Dopaminergic Neuromodulation of Semantic Processing: A 4-T fMRI Study with Levodopa

There is emerging evidence that alterations in dopaminergic transmission can influence semantic processing, yet the neural mechanisms involved are unknown. The influence of levodopa (L-DOPA) on semantic priming was investigated in healthy individuals (n = 20) using event-related functional magnetic resonance imaging with a randomized, double-blind crossover design. Critical prime–target pairs consisted of a lexical ambiguity prime and 1) a target related to the dominant meaning of the prime (e.g., bank-money), 2) a target related to the subordinate meaning (e.g., fence-sword), or 3) an unrelated target (e.g., ball-desk). Behavioral data showed that both dominant and subordinate meanings were primed on placebo. In contrast, there was preserved priming of dominant meanings and no significant priming of subordinate meanings on L-DOPA, the latter associated with decreased anterior cingulate and dorsal prefrontal cortex activity. Dominant meaning activation on L-DOPA was associated with increased activity in the left rolandic operculum and left middle temporal gyrus. These findings suggest that L-DOPA enhances frequency-based semantic focus via prefrontal and temporal modulation of automatic semantic priming and through engagement of anterior cingulate mechanisms supporting attentional/controlled priming.

Keywords: brain imaging, dopamine, fMRI, language, lexical ambiguity, semantic priming

Introduction

The role of dopamine (DA) in human cognition, including its possible neural mechanisms, has been primarily investigated with respect to working memory and learning (e.g., Cools 2006; Cools et al. 2007; Rowe et al. 2008). Yet, there is also emerging evidence that DA modulation influences language function and, in particular, semantic processing in healthy subjects (Kischka et al. 1996; Copland, Chenery, et al. 2003; Angwin et al. 2004; Roesch-Ely et al. 2006) and in neurocognitive disorders such as Parkinson’s disease (PD) (Angwin, Chenery, et al. 2006) and schizophrenia (Goldberg et al. 2000). However, the nature of the neuromodulatory role played by DA in semantic processing is unclear, as are the neural systems it engages.

The present study employed a semantic priming functional magnetic resonance imaging (fMRI) task to investigate the neuromodulatory role of DA in semantics. The semantic priming effect refers to the increased speed and accuracy in word recognition tasks, such as lexical decisions (word/nonword), made on target words when preceded by a semantically or associatively related prime word (e.g., doctor-nurse), compared with an unrelated word (e.g., bread-nurse). Semantic priming effects are assumed to reflect automatic spreading activation within semantic memory and/or attentional processes including expectancy generation, where the subject develops an expectancy set based on the prime, and postlexical semantic checking, where the relationship between the target and the prime is judged (Neely 1991). It is generally assumed that employing a short prime–target interval or stimulus-onset asynchrony (SOA) taps into primarily automatic priming mechanisms, whereas controlled or attentional priming mechanisms are invoked with longer SOAs and by increasing expectancies by manipulations of instructions or the proportion of related targets (Neely 1991).

Kischka et al. (1996) first observed that, compared with a placebo group, healthy individuals who have ingested l-DOPA (a DA precursor) show reduced indirect priming (e.g., summer–snow). This observation led to the proposal that DA focuses spreading activation within semantic networks, reducing the activation of distantly related items, consistent with increasing signal-to-noise ratio (SNR) of information processing. A subsequent study found that l-DOPA ingestion by healthy subjects performing a masked semantic priming task appeared to both speed up semantic activation at a short SOA and attenuate both direct and indirect priming effects at longer SOAs (Angwin et al. 2004), consistent with a role in accelerating lexical activation in terms of both gain and decay but not fully in keeping with an enhanced SNR within semantic networks as proposed previously (Kischka et al. 1996). A more recent study observed a trend toward decreased indirect priming for targets presented to the right visual field/left hemisphere when healthy subjects received pergolide (a D1/D2 agonist) but not bromocriptine (a D2 agonist) (Roesch-Ely et al. 2006), suggesting that DAergic semantic modulation may occur via D1 mechanisms influencing semantic associations. Although the use of a divided visual field paradigm indirectly implicates left hemisphere involvement in DA neuromodulation of semantics, the actual neural substrates remain unknown.

