Published in final edited form as:

Cogn Behav Neurol. 2008 September ; 21(3): 134–137. doi:10.1097/WNN.0b013e318185e6f2.

Dopaminergic Modulation of Semantic Priming in Parkinson

Disease Running head:

Parkinson disease, semantics & dopamine

Andrew S. Pederzoli¹⁾, Madalina E. Tivarus^{2),3)}, Punit Agrawal⁴⁾, Sandra K. Kostyk⁴⁾, Karen M. Thomas⁴⁾, and David Q. Beversdorf^{2),4)}

¹⁾The Ohio State University College of Medicine and Public Health

²⁾Program in Biophysics, The Ohio State University

³⁾Department of Imaging Sciences and The Rochester Center for Brain Imaging, University of Rochester

⁴⁾Department of Neurology, The Ohio State University

Abstract

Objective—Our purpose is to examine the effect of D2/D3 agonists on semantic priming.

Background—Dopamine appears to restrict the semantic network in semantic priming. However, which dopamine receptor mediates this effect is unknown.

Methods—To better understand the receptors involved, 15 nondemented Parkinson disease patients performed a lexical decision task before and one hour after they received their first morning medication dose, eight after D2 and D3 agonists pramipexole or ropinirole, and seven after levodopa. Semantic priming was measured for closely, distantly, and unrelated word pairs across a stimulus onset asynchrony of 700 ms.

Results—Closely related pairs were recognized significantly faster than unrelated and distantly related pairs before the drugs, as well as after D2/D3 agents. After levodopa, closely related pairs remained faster than unrelated, but not faster than distantly related pairs.

Conclusion—This suggests that D₁ receptors may mediate the dopaminergic modulation of semantic priming.

Keywords

dopamine; semantic; priming; language; Parkinson disease

Introduction

Dopamine is distributed to the frontal cortex via the mesocortical pathway from the ventral tegmentum in the midbrain. In addition to its well known motor effects, the dopaminergic system also has effects on processing of semantic information. Kischka et al [1] showed that in healthy individuals, semantic priming allowed more rapid recognition of words in a lexical decision task if the prime was directly related (summer - winter) or indirectly related (summer-

snow) to the target word at a stimulus onset asynchrony (SOA) of 700ms (when subjects are asked whether the second word is a word 700ms after presentation of the first). However, after administration of 100mg L-dopa, semantic priming no longer occurred for indirectly related words. This was believed to result from a restriction of the semantic network due to dopamine. In a study on healthy volunteers, Angwin et al [2] found a loss of both direct and indirect semantic priming with 100mg L-dopa at an SOA of 500ms. Direct and indirect semantic priming both present in both drug conditions at shorter SOAs (250ms), and no direct or indirect semantic priming present in either drug condition at longer SOAs (1200ms). However, as L-dopa affects all dopamine receptors, less is known about the specific dopaminergic receptors mediating the semantic priming effect of L-dopa.

Patients with Parkinson disease (PD) have degeneration of the dopaminergic system. PD patients show abnormal processing of semantic information with slower than normal activation and decay rates. A significant facilitation and the absence of inhibition at longer SOAs (500-2000ms) is found in the setting of a low proportion of related words as compared to unrelated words in the priming experiment, whereas the facilitation in normals occurs at SOAs of as early as 250ms, but not at the higher SOAs [3]. This is proposed to be due to a decreased signal to noise ratio associated with decreased dopamine due to PD that slows semantic activation and interferes with the focusing of limited attentional resources. However, varying results have been found with differing task parameters in PD patients [4,5].

Regardless of the specific effects in PD, these effects in PD patients also support the idea that dopamine has a modulatory role in the semantic network. However, as described above, less is known about the specific receptors involved with modulation of semantic processing. Recent evidence has suggested that in healthy individuals, dopaminergic modulation of semantic priming occurs only with agents that affect D1 receptors [6]. However, as baseline levels of dopamine are normal in such individuals, it is unknown how this may manifest in PD patients where dopamine levels are decreased.

