Acute nicotine enhances strategy-based semantic processing in Parkinson’s disease

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Abstract

Nicotinic mechanisms may play a role in the cognitive deficits of Parkinson’s disease (PD). Recently, on a cognitively demanding strategy-based priming task, nicotine selectively affected controlled semantic processing in young adult non-smokers as reported by Holmes et al. (International Journal of Neuropsychopharmacology 11, 389–399, 2008). Such controlled semantic processing is compromised in PD. This study investigated the effects of acute transdermal nicotine on controlled semantic processing in non-smokers with PD (n=10) and non-smoking matched controls (n=16) using a strategy-based semantic priming paradigm. Transdermal nicotine patches (7 mg/24 h) were administered in a double-blind, placebo-controlled, crossover design. Participants were instructed to expect target words from specified semantic categories based on the primes, while unexpected targets were also presented. Priming conditions included those concurring with trained expectations (expected-related and expected-unrelated), those which did not (unexpected-related and unexpected-unrelated), and neutral-baseline conditions. Controls evidenced significant expectancy effects (i.e. reaction-time differences for expected vs. unexpected conditions) under both drug states. An expectancy effect was not evident for PD under placebo due to a lack of reaction-time slowing for unexpected conditions. However, under nicotine an expectancy effect was present for PD at a level comparable to controls. Overall the findings indicate that nicotine can improve impaired controlled semantic processing in PD possibly via enhanced expectancy or inhibitory mechanisms.

Introduction

Evidence suggests that cholinergic, particularly nicotinic, mechanisms may play a contributory role in the cognitive sequelae of Parkinson’s disease (PD) (for reviews see Picciotto & Zoli, 2002; Rusted et al. 2000). However, only a few controlled studies investigating nicotine effects in PD have included cognitive measures (Kelton et al. 2000; Lemay et al. 2004; Vieregge et al. 2001), and the results have been inconsistent. Vieregge et al. reported no effect on Mini Mental State Examination scores following 3 wk of nicotine patch administration. Kelton et al. reported positive effects of acute intravenous nicotine on critical flicker fusion, choice reaction time, divided attention, and tracking errors, while chronic open-label patch application reported only improved choice reaction time. Kelton et al.’s study, however, has been criticized for a lack of matched controls, and possible practice effects. Lemay et al. conducting the most rigorous of the studies also involving an open-label trial, reported no effect of nicotine on cognitive performance. However, Lemay et al. only investigated the effects of chronic nicotine patch administration. To date, no controlled studies have investigated the effects of acute nicotine on semantic processing in PD with semantic priming paradigms. Semantic priming is the phenomenon where reaction times (RTs) are comparatively faster for real-word targets (e.g. owl) preceded by related-word primes (e.g. night) than unrelated-word primes (e.g. hut) (Meyer & Schvaneveldt, 1971). When RTs for targets in such priming trials are compared to a neutral-prime baseline (e.g. blank), positive differences
inflecting novel verbs (Longworth et al. during a flanker-type task (Mari-Beffa et al. priming paradigm we recently observed that nicotine (878 lexical ambiguities (Copland, 2003; Copland et al. b meanings of a word: (a) meanings of lexical ambiguities (Copland, 2003; Copland et al. 2009); (b) semantically appropriate alternatives when inflecting novel verbs (Longworth et al. 2005); and (c) lexical-semantic information carried by distractors during a flanker-type task (Mari-Beffa et al. 2005).