Lexical ambiguities (words with multiple meanings) provide an ideal avenue for investigating how DA influences the processing of competing representations (Cohen and Servan-Schreiber 1992). In the absence of context, meanings of ambiguities are selected and suppressed on the basis of preexisting meaning biases (Simpson and Burgess 1985), thus providing a means of testing the ability to select and inhibit competing information in the domain of semantic processing. The lexical ambiguity priming task employed in the present study involves priming of dominant-related (e.g., bank-money) versus subordinate-related (e.g., bank-river) word pairs. This paradigm is sensitive to semantic processing alterations in PD (Copland 2003) and to l-DOPA-induced priming modulation in healthy individuals (Copland, Chenery, et al. 2003), where reduced subordinate meaning priming was observed in healthy conditions.
individuals who have ingested L-DOPA (Copland, Chenery, et al. 2003), providing further evidence of increased focusing of activation within semantic networks.

To examine the neuromodulation of semantic processing by DA, we investigated the brain mechanisms associated with L-DOPA-induced modulation of semantic priming in healthy individuals with fMRI. L-DOPA is taken up into DAergic neurons, enzymatically converted to DA, and can be released into the synaptic cleft in a phasic manner (Robinson et al. 2003). In the present study of lexical ambiguity priming on L-DOPA, we employed a short prime–target SOA of 150 ms to capture the activation of multiple competing meanings (Simpson and Burgess 1985). Cohen and Servan-Schreiber (1992) have argued that the selection of meanings for lexical ambiguities represents a situation where a change in DAergic activity may alter behavior, as witnessed in schizophrenia. As per our previous behavioral findings, we predicted that ingestion of L-DOPA in healthy individuals would enhance dominant meaning activation and/or reduce subordinate meaning activation, as opposed to the comparable priming of dominant and subordinate representations on placebo (Copland, Chenery, et al. 2003).

Previous neuroimaging studies of semantic priming indicate that both the regions engaged, and the direction of blood oxygen level-dependent (BOLD) signal change for related versus unrelated conditions varies as a function of the degree of automatic versus controlled processing mechanisms engaged (typically via manipulations of the prime–target interval) and the type of relationship between the prime and target (e.g., Twilley et al. 2006). Previous event-related neuroimaging studies of semantic priming that have employed a lexical decision task with a short prime–target interval (see Table 1) suggest that more automatic aspects of semantic priming typically engage portions of the left temporal lobe (including superior, middle, and inferior temporal regions) (Kotz et al. 2002; Copland, de Zubicaray, et al. 2003; Rissman et al. 2003; Gold et al. 2006) and frontal regions including the left inferior frontal gyrus (Kotz et al. 2002; Copland, de Zubicaray, et al. 2003) and middle frontal gyrus (MFG, Kotz et al. 2002; Rissman et al. 2003). Controlled or attentional forms of semantic priming have been associated with modulated activity in the left middle temporal gyrus, left inferior prefrontal cortex, and the anterior and posterior cingulate (Matsumoto et al. 2005; Gold et al. 2006; Tivarus et al. 2006; Copland et al. 2007; O’Hare et al. 2008).

As the present study employed a short prime–target interval, it was hypothesized that L-DOPA would modulate activity within the network of regions engaged during automatic semantic priming discussed above. Of these regions, the prefrontal cortex, and particularly the dorsolateral prefrontal cortex, has been strongly implicated in DAergic modulation of cognition (Arnsten 1998; Mattay et al. 2002; Cools 2006). An alternative hypothesis is that DA enhances attentional capacity during information processing (Clark et al. 1987), and subjects on L-DOPA will therefore engage a network of regions associated with more attentional or strategic forms of semantic priming. Of these regions, the anterior cingulate has been linked to DAergic modulation of cognition in both healthy individuals and in PD (Mattay et al. 2002; Aalto et al. 2005). Given the proposal that DA may enhance semantic salience and/or accelerate lexical processing, the behavioral effects we expected were an increased selectivity of meaning activation either through increased priming of dominant targets and/or inhibition of subordinate targets on L-DOPA relative to placebo.

### Materials and Methods

#### Subjects

Twenty young healthy right-handed volunteers (8 females) were recruited from The University of Queensland (mean age = 27.3 years; mean education = 15.3 years). Exclusion criteria included any psychotropic, antidepressant, or antihypertensive medications; pregnancy; and any history of mental illness or neurological disease or trauma. Subjects undertook a medical interview to confirm suitability for the study. This study was approved by The University of Queensland Medical Research Ethics Committee. All subjects gave informed written consent prior to participation and received $30 per session for participation.

