic representations is unimpaired in Parkinson’s disease, yet Parkinson’s disease is associated with aberrant semantic priming at long SOAs either due to reduced attentional mechanisms or early decay of activation of lexical-semantic representations. Considering that controlled semantic priming is modulated by STN stimulation implies a link between controlled semantic priming and impairment of basal ganglia-thalamocortical circuits. Furthermore, a link between semantic priming at long SOAs and activity in the ACC (Gold et al., 2006) suggests that STN stimulation may act to re-establish semantic priming via ACC basal ganglia-thalamocortical neuromodulation.

**Affective priming**

When isolating affective priming effects in the present study, significant priming effects were only evident at the short SOA for both Parkinson’s disease (on and off stimulation conditions) and control participants. The lack of affective priming at long SOAs is consistent with the majority of affective priming studies that have suggested that affective priming only occurs at short SOAs (Fazio et al., 1986; Hermans et al., 1994, 2001; Klauer et al., 1997; De Houwer et al., 1998; Fazio, 2001; Klauer and Musch, 2003). The presence of affective priming at short SOAs and the lack of affective priming at long SOAs is a reflection of the automatic activation of emotional evaluations, which is likely to occur at the pre-lexical stage of processing. In the present study, affective priming effects at either SOA were comparable for participants with Parkinson’s disease and controls. Thus, the automatic activation of emotional evaluations appears to be unimpaired in Parkinson’s disease. Furthermore, modulation of basal ganglia-thalamocortical circuits via STN stimulation does not result in alterations to affective priming effects in Parkinson’s disease, indicating that these circuits are not likely to be involved in the automatic activation of emotional evaluations. This finding is supported by the observation that event-related brain potentials of early stage emotional processing of emotionally valenced pictures were no different for participants with Parkinson’s disease compared with controls (Wieser et al., 2006). The present study also investigated the incidental processing of negatively and neutrally valenced written word stimuli. In utilizing a lexical decision task which consisted of negative and neutral targets, a direct emotional valence judgement was not required; however, differential RTs to negative versus neutral stimuli whilst making a lexical decision task provides a measure of the implicit evaluation of negatively and neutrally valenced stimuli. This will be discussed in more detail later.

**Valence processing**

In the present study, responses to negative targets were significantly slower in comparison to neutral targets for control participants and participants with Parkinson’s disease in the on stimulation condition, regardless of affective congruency or semantic relatedness of word pairs. Rossell and Nobre (2004) similarly found that lexical decision times to negative stimuli are typically delayed compared with both neutral and positive targets in healthy controls. Also, other studies requiring decisions on negatively versus neutrally or positively valenced stimuli have also shown delays in the processing of negative stimuli (e.g. White, 1996; Dahl, 2001). Functional neuroimaging studies have shown greater activation in the right ACC, bilateral middle temporal gyrus, left posterior gyrus and the amygdala bilaterally, when healthy controls are making lexical decisions on negatively valenced stimuli compared with neutral stimuli (Nakic et al., 2006). Kuchinke et al. (2005), however, only found greater activation in the right inferior frontal gyrus (including the dorsolateral prefrontal cortex) during the processing of negative versus neutral stimuli. Left ACC activity was associated with the
processing of neutral stimuli compared with less activity with negative stimuli.

Interestingly, differential processing of negative versus neutral targets was not evident in participants with Parkinson’s disease without STN stimulation in the present study. Whilst participants with Parkinson’s disease in the off stimulation condition did not display impairment in the automatic activation of emotional evaluations via affective priming effects, it would appear that abnormal processing of negative stimuli is evident. Specifically, a lack of dissociation between negative and neutrally valenced stimuli in the off stimulation condition may be indicative of a deficit in the evaluation of negative valence via lexical decision in the present study. An alternative interpretation of these findings is that the different pattern of negative versus neutral RTs on and off stimulation may reflect a slowing of neutral RTs in the off stimulation condition, compared with the on condition. However, such direct comparisons of the neutral RTs (between on and off stimulation conditions) are not as valid as within condition contrasts, due to increased variability between stimulus testing sessions.

Limited research has been conducted with respect to the processing of negative emotionally valenced words in participants with Parkinson’s disease; however, as discussed previously, impairments have been reported in the processing of negative emotions in facial expression (Jacobs et al., 1995; Yip et al., 2003), the accurate processing of affective prosody (Pell, 1996; Pell and Leonard, 2003), affectively loaded sentences (Benke et al., 1998) and emotional discourse (Crucian et al., 2001), suggestive of an impairment in emotional processing in Parkinson’s disease. This is the first study to extend these results to include a deficit in the incidental processing of negatively versus neutrally valenced words in Parkinson’s disease.

Whilst the processing of negatively versus neutrally valenced stimuli appears impaired in participants with Parkinson’s disease when not receiving stimulation of the STN, the present data suggests that when STN stimulation is applied, the processing of such stimuli is comparable to control participants. That is, consistent with the results from control participants, when participants with Parkinson’s disease were assessed in the STN stimulation condition, delayed RTs when incidentally processing negative stimuli compared with neutral stimuli were evident. Therefore, STN stimulation may act to restore activity within the basal ganglia-thalamocortical circuits to allow lexical detection of word stimuli representing negative emotional connotation. These results are consistent with other reported improvements in affective processing with STN stimulation (Schneider et al., 2003). The results of the present study, however, are in contrast with studies investigating facial discrimination deficits in Parkinson’s disease with STN stimulation (Dujardin et al., 2004; Schroeder et al., 2004; Bisel et al., 2005). It should be noted that these facial discrimination deficits associated with STN stimulation have been isolated to the discrimination of angry emotions (Schroeder et al., 2004), or have explored the effects of STN stimulation on emotional processing in a preoperative versus on stimulation comparison, rather than a direct measure of stimulation via an on stimulation versus off stimulation condition (Dujardin et al., 2004; Bisel et al., 2005).

In conclusion, the present study indicates that automatic lexical-semantic and evaluative processes are unimpaired in Parkinson’s disease and the neuromodulation of basal ganglia-thalamocortical circuits does not influence these processes. In contrast, participants with Parkinson’s disease showed a pattern of aberrant controlled lexical-semantic processing as evidenced by a lack of semantic priming effects at a long SOA condition for participants with Parkinson’s disease in the off stimulation condition. Controlled semantic priming was restored, however, when the participants with Parkinson’s disease were receiving stimulation of the STN, suggesting that STN stimulation modulates basal ganglia-thalamocortical circuits that are involved in such processes. Finally, the lack of dissociation between RTs on negative versus neutral targets in participants with Parkinson’s disease in the off stimulation condition and presence of dissociation in participants with Parkinson’s disease in the on stimulation condition along with controls, supports aberrant incidental evaluation of negatively versus neutrally valenced stimuli in Parkinson’s disease and the subsequent restoration of such processing when disrupted basal ganglia-thalamocortical circuits are modulated by STN stimulation.

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