Using a cognitively demanding strategy-based priming paradigm we recently observed that nicotine selectively affected controlled semantic processing in young adult non-smokers (Holmes et al. 2008). Under nicotine, a dominance of inhibition effects (i.e. slowed RTs compared to a neutral-prime baseline) for conditions that involved unexpected stimuli suggested that nicotine may specifically influence inhibitory mechanisms. The current study used this strategy-based priming paradigm to investigate the effects of acute transdermal nicotine on controlled semantic processing in PD. In this paradigm, participants are trained to expect targets from specific categories based on the prime word, although, unexpected targets are also presented. Thus two conditions concur with trained expectations (expected-related, ExR; expected-unrelated, ExU) and two do not (unexpected-related, UxR; unexpected-unrelated, UxU). As controlled semantic processing is thought to be impaired in PD, possibly due to disturbed inhibitory mechanisms, it was hypothesized that under placebo such deficits would manifest in reduced or absent expectancy effects (i.e. reduced or absent RT differences for unexpected vs. expected priming conditions), underpinned by reduced facilitation for the ExU condition and a lack of inhibition effects for the UxR and UxU conditions. It was further hypothesized that nicotine would improve controlled semantic processing in PD leading to expectancy effects comparable to that of controls, with a restoration of facilitation effects for the ExU condition, and inhibition effects for the UxR and UxU conditions.

Methods

Participants

Twelve patients diagnosed with idiopathic PD (mean duration of illness, 9 ± 4.8 yr) and 17 controls were recruited. All had English as a first language and were right-handed. All were also non-smokers at the time of recruitment. Three participants from each group reported a previous history of smoking with a minimum of 8 yr since quitting smoking. Previous studies with PD participants have used a minimum 2-yr cut-off for non-smoking classification (e.g. Lemay et al. 2004; Vieregge et al. 2001). Participants were excluded if they had: (a) uncorrected visual impairment; (b) a history of drug or alcohol withdrawal/abuse; (c) a history of neurological, psychiatric or language disorder (besides PD), or (d) any contraindication for the use of a nicotine patch. A summary of the groups’ demographic information is presented in Table 1. The two groups did not differ with respect to age, education or score on the Dementia Rating Scale-2 (Jurica et al.
2001). The Geriatric Depression Scale – Short form (GDS; Sheikh & Yesavage, 1986) was used to exclude participants likely to be suffering from depression. Although the difference in GDS scores for the two groups did reach significance \[ t(27) = 3.6, p = 0.001 \], no PD participant scored higher than the recommended level.

All PD participants were taking and maintained levodopa in combination with benserazide, carbidopa and/or carbidopa and entacapone. Daily levodopa dosage was \( 802.08 \pm 255.05 \text{ mg} \) (range 400–1400 mg). Five participants were taking cabergoline \( 2.6 \pm 1.2 \text{ mg} \) (range 1–4 mg) in addition to their levodopa preparations. Those treated with anticholinergic or psychoactive medications were excluded. The study was approved by University of Queensland Medical Research Ethics Committee and all participants provided written informed consent.

Stimuli and procedures

The task was a variation of Neely’s (1977) and Burke et al.’s (1987) strategy-based lexical-decision priming paradigms. The task, stimuli and procedures have been published previously with young healthy adults (Holmes et al. 2008). Task instructions combined with a long SOA were used to invoke controlled semantic processing. In addition to the ExR, ExU, UxR and UxU conditions, neutral conditions (neutral-expected, NEx; neutral-unexpected, NUx) were included to permit primary investigations of facilitation and inhibition effects in line with Neely (1977). Non-word target pairs were included to make the task lexical decision. Two sets of stimulus items were presented in a counterbalanced fashion across two testing sessions. One stimulus set was based on the semantic categories of Vehicles, Chemical Elements, Clothing, and Tools; the other on Animals, Weapons, Body Parts, and Furniture. For example, participants were trained to expect that if the prime word was vehicle, the target word following would be a type of vehicle. Conversely, when the prime was element, the target would be a type of clothing (i.e. a target from a different but specified category). Participants were told to attempt to use this information to predict the target, even though the target would not always be a real word.

For the neutral condition, participants were informed that when the prime word was blank, there was no need to try and predict the target, as it could be any word.

An experimental trial is detailed in Fig. 1. Participants were instructed to respond as quickly and accurately as possible to targets by pressing a ‘yes’ button if the target was a real word, regardless of whether the target word met their expectations based on the given strategies (i.e. even if it was an unexpected real word), or to press a ‘no’ button if the target was not a real word. Stimulus presentation and target RTs were controlled and timed by E-Prime version 1.1 (Psychology Software Tools, Inc: http://pstnet.com) software running on a Pentium PC with a Model 200a PST serial response box. All participants completed a prime to expected-target matching task and a priming task practice prior to experimental sessions.