#### Drugs and Study Design

A randomized double-blind, placebo-controlled crossover design was employed. Subjects were randomly assigned to receive either placebo or L-DOPA in session 1 and the other treatment in session 2 at least 6 days later. Order of drug and placebo was randomized and administered by a research nurse (blind to participants and investigators). A Madopar capsule containing 100 mg L-DOPA and 25 mg benserazide (a peripheral decarboxylase blocker) was administered. Testing took place 45 min after ingestion of the capsule. This time delay is consistent with peak plasma L-DOPA levels (Olson et al. 2000). The dose is identical to that previously used in semantic priming tasks (Kischka et al. 1996), and we have used this dosage and time delay successfully in a cohort of 39 university students to demonstrate altered semantic priming without any adverse side effects (Angwin, Chenery, et al. 2006). Blood pressure and heart rate were taken prior to tablet ingestion and following the scan. Plasma DA levels were measured (blood samples were taken immediately prior to scanning) by reverse-phase high-performance liquid chromatography with electrochemical detection. The mood of subjects was measured immediately prior to scanning using the Bond and Lader measure of subjective feelings (Bond and Lader 1974).

#### Priming Experiment and Procedure

The priming experiment was adapted from a previous fMRI study of lexical ambiguity priming in healthy individuals (Copland, de Zubicaray, et al. 2003). Lexical ambiguities (words with one form and multiple independent meanings) were selected from norms (Nelson et al. 1980; Twilley et al. 1994) and further pretested on a separate group of young healthy participants to ensure that all ambiguities had 2 independent meanings, a dominant meaning provided at least 70% of the time by respondents and a subordinate meaning provided less than 30% of the time. One hundred and fifty lexical ambiguities were used as primes paired with targets that were a dominant associate (e.g., bank-money), a subordinate associate (e.g., fence-sword), an unrelated associate (e.g., ball-desk), or a legal nonword (e.g., mint-blark). Each critical condition consisted of 30 word pairs. There were 60 word–nonword pairs. There

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**Table 1**

Main regions involved in automatic semantic priming observed in event-related lexical decision fMRI studies.

<table>
<thead>
<tr>
<th></th>
<th>Middle/superior temporal</th>
<th>Inferior temporal</th>
<th>Inferior frontal</th>
<th>Middle frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copland, de Zubicaray, et al. 2003</td>
<td>L MTG</td>
<td>L IFG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold et al. 2006</td>
<td>L MTG, planum temporale</td>
<td>L fusiform</td>
<td>IFG, frontal</td>
<td>MFG, R MFG</td>
</tr>
<tr>
<td>Kotz et al. 2002</td>
<td>L STG</td>
<td></td>
<td>MFG</td>
<td>R MFG</td>
</tr>
<tr>
<td>Rissman et al. 2003</td>
<td></td>
<td></td>
<td>L MFG, R MFG</td>
<td></td>
</tr>
</tbody>
</table>

Note: L, left; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; R, right; STG, superior temporal gyrus.
was no significant difference ($P > 0.05$) between the primes of the critical conditions in terms of word length, frequency (Kucera and Francis 1967), and concreteness (MRC Database) (see Table 2 for stimuli characteristics). There was no significant difference ($P > 0.05$) between the matched targets of the different conditions in terms of length, frequency, concreteness, or lexical decision reaction time in isolation (Balota et al. 1999).

Following a warning, the prime word was presented for 150 ms followed by target presentation for 2 s, during which time the response was recorded. Five trial types (4 priming conditions in addition to null trials) were presented randomly, across 2 imaging sessions; 75 word pairs were presented in each session. The intertrial intervals were randomized to ensure optimal statistical efficiency (Dale 1999; range approximately 120 fixation [null] trials) and a practice block of 20 items was completed prior to commence-ment of the experiment.

Image Acquisition
Images were acquired with a 4-T Bruker MedSpec system using a transverse electromagnetic head coil (Vaughan et al. 2002). A total of 570 echo planar imaging (EPI) images were acquired over 2 runs (time echo [TE] = 30 ms, time repetition [TR] = 2100 ms). Each brain volume consisted of 36 planes, in-plane resolution 3.6 mm, and slice thickness 3 mm (0.6-mm gap). A high-resolution magnetization-prepared rapid gradient-echo (MP-RAGE) 3D T1 image was acquired within the same session (time to inversion [TI] = 700 ms, TR = 1500 ms, TE = 3.35 ms, resolution 0.9 x 0.9 x 0.9 mm). The first 5 volumes in each session were ignored so that magnetization could reach steady state. Foam padding was used to limit head movement.