Therefore, in order to better understand how dopamine regulates semantic activation in PD, the aim of this study is to begin to determine which dopamine receptors modulate semantic activation by examining the effects of various dopaminergic drugs on semantic priming in PD patients.

Experimental Design and Methods

Subjects

10 female and 5 male nondemented Parkinson's disease patients on monotherapy for dopaminergic agents were recruited (average age 61.5 ± 9.1 (std dev) years). Eight subjects were taking pramipexole (average dose $=1.03 \pm 0.3$ mg) or ropinirole (average dose $=6.0 \pm 0.0$ mg) as monotherapy, which are D₂ and D₃ agonists [7], and seven were taking carbidopa/levodopa (average dose levodopa $=120 \pm 52$ mg) as monotherapy, which, as its centrally active ingredient (levodopa) converts to dopamine, affects D₁, D₂, and D₃ receptors in the brain. Severity did not differ between the two groups (mean Hoehn and Yahr [8] scores for D₂ & D₃ $=2.21 \pm 0.27$, for levodopa $=2.31 \pm 0.26$, $t(13)=0.72$, $p=0.48$, n.s.). The subjects were tested immediately before and 60 minutes after they received their first morning regular daily dosage, allowing for peak concentrations of all 3 drugs to be reached [7]. In compliance with the Institutional Review Board of The Ohio State University, all subjects gave signed consent and subjects with a reported history of learning disabilities such as dyslexia were excluded. English was the native language for all subjects.

Priming paradigm

Prime (200ms)	+	Target (1000ms)	Blank Screen (1000ms)
------------------	---	--------------------	--------------------------

Each subject performed two distinct sets of a lexical decision paradigm consisting of 30 randomly presented pairs each of closely (C) related words (e.g. farmer - field), distantly (D) related words (e.g. summer - snow), and unrelated (N) words (e.g. water - computer), mixed with 60 pairs where the second word is a nonword (NW), using stimuli derived from our previous research [9]. One set was presented prior to taking their medication and the other set one hour after taking their AM dose of medication.

For each test, the subjects were presented a set of the stimulus word pairs with an SOA of 700 msec (as per Kischka et al. [1]). They were asked to press a button as quickly as possible when they recognized whether the second word in the pair is a real word or not a word. Response times and accuracy were recorded using SuperLab.

Initial Analysis of Variance (ANOVA) was performed to compare each pair of semantic distances before and after treatment for each drug to test for interaction effects. Based on the results of the ANOVA and the specific hypothesis of a D1 effect based on previous research [6], and to examine the specific priming effects, subsequent t-tests were used to compare response latencies within subject between closely, distantly, and unrelated word pairs in order to define the semantic priming effects before drug administration. This was then repeated after drug administration for each drug group, in order to determine which drug yielded differing patterns of priming effects before and after drug.

Results

For levodopa, a weak trend was observed for an interaction effect between semantic distance and treatment between for closely and distantly related words ($F(1,203)=2.07$, $p=0.152$). To examine the specific priming effects, due to previous studies suggesting a D1 effect in healthy subjects [6], closely related word pairs were recognized significantly faster than the unrelated ($t(203)=3.502$, $p=0.001$) and distantly related ($t(205)=3.143$, $p=0.002$) word pairs before drug (mean response latencies: closely=1042ms, distantly=1159ms, unrelated=1185ms). Therefore, prior to drug, priming occurred only with closely related words. Closely related word pairs remained faster than the unrelated word pairs ($t(201)=2.012$, $p=0.046$), for which the interaction effect trend was observed, but not the distantly related word pairs after drug ($t(207)=1.028$, $p=0.305$) (mean response latencies: closely=1096ms, distantly=1148ms, unrelated=1178ms), suggesting the potential of an effect of L-dopa on semantic priming in Parkinson disease patients.