A double-blind, placebo-controlled, crossover design was used. Participants were randomly assigned to receive either a transdermal nicotine patch (7 mg/24 h, NicabateCQ, GlaxoSmithKline) or placebo (an identical patch in size and colour) in the first session with the alternate patch in the following session. Patches were covered with an opaque plaster and applied to the upper arm. Participants were instructed to abstain from caffeinated or alcoholic beverages, and any illicit substances 12 h and 24 h, respectively, prior to patch application. Experimental sessions commenced approximately 4 h after patch application at the same time of day for a participant (all sessions commenced between 12:15 and 14:30 hours) and were 7–10 d apart. Patient sessions were scheduled to coincide with subjective reports of optimal benefit from anti-parkinsonian medication (typically 30 min–1 h post-ingestion).

Data analysis

Linear mixed model (LMM) analyses were performed on the RT data for correct responses to real-word targets. First, parallelling Burke et al.’s (1987) analysis, a LMM analysis with expectancy and relatedness factors was conducted. Expectancy and relatedness effects reflect RT differences in unexpected vs. expected
priming conditions, and unrelated vs. related conditions, respectively. Second, a condition factor LMM paralleling Neely’s (1977) analysis was conducted to examine facilitation and inhibition effects in order to further probe underlying cognitive mechanisms influenced by nicotine.

Results
Preliminary analyses indicated that the weapon category stimuli were processed differently, possibly due to such stimuli having negative affective valence (Rossell & Nobre, 2004), and were thus excluded. A control and two PD participants were identified as having high error rates (>10%) and were excluded from the analysis. After the removal of these data, the overall error rate was 1% for real-word and non-word trials for both groups, thus no error analysis was conducted. RT data were excluded if <300 ms or >1300 ms, and if >2 standard deviations above or below the condition mean per subject and per group (7.5% of the data removed). Assumptions of normality and homogeneity of variance were not violated. Preliminary analyses indicated no interactions of session \(F(1, 1106) = 0.824, p = 0.364\) or patch order \(F(1, 984) = 1.09, p = 0.296\] with expectancy and relatedness, and were thus omitted from further analyses. Table 2 presents the mean RTs for each condition as a function of drug and group.

### Table 2. Mean RT for each condition as a function of drug and group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>PD</td>
</tr>
<tr>
<td>ExR</td>
<td>620 (18)</td>
<td>620 (23)</td>
</tr>
<tr>
<td>ExU</td>
<td>627 (19)</td>
<td>644 (24)</td>
</tr>
<tr>
<td>UxR</td>
<td>681 (23)</td>
<td>636 (28)</td>
</tr>
<tr>
<td>UxU</td>
<td>727 (20)</td>
<td>652 (25)</td>
</tr>
<tr>
<td>NEx</td>
<td>657 (19)</td>
<td>641 (24)</td>
</tr>
<tr>
<td>NUx</td>
<td>656 (19)</td>
<td>654 (25)</td>
</tr>
</tbody>
</table>

RT, Reaction time; PD, Parkinson’s disease; ExR, expected-related; ExU, expected-unrelated; UxR, unexpected-related; UxU, unexpected-unrelated; NEx, neutral-expected; NUx, neutral-unexpected. Mean RT values are in ms (s.e.m.).

A LMM on the RT data for category-prime conditions (ExR, ExU, UxR, UxU) was conducted with expectancy (expected, unexpected), relatedness (related, unrelated) and drug (nicotine, placebo) as within-subject fixed factors, and group (control, PD) as a between-subject fixed factor. Subject RT variations in addition to subject variation across testing sessions were treated as random factors. The analysis revealed main effects of expectancy \(F(1, 1065) = 123.46, p < 0.001\), and relatedness \(F(1, 1065) = 5.11, p = .024\), and significant interactions of group \(\times\) expectancy \(F(1, 1065) = 14.17, p < 0.001\), and drug \(\times\) expectancy \(F(1, 1065) = 11.09, p = 0.001\). Both interactions were subsumed by a group \(\times\) drug \(\times\) expectancy interaction \(F(1, 1065) = 3.9, p = .052\).