Image Processing and Analysis
Data were preprocessed and analyzed using statistical parametric mapping (SPM) software (SPM2; Wellcome Department of Cognitive Neurology, Queens Square, London, UK). Data were slice timing corrected, spatially normalized via nonlinear basis function to T1 and EPI template images, and smoothed (full width at half maximum [FWHM] 8 mm Gaussian). A general linear model was applied to the signal intensity time course of each voxel (Worsley and Friston 1995). The fixed-effects model included separate covariates consisting of a transient hemodynamic response function (HRF) and its temporal derivative for transient BOLD responses to 5 different trial types: correctly performed trials from dominant, subordinate, unrelated, and nonword conditions and errors. Realignment parameters were used within the design as covariates of no interest. Planned contrasts were employed to compare the HRF parameter estimates only for the experimental conditions for each participant. Drug main effects were examined by collapsing dominant, subordinate, and unrelated conditions. Drug-by-condition interactions were examined for each priming comparison (dominant vs. subordinate, dominant vs. unrelated, and subordinate vs. unrelated). The resulting contrast images from the single within-subject fixed-effects analyses were masked to include only gray matter voxels using the mask provided in SPM2 and entered into 1-tailed $t$-tests in group random-effects analyses to allow inferences about condition-by-drug interactions and drug main effects across participants.

Following Mehta et al. (2000), for drug-by-condition interactions, voxels exceeding $P < 0.001$ (uncorrected) with a minimum cluster of 5 voxels are reported for regions where we had reasonable a priori expectations of modulated priming-related activity on L-DOPA (see Introduction). Exploratory whole-brain analyses were also conducted using a significance level of $P < 0.05$, corrected, as per (Mehta et al. 2000).

Results

Cardiovascular and Mood Effects
Plasma DA levels were increased on L-DOPA (mean = 7145 pmol/L) versus placebo (mean = 302 pmol/L). Paired-sample $t$-tests showed that there were no significant differences on placebo versus L-DOPA in self-rated subjective mood (Bond and Lader 1974) or in blood pressure or heart rate measured at baseline and immediately after testing ($P > 0.05$).

Behavioral Effects
Behavioral reaction time (RT) analyses were conducted on correct real-word lexical decisions. Errors were only made on 1.69% of real-word trials overall, with no main effect of drug ($P > 0.13$) and no drug-by-condition interaction ($P > 0.13$). Prior to behavioral latency analysis, outliers (RTs > 2 standard deviation from the mean per the subject condition) were replaced with mean estimator for that condition (1.8% of trials were replaced in this way). The mean correct lexical decision RTs are shown in Table 3 as a function of priming condition and drug. A repeated-measures analysis of variance (ANOVA) was performed with the factors of drug (L-DOPA, placebo) and condition (dominant, subordinate, unrelated). There was no main effect for drug ($P = 0.987$), but there was a significant main effect of condition ($F_{2,18} = 34.444, P < 0.0001$) and a significant drug-by-condition interaction ($F_{2,18} = 3.872, P = 0.040$). To further examine this interaction, we conducted repeated-measures ANOVAs on dominant and subordinate priming separately and performed paired-sample $t$-tests on priming effects (dominant vs. unrelated, subordinate vs. unrelated) separately on L-DOPA and on placebo. A repeated-measures ANOVA on dominant priming (i.e., dominant and unrelated conditions) indicated a main effect of condition ($F_{1,19} = 66.764, P < 0.0001$) but no significant main effect for drug ($P = 0.618$) or drug-by-condition interaction ($P = 0.699$). Paired-sample $t$-tests indicated significant dominant priming both on L-DOPA and placebo ($P < 0.0001$). A repeated-measures ANOVA on subordinate priming effects (i.e., subordinate and unrelated conditions) indicated a main effect for condition ($F_{1,19} = 14.320, P = 0.001$) and a marginal drug-by-condition interaction ($F_{1,19} = 4.062, P = 0.058$), with paired-sample $t$-tests indicating significant subordinate priming on placebo ($P = 0.001$) but no significant subordinate priming on L-DOPA ($P > 0.05$).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dominant</th>
<th>Subordinate</th>
<th>Unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>547 (138)</td>
<td>564 (140)</td>
<td>592 (161)</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>539 (121)</td>
<td>576 (143)</td>
<td>588 (138)</td>
</tr>
</tbody>
</table>

Note: Standard deviations are in parentheses.