One subject taking a D2 & D3 agonist was excluded from further analysis because of consistent inability to perform the buttonpress within 2 seconds (average latency >2 seconds). For the remaining subjects taking pramipexole and ropinirole, no interaction effect was observed between semantic distance and treatment for any combination of semantic distances. To examine specific priming effects, closely related word pairs were significantly faster than unrelated ($t(175)=2.240$, $p=0.026$) and distantly related ($t(174)=2.599$, $p=0.010$) word pairs before the consumption of drug (mean response latencies: closely=895ms, distantly=993ms, unrelated=971ms). Therefore, prior to drug, as with prior to L-dopa, priming occurred only with closely related words. The closely related words remained significantly faster than unrelated ($t(200)=2.704$, $p=0.007$) and distantly related ($t(199)=2.175$, $p=0.031$) word pairs after drug administration (mean response latencies: closely=743ms, distantly=803ms, unrelated=820ms), further supporting a lack of effect of these dopaminergic agonists on

semantic priming. Whereas the overall response rate was faster after drug, the lack of a change in the relationship between the semantic conditions suggests no effect on semantic priming by these drugs in Parkinson's disease patients.

Incorrect responses were rare in all conditions (<5% for each condition).

Discussion

Levodopa appeared to have some modulatory role in the semantic priming effect, while pramipexole and ropinirole had no such effect.

As described above levodopa affects D1, D2, and D3 dopamine receptors and pramipexole and ropinirole specifically affect D2 and D3 dopamine receptors. All three receptors are present on cortical neurons. D1 receptors are known to be located in the zona compacta of the substantia nigra and presynaptically on striatal axons coming from the cortical neurons. These receptors are excitatory in nature. Therefore, it might be expected that the modulatory effect of dopamine on the semantic network would be mediated by this excitatory system. In the cerebral cortex, D2 and D3 receptors are inhibitory. D2 receptors are known to be located postsynaptically on striatal neurons and presynaptically on axons in the substantia nigra belonging to neurons in the basal ganglia [10]. Research in animal models has shown varying effects of different dopaminergic agents affecting various receptor subtypes on set-shifting tasks [11]. In particular agonists of both D1 and D2 had no effect on set-shifting whereas D2 antagonists impaired set-shifting in rodents. NMDA receptors in the prefrontal cortex and the nucleus accumbens core also interact to affect set shifting [12,13]. D2 antagonists have also been shown to impair set-shifting in human volunteers [14]. A computational model has been proposed wherein phasic stimulation of D2 receptors in the striatum drives flexible adaptation of cognitive representations maintained by the prefrontal cortex [15]. This is in contrast to our study, comparing L-dopa to pramipexole and ropinirole (which act on D2 and D3 receptors), which suggests that the D1 dopamine receptor may be involved in semantic priming effects. Therefore, the receptors mediating dopaminergic effects on set-shifting appear to be distinct from those mediating semantic priming effects. However, due to L-dopa's effects on all dopamine receptors, and its conversion to norepinephrine, we cannot exclude the possibility that any effect of priming due to L-dopa in this study being from other dopaminergic or noradrenergic receptors. The previous research examining dopaminergic agonists with and without D1 effects in healthy controls [6], though, does suggest that our findings may have also been due to D1 effects. The role of NMDA activity in semantic priming is unknown.

The priming effect may differ in Parkinson's disease patients. As described above, Arnott et al. [3] found in Parkinson's subjects that semantic activation in priming emerged at 500ms and persisted, where as in control subjects semantic activation emerged at 200ms was degraded by 500ms. These findings were proposed to be consistent with the decreased signal-to-noise ratio in semantic processing demonstrated by Parkinson's patients and the subsequent improvement in semantic priming effects with the administration of dopamine. Previous research has also shown that the interactions between dopaminergic agonists and Parkinson's disease and their effect on cognition is a highly complex relationship for cognitive flexibility and working memory tasks [16].