### Expectancy and relatedness factors analysis

Fig. 1. Trial outline: example of the expected-unrelated condition.
Table 3. Mean reaction time (RT) as a function of expectancy, drug and group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls PD</td>
<td>Controls PD</td>
</tr>
<tr>
<td>Expected</td>
<td>624 (17) 626 (22)</td>
<td>599 (17) 608 (22)</td>
</tr>
<tr>
<td>Unexpected</td>
<td>712 (18) 644 (23)</td>
<td>698 (18) 681 (23)</td>
</tr>
<tr>
<td>Expectancy effect</td>
<td>88 (10)* 18 (12)</td>
<td>99 (10)* 73 (12)*</td>
</tr>
</tbody>
</table>

Mean RT values are in ms (S.E.M.).

*p < 0.001.

The three-way group × drug × expectancy interaction appeared to reflect a difference in expectancy effects across the groups under placebo but not under nicotine. Table 3 presents mean RTs as a function of group and drug for the expected and unexpected conditions collapsed across relatedness. Pairwise contrasts confirmed significant expectancy effects for the control group under both drug states (p values < 0.001). In contrast, the expectancy effect was not significant for the PD group under placebo (p = 0.147), and was significantly reduced compared to that for the control group (p < 0.001). Under nicotine, however, the PD group demonstrated a significant expectancy effect (p < 0.001) which was larger than the non-significant expectancy effect under placebo (p = 0.002) and comparable in magnitude to the expectancy effects under both placebo (p = 0.345) and nicotine (p = 0.094) for the control group. Closer inspection of the data suggested the absence of an expectancy effect under placebo for the PD group compared to that for controls was due to a lack of RT slowing for unexpected conditions. Pairwise comparisons confirmed that under placebo RTs were significantly faster for unexpected conditions for the PD group compared to controls (p = 0.026), while under nicotine unexpected-condition RTs were not different to controls (p = 0.563). Although the comparison of RTs under nicotine and placebo for the unexpected condition did not reach significance for the PD group (p = 0.084), the slowing of unexpected-condition RTs under nicotine was sufficient to reveal a significant expectancy effect for the PD group.

Condition factor analysis

To probe for further evidence of the mechanisms (e.g. facilitation and inhibition) underlying the nicotinic influence on expectancy effects above, a LMM analysis was conducted on the RT data with condition (ExR, ExU, UxR, UxU, NEx,NUx) and drug (nicotine, placebo) as within-subject fixed factors, and group (control, PD) as a between-subject fixed factor. Subject RT variations in addition to subject variation across testing sessions were treated as random factors. The analysis revealed a main effect of condition [F(5,1582) = 31.81, p < 0.001], and interactions of group × condition [F(5, 1582) = 3.98, p = 0.001], and drug × condition [F(5, 1573) = 2.97, p = 0.011]. However, the critical group × drug × condition interaction failed to reach significance [F(5,1573) = 1.25, p = 0.282], preventing further investigation of facilitation and inhibition effects. Furthermore, the validity of investigating facilitation and inhibition effects via comparisons with neutral conditions was compromised given contrasts indicated that the drug × condition interaction reflected faster neutral-condition RTs under nicotine than placebo when collapsed across the groups (NEx, p = 0.035; NUx, p = 0.028). There was a trend of faster RTs for expected conditions (ExR, p = 0.068; ExU, p = 0.111) and slower RTs for the UxR condition (p = 0.092) but all failed to reach significance.

Transdermal patch tolerance

No participant withdrew from the study due to experiencing patch side-effects, consistent with other studies that have reported good tolerance of low-dose patches administered acutely to non-smokers (e.g. Levin et al. 1998; McClernon et al. 2003). Of the 29 participants, one person with PD and two controls reported experiencing side-effects of a mild severity (slight headache, fuzzy-headed, or light-headed). No participant excluded from data analysis due to a high error rate reported experiencing side-effects. Patch order identification was below chance at 29%. The Bond & Lader (1974) mood rating scale was administered to determine if participants’ subjective feelings varied with drug state. Paired-samples t tests were conducted on the three Bond & Lader factors (alertness, contentedness, calmness). There was no significant effect of drug for any factor for either group (p values > 0.05).