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Table 2

<table>
<thead>
<tr>
<th>Word length (letters)</th>
<th>Frequency*</th>
<th>Concreteness score (100-700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant primes</td>
<td>4.2 (0.8)</td>
<td>57.4 (52.3)</td>
</tr>
<tr>
<td>Subordinate primes</td>
<td>4.5 (0.8)</td>
<td>39.4 (33.7)</td>
</tr>
<tr>
<td>Unrelated primes</td>
<td>4.8 (1.1)</td>
<td>54.1 (67.3)</td>
</tr>
<tr>
<td>Dominant targets</td>
<td>4.2 (0.8)</td>
<td>85.7 (52.6)</td>
</tr>
<tr>
<td>Subordinate targets</td>
<td>4.3 (0.8)</td>
<td>79.8 (79.2)</td>
</tr>
<tr>
<td>Unrelated targets</td>
<td>4.4 (0.7)</td>
<td>85.6 (103.2)</td>
</tr>
</tbody>
</table>

*In words per million (Kucera and Francis 1967).
**Imaging Results**

Drug-by-condition interactions were investigated for each priming comparison (see Table 4 and Figs 1 and 2) using a threshold of $P < 0.001$ uncorrected for regions where we had reasonable a priori expectations of DAergic modulation of priming (see Introduction), as per Mehta et al (2000). Significant interactions were further explored by first calculating for each subject the mean signal in a 6-mm sphere centered on the peak maxima for each condition using Marsbar software (http://www.marsbar.sourceforge.net) and then conducting paired $t$-tests on the conditions showing a significant interaction separately for l-DOPA and placebo conditions.

A significant drug-by-condition interaction was obtained for the dominant versus unrelated contrast in the left rolandic operculum, where there was a significantly increased signal for the dominant condition relative to the unrelated condition on l-DOPA ($P = 0.025$), whereas on placebo, there was marginal decrease in signal for the dominant condition relative to the unrelated condition ($P = 0.06$). There was also a significant drug-by-condition interaction for the dominant versus unrelated conditions in the left middle temporal gyrus, where again there was a significant increase in signal for the dominant condition compared with the unrelated condition ($P = 0.043$) but no difference on placebo. A significant drug-by-condition interaction was observed for the subordinate versus unrelated contrast in the left MFG and adjacent superior frontal gyrus. In the left MFG, the BOLD signal for the subordinate condition was significantly greater than the unrelated condition on placebo ($P = 0.029$) but significantly reduced on l-DOPA ($P = 0.012$). There were no significant pairwise differences in the left superior frontal gyrus. A direct comparison of dominant versus subordinate conditions across drug treatments showed a significant increase for the dominant condition in the left superior temporal gyrus, MFG, superior temporal gyrus, parahippocampal...
gyrus, and middle cingulate in addition to increases in the right thalamus and middle temporal gyrus.

Discussion
To our knowledge, this study provides the first evidence of the brain mechanisms associated with DAergic modulation of semantic processing. The behavioral effect of L-DOPA was to extinguish priming of subordinate meanings, consistent with a DA-induced enhancement of semantic salience or, from an information processing perspective, focusing of activation in semantic networks through inhibition or restricted spreading of activation to weaker representations. We expected priming-related modulation of the network normally engaged during automatic semantic priming on L-DOPA. Priming of dominant meanings was not significantly altered on L-DOPA; however, there was increased activity in the left rolandic operculum and the middle temporal gyrus, with the latter involvement consistent with modulation of automatic semantic priming mechanisms. The lack of behavioral priming for subordinate meanings on L-DOPA was associated with decreased anterior cingulate and dorsal prefrontal cortical activity, suggesting that L-DOPA enhances frequency-based semantic focus via prefrontal modulation of automatic semantic priming and through engagement of anterior cingulate mechanisms supporting attentional/controlled priming.

Table 5
Regions showing a main effect for L-DOPA versus placebo

<table>
<thead>
<tr>
<th>Region</th>
<th>Z score</th>
<th>Coordinates</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA &gt; placebo&lt;br&gt; Left superior temporal gyrus</td>
<td>3.74</td>
<td>-54 -45 15</td>
<td>0.000</td>
</tr>
<tr>
<td>Right insula</td>
<td>3.66</td>
<td>42 12 -9</td>
<td>0.000</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>3.59</td>
<td>-30 -27 -12</td>
<td>0.000</td>
</tr>
<tr>
<td>Left insula</td>
<td>3.53</td>
<td>-36 15 -12</td>
<td>0.000</td>
</tr>
<tr>
<td>L-DOPA &lt; placebo&lt;br&gt; Right parahippocampal complex</td>
<td>3.71</td>
<td>21 -6 -24</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 6
Regions showing a significant main effect for priming condition

<table>
<thead>
<tr>
<th>Region</th>
<th>Z score</th>
<th>Coordinates</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant &gt; unrelated&lt;br&gt; L inferior frontal gyrus, operculum</td>
<td>4.35</td>
<td>-36 9 27</td>
<td>0.000</td>
</tr>
<tr>
<td>R supramarginal gyrus</td>
<td>3.89</td>
<td>60 -27 21</td>
<td>0.000</td>
</tr>
<tr>
<td>R inferior frontal gyrus, operculum</td>
<td>3.78</td>
<td>57 18 15</td>
<td>0.000</td>
</tr>
<tr>
<td>R middle cingulate</td>
<td>3.52</td>
<td>9 -24 39</td>
<td>0.000</td>
</tr>
<tr>
<td>Dominant &lt; unrelated&lt;br&gt; R superior temporal gyrus</td>
<td>3.47</td>
<td>54 -9 -15</td>
<td>0.000</td>
</tr>
<tr>
<td>Subordinate &gt; unrelated&lt;br&gt; L thalamus</td>
<td>3.60</td>
<td>-9 -9 12</td>
<td>0.000</td>
</tr>
<tr>
<td>Subordinate &lt; unrelated&lt;br&gt; L middle frontal gyrus</td>
<td>3.59</td>
<td>-33 15 51</td>
<td>0.000</td>
</tr>
<tr>
<td>Dominant &gt; subordinate&lt;br&gt; L superior occipital</td>
<td>4.56</td>
<td>-18 -69 27</td>
<td>0.000</td>
</tr>
<tr>
<td>R thalamus</td>
<td>4.06</td>
<td>9 -18 -3</td>
<td>0.000</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>3.79</td>
<td>-27 12 48</td>
<td>0.000</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>3.58</td>
<td>-63 -45 18</td>
<td>0.000</td>
</tr>
<tr>
<td>L parahippocampal gyrus</td>
<td>3.47</td>
<td>-24 -36 -9</td>
<td>0.000</td>
</tr>
<tr>
<td>R middle temporal gyrus</td>
<td>3.43</td>
<td>60 -27 -9</td>
<td>0.000</td>
</tr>
<tr>
<td>L middle cingulate</td>
<td>3.31</td>
<td>-9 -27 36</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: L, left; R, right.

Figure 2. Bar graphs indicating mean percent BOLD signal change across subjects (n = 20) as a function of drug and priming condition (error bars indicate standard error). White = dominant, gray = subordinate, black = unrelated.
The clear effect of l-DOPA on behavioral priming was to reduce activation of subordinate or weaker competing representations, reflecting increasing semantic focus or salience on the basis of meaning frequency, as per our earlier behavioral data (Copland, Chenery, et al. 2003). This finding suggests the need to reconceptualize earlier proposals that DA is called upon during lexical disambiguation primarily when internal representations of contexts are required and dominant meaning biases must be overcome (Cohen and Servan-Schreiber 1992). Instead, it appears that in the absence of context, increasing DAergic transmission may still enhance selection from competing representations but in this instance via the heightening of frequency-based differences. This finding provides further evidence that DA acts to increase the SNR within semantic networks by increasing focus on relevant representations and reducing activity for distracting or irrelevant representations, consistent with the information processing account proposed by Kischka et al. (1996). The current interpretation is similarly based on the assumption that a DA-induced increase in SNR within semantic networks occurs on the basis of meaning frequency when ambiguities are presented without context. The inclusion of a neutral condition in future studies may allow us to further determine the role of DA in selecting and/or inhibiting semantic representations.