Discussion

The present study investigated the effects of acute transdermal nicotine on controlled semantic processing in PD using a strategy-based semantic priming paradigm. Of empirical import was the absence of an expectancy effect for the PD group under placebo due to a lack of RT slowing for unexpected conditions.
compared to controls. Under nicotine, however, the PD group showed an expectancy effect of similar magnitude to that demonstrated by controls. The positive nicotinic influence in PD, while contrasting with the findings of Lemay et al. (2004) of no effect of chronic nicotine in PD, is in line with the findings of Kelton et al. (2000) of enhanced aspects of cognition in PD with acute nicotine. The following discusses how the current findings may reflect an effect of nicotinic stimulation on controlled semantic processing and/or active inhibition in PD with potential underlying neurophysiological mechanisms speculated.

The finding of no expectancy effect for the PD group under placebo is in line with other studies reporting an absence of controlled priming effects in PD with various priming paradigms (e.g., Angwin et al. 2005; Arnott et al. 2001; Castner et al. 2007). One theory proposed by Arnott et al. (2001) to account for a lack of controlled priming effects (i.e., facilitation but no inhibition effects under controlled processing conditions) was a failure in PD to develop expectancy sets in a normal manner. Specifically, it was proposed that the expectancy sets generated by the PD group may have been small. Such an account may also explain the current findings in the placebo condition of no expectancy effect for the PD group underpinned by a lack of RT slowing for unexpected conditions.

According to Becker’s (1980) expectancy framework, category-prime stimuli as used in the current study are thought to generate relatively large expectancy sets. In comparison to a small expectancy set, when an expectancy set is large the delay in processing an unexpected target is greater due to the time wasted conducting an exhaustive search of the set, of which the unexpected target is not represented. In this instance, slowed RTs for unexpected conditions drive expectancy effects rather than the speeded processing of expected targets. Thus, abnormally small expectancy sets for the PD group relative to the controls may explain the current findings of no expectancy effect for the PD group under placebo with significantly different RTs between the PD and control groups for the unexpected conditions (i.e., faster unexpected RTs for the PD group) but no RT differences between the groups for the expected conditions. Comparatively small expectancy sets for the PD group, due to either abnormalities in the generation or maintenance of the set, may not have delayed/slowed the processing of unexpected targets sufficiently to result in a significant expectancy effect. The notion of impaired expectancy mechanisms in PD is consistent with evidence linking controlled expectancy with executive processing/attentional control (Hutchison, 2007) and proposals that such processing, subserved by prefrontal cortex (PFC) and frontostriatal circuitry, is generally compromised in PD (Owen, 2004; Zgaljardic et al. 2003).

Thus, the emergence of an effect of expectancy under nicotinic stimulation for the PD group suggests a nicotine-induced improvement in executive semantic functioning. This improvement may reflect an influence of nicotine on cholinergic signalling in PD, particularly within the PFC. Degeneration of cells in the basal forebrain, the main cortical cholinergic projection system, in addition to decreased cortical cholinergic markers and nicotinic receptor binding has been described in PD and may contribute to the so-called subcortico-frontal deficits/dysexecutive syndrome of PD (for reviews see Lemay et al. 2004; Rusted et al. 2000). Furthermore, burgeoning evidence from animal models implicate prefrontal acetylcholine efflux in mediating attentional effort (Sarter et al. 2006, 2009), and nicotine has been shown to enhance performance in such models (Young et al. 2004, 2007).

Alternatively, the improvement may reflect an influence of nicotine on compromised dopamine signalling within frontostriatal circuitry in PD. At present the relative contributions of cortical and striatal dopamine loss to cognitive dysfunction in PD remains to be determined, with evidence supporting intrinsic cortical dysfunction, or abnormal processing within fronto-striatal circuitries due to intrinsic striatal dysfunction (Dagher & Nagano-Saito, 2007). Nonetheless, animal models have begun to unveil the complexity of the interactions of nicotinic acetylcholine receptors (nAChRs) and ascending dopamine pathways, and the possible influences of nicotine (Exley & Cragg, 2008; Livingstone et al. 2009).