The behavioral pattern of results appears consistent with direct evidence from animal studies (Seamans and Yang 2004) and complementary proposals in humans (Cools 2006) that DA serves to sharpen and stabilize representations in the prefrontal cortex by inhibiting weaker representations and narrowing the focus to a single representation or fewer representations that are subsequently maintained. l-DOPA is taken up into DA neurons, converted to DA, and released from vesicles into the synaptic cleft in a stimulation-dependent manner. Its administration may thus modulate DA neurons by 2 independently regulated DA release states (Grace 1991), 1) a tonic release of DA from DA terminals that regulate slow irregular (steady state) firing that may maintain alertness during learning and may influence some aspects of working memory and 2) a rapid phasic release of DA induced by activation of the DA neurons in a stimulus-dependent manner (occurring approximately 80–150 ms after stimulus onset), leading to burst firing that can signal stimulus salience (Schultz 2002). Neuromodulation of alertness, maintenance of representations, and rapid signaling of salience provide plausible mechanisms accounting for the changes in semantic priming we observed on l-DOPA. The precise manner in which these DA transmission mechanisms influence semantic priming is presently unclear.

Given that the present study employed a lexical decision priming task with a short SOA, it was expected that l-DOPA would modulate activity within the network of regions typically involved in automatic semantic priming (see Table 1). Indeed, priming of dominant meanings was associated in increased activity in the left middle temporal gyrus on l-DOPA compared with placebo, suggesting increased engagement of the neural mechanisms underpinning automatic semantic priming (Copland, de Zubicaray, et al. 2003) and consistent with evidence of DA receptors in the temporal lobe (Goldsmith and Joyce 1996). The left MFG has also been implicated in semantic priming with a short SOA on several occasions (Kotz et al. 2002; Rissman et al. 2003). In the present study, behavioral priming of subordinate meanings on placebo was associated with increased left MFG activity for the subordinate versus unrelated conditions. On l-DOPA, there was reduced (i.e., negative) left MFG activity for the subordinate condition compared with a positive signal for the unrelated condition. The reduced activity for the subordinate condition on l-DOPA in this region may reflect a direct modulation of automatic priming in the form of reduced spreading of activation to weaker meanings. However, the change from a positive to negative BOLD signal for the subordinate condition may be more consistent with l-DOPA-based suppression of weaker meanings. The involvement of the left MFG in the DAergic modulation of priming observed here is consistent with strong evidence from human and animal studies that the prefrontal cortex (especially the MFG) is a key substrate for the DAergic influences on cognition (Arnsten 1998; Kimberg et al. 2001; Mattay et al. 2003; Williams and Castner 2006) but further extends this modulatory role to semantics.

The second mechanism by which l-DOPA may influence priming in the present study is to engage neural mechanisms supporting attentional or strategic forms of priming. In the absence of drugs, selective priming of the dominant and not subordinate condition is typically witnessed at longer SOAs, (Simpson and Burgess 1985), where it is assumed that attentional mechanisms are usually engaged over time to inhibit subordinate meanings and sustain dominant meaning activation. The observation of this priming pattern on l-DOPA at a short SOA in the present study supports the notion that increased DA accelerates lexical processing, consistent with previous evidence of earlier semantic activation in healthy individuals on l-DOPA compared with placebo (Angwin et al. 2004) and the finding that lexical activation is slowed in PD where DA deafferentation occurs (Angwin, Copland, et al. 2006). A systematic examination of the time course of lexical activation on l-DOPA with multiple SOAs and noncompeting lexical representations would allow further testing of this proposal and whether such speeded lexical activation occurs when semantic salience is not explicitly manipulated. Whereas a neutral condition is needed to verify the presence of inhibition, the increased semantic selectivity observed here on l-DOPA suggests that DA facilitates increased and earlier attentional processing. Such an effect is consistent with previous evidence that DA enhances attentional capacity during information processing (Clark et al. 1987) and that enhanced DAergic transmission improves performance when attentional mechanisms are required to extract relevant information in situations of representational conflict (Cohen and Servan-Schreiber 1992).

The influence of l-DOPA on attentional mechanisms is also suggested by increased activity for the primed dominant condition and decreased activity for the subordinate condition observed in the anterior cingulate, a region that did not appear to be involved in priming on placebo, as per our predictions. Posner and DiGirolamo (1998) proposed that the anterior cingulate is responsible for “top-down” attentional processes required for selection among competing representations, including the selection of one meaning for lexical ambiguities (but see Botvinick et al. 2001). Whereas the lexical decision priming paradigm employed here does not require active meaning selection for successful task completion, the preserved and selective priming of the dominant condition observed demonstrates that meaning selection had occurred at the semantic level under l-DOPA. In terms of attentional priming mechanisms, expectancy-based priming is unlikely to
develop with such a short SOA (Neely 1991); however, controlled postlexical semantic matching processes, where the subject looks for a semantic relationship between the target and the prime, are possible within this time frame (Degroot 1985). Critically, the anterior cingulate has been associated with strategic inhibitory mechanisms in semantic priming (Mummery et al. 1999; Gold et al. 2006) and in strategic lexical ambiguity priming employing the same paradigm as the present study with a longer SOA (Copland et al. 2007). The present findings suggest that \( \text{l-DOPA} \) facilitates anterior cingulate-based attentional priming mechanisms that are not engaged on placebo, as demonstrated by the lack of anterior cingulate involvement on placebo in the present study.

The ACC is richly innervated by DA projections (Gaspar et al. 1989). Furthermore, DAergic modulation of cognitive function has been linked to the anterior cingulate. For instance, increased anterior cingulate activity has been observed in response to DAergic augmentation in individuals with schizophrenia during verbal fluency tasks (Dolan et al. 1995), and anterior cingulate activity is modulated during working memory performance in individuals with PD on versus off \( \text{l-DOPA} \) (Mattay et al. 2002). There is also positron emission tomography evidence consistent with increased DA release in the anterior cingulate during working memory and attentional tasks in healthy individuals (Aalto et al. 2005). \( \text{l-DOPA} \) may engage the anterior cingulate that enables increased attentional processing during the semantic priming task, resulting in accelerated meaning selection and suppression. Comparison of automatic and controlled aspects of semantic priming under \( \text{l-DOPA} \) may shed further light on the attentional role of the anterior cingulate.

With regard to regions associated with \( \text{l-DOPA} \)-induced changes in behavioral priming, modulated anterior cingulate and prefrontal activity may arise through 2 distinct mechanisms. The drug may affect brain regions rich in DA receptors directly or have an indirect influence on areas with few DA receptors "downstream" from the former regions (Kimberg et al. 2001). In the present case, it appears more likely that \( \text{l-DOPA} \) modulated neuronal activity in these regions directly, given evidence of substantial DA receptors in anterior cingulate and prefrontal cortical regions and the fact that in those conditions where behavioral changes were witnessed on \( \text{l-DOPA} \) changes in brain activity were not observed "upstream" in regions more densely populated with DA receptors. However, a limitation of the current study is that DAergic transmission was not directly measured.

It is also important to consider whether the current findings reflect generalized vasodilatory effects of \( \text{l-DOPA} \) on cerebral blood flow. We argue that this is unlikely on several grounds. First, the regions showing a significant drug-by-condition interaction relevant to the behavioral effects of \( \text{l-DOPA} \) did not overlap with regions showing a main effect for drug. Second, the drug-by-priming interactions reflected both increased and decreased BOLD signal, depending on the priming condition. The interactions observed are, therefore, interpreted as possibly reflecting the effects of \( \text{l-DOPA} \) on local neuronal firing in particular task-relevant brain regions, as per other imaging studies of \( \text{l-DOPA} \) with similar findings against generalized vascular mechanisms (Cools et al. 2002). Finally, it is acknowledged that \( \text{l-DOPA} \) is also a precursor to norepinephrine; however, it is argued that the regions identified in the present study as being involved in the modulation of semantic processing are more strongly linked to DAergic than noradrenergic systems (see also Kischka et al. 1996).

Overall, the present findings are consistent with DAergic enhancement of SNRs within semantic networks through modulating prefrontal and temporal mechanisms involved in automatic priming and via engagement of attentional mechanisms that may support the suppression of weaker competing representations. Future imaging studies of priming with selective DA agonists and with other DA imaging techniques will provide further insights into the neural basis of these modulatory effects. The current findings provide some clues regarding the neural mechanisms underpinning altered semantic processing in populations with DAergic dysregulation, including individuals with schizophrenia (Goldberg et al. 2000) and PD (Copland 2003).

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**References**


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