An alternative account for the current findings in the placebo condition of no expectancy effect for the PD group underpinned by an absence of unexpected-condition RT slowing is an impairment of active inhibitory mechanisms in PD. This account is consistent with studies reporting impaired attentional semantic inhibitory mechanisms in PD with various paradigms (Copland, 2003; Copland et al. 2009; Longworth et al. 2005; Mari-Beffa et al. 2005). The presence of expectancy effects underpinned by a normalization of RTs for unexpected conditions may thus reflect a nicotinic enhancement of inhibitory mechanisms in PD. Such an account is line with findings from young healthy adults suggesting nicotinic enhancement of active inhibitory mechanisms (Edginton & Rusted, 2003; Holmes et al. 2008; Rusted & Alvares, 2008).

Nicotine-induced improvements in semantic inhibition in PD could be due to nicotine modulating intrinsic inhibitory mechanisms of the lexical-semantic
network consistent with human and rodent studies that have implicated nAChRs in the modulation of inhibitory neocortical networks (Alkondon et al. 2000; Bandyopadhyay et al. 2006). Alternatively, the results could reflect an influence of nicotine on striatal dopaminergic function in PD. Mounting evidence supports the hypothesis that the striatum plays an inhibitory role in the integrational stages of language processing requiring the suppression of competing alternatives (Longworth et al. 2005). In medicated people with PD, a dopamine ‘overdose’ is thought to underlie the impairment of some cognitive functions (Granon et al. 2000; Phillips et al. 2004). One proposed mechanism is that medication-induced increases in tonic dopamine may ‘fill in’ phasic dopamine dips within the striatum, which serve to modulate activity within the indirect inhibitory pathway (Frank, 2005; Frank et al. 2004). Neurophysiological studies indicate that nicotine may enhance the contrast of such dopamine signalling, particularly dopamine dips, within the striatum (Rice & Cragg, 2004; Zhang & Sulzer, 2004).

The absence of effects of nicotine for the controls, while not explicitly predicted, contrasts with our previous findings of nicotine effects with young adult non-smokers (Holmes et al. 2008). The lack of observable nicotine effects for the older controls may be due to their baseline performance levels being at or near ceiling and thus decreasing the ability to detect an improvement with nicotinic stimulation (Newhouse et al. 2004). Inspection of the previously reported data for the young adults under placebo indicates an expectancy effect (43 ms) approximately half the magnitude of that for the current older controls (88 ms), while under nicotine the magnitude of the expectancy effect for the young adults (71 ms) was more similar to that for the older controls (99 ms). Thus the older controls performing near ceiling may account for a failure to detect nicotine effects. Another unpredicted finding was the overall speeding of neutral-condition RTs when collapsed across groups. This finding is consistent with a recent meta-analysis indicating that of the nicotine literature to date, domains of attention (e.g. alerting, orienting attention) show reliable positive effects of acute nicotine stimulation (Heishman et al. 2010). However, the pattern of results deviates from a purely non-specific nicotine-induced enhancement of processing which would be reflected as an overall reduction in RTs.

Although the current study was strengthened by the use of a placebo-controlled crossover design with a matched control group, the study was limited by small sample sizes and a disproportionate male/female ratio. Additionally, the study was limited by a lack of plasma nicotine assay, which may have resulted in a clearer picture of the acute effects of nicotine and dose–response functions. In summary, the current findings indicate that impaired expectancy processing in PD, reflected by an absence of an expectancy effect underpinned by a lack of unexpected-condition RT slowing can be improved with acute nicotine administration. The exact nature of the underlying neurocognitive and neurophysiological mechanisms responsible for the acute nicotinic enhancement of expectancy processing in PD remain matters for future research.

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Statement of Interest

GlaxoSmithKline supplied the patches for this study but was not involved in the study design, testing, analysis, interpretation, or writing.

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