In our study, both direct (closely vs. unrelated words) and indirect (distantly vs. unrelated words) priming were examined. Where in normal patients both types of priming effects were observed [1], there was no indirect priming effect in Parkinson's disease patients in our study before drug (distantly vs. unrelated revealed no difference under any condition). This is of interest because increased dopamine has been proposed to restrict the semantic network in previous priming experiments, since Kischka et al. [1], as described above, found that by

increasing the level of dopamine in normal patients through the administration of levodopa, the indirect priming effect was reduced significantly. With this in mind, one might expect that in the dopamine depleted state of Parkinsonism, an increase in the indirect priming effect would be seen in untreated patients. However, our study demonstrated an absence of the indirect priming effect in the decreased dopamine state of Parkinson's patients, perhaps due to the effects of delayed semantic activation in the indirect condition. This further raises the suspicion that the drug effects on priming observed in Parkinson's disease may also be different from what would be observed in normal individuals. This warrants further investigation. However, since levodopa, but not the D2/D3 receptor activating agonists, alters the semantic priming effect in patients with Parkinson's disease, these results still do suggest that the D1 receptor may mediate the dopaminergic modulation of the semantic priming effect, and provides converging evidence with previous studies in healthy controls [6]. Further work will be needed examining both healthy individuals and individuals with Parkinson's disease to better understand the clinical implications of these findings.

Acknowledgments

This research was funded in part by a grant from NINDS (K23 NS43222). Andrew Pederzolli was funded by the Roessler Scholarship Fund of The Ohio State University. Preliminary results from this work were presented at the American Academy of Neurology in 2006.

References

1. Kischka U, Kammer TH, Maier S, Weisbord M, Thimm M, Spitzer M. Dopaminergic Modulation of Semantic Network Activation. *Neuropsychologia* 1996;34:1107–1113. [PubMed: 8904748]
2. Angwin AJ, Chenery HJ, Copland DA, Arnott WL, Murdoch BE, Silburn PA. Dopamine and Semantic Activation: An Investigation of Masked Direct and Indirect Priming. *J Int Neuropsychol Soc* 2004;10:15–25. [PubMed: 14751003]
3. Arnott WL, Chenery HJ, Murdoch BE, Silburn PA. Priming in Parkinson's Disease: Evidence for Delayed Spreading of Activation. *J Clin Exp Neuropsychol* 2001;23:502–519. [PubMed: 11780949]
4. Brown GG, Brown SJ, Christenson G, Williams SE, Kindermann SS, Loftis C, et al. Effects of task structure on category priming in patients with Parkinson's disease and in healthy individuals. *J Clin Exp Neuropsychol* 2002;24:356–369. [PubMed: 11992217]
5. Filoteo JV, Friedrich FJ, Rilling LM, Davis JD, Prenovitz M. Semantic and Cross-Case Identity Priming in Patients with Parkinson's Disease. *J Clin Exp Neuropsychol* 2003;25:441–456. [PubMed: 12911099]
6. Roesch-Ely D, Weiland S, Scheffel H, Schwaninger M, Hundemer H-P, Kolter T, Weisbrod M. Dopaminergic modulation of semantic priming in healthy volunteers. *Biol Psychiatry* 2006;60:604–11. [PubMed: 16603132]
7. Nyholm D. Pharmacokinetic optimisation in the Treatment of Parkinson's Disease: an update. *Clin Pharmacokinet* 2006;45:109–136. [PubMed: 16485914]
8. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–42. [PubMed: 6067254]
9. Tivarus ME, Ibinson JW, Hillier A, Schmalbrock P, Beversdorf DQ. An fMRI study of semantic priming: modulation of brain activity by varying semantic distances. *Cogn Behav Neurol* 2006;19:194–201. [PubMed: 17159615]
10. Katzung, BG. Basic and Clinical Pharmacology. Vol. 10th Edition. McGraw-Hill Companies; New York: 2007.
11. Floresco SB, Magyar O, Ghods-Sharifi S, Vexelman C, Tse MTL. Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. *Neuropsychopharmacol* 2005;31:297–309.
12. Stefani MR, Moghaddam B. Systemic and prefrontal cortical NMDA receptor blockade differentially affect discrimination learning and set-shift ability in rats. *Behav Neurosci* 2005;119:420–428. [PubMed: 15839788]

13. Floresco SB, Ghods-Sharifi S, Vexelman C, Magyar O. Dissociable roles for the nucleus accumbens core and shell in regulating set shifting. *J Neurosci* 2006;26:2449–2457. [PubMed: 16510723]
14. Mehta MA, Manes FF, Magnolfi G, Sahakian BJ, Robbins TW. Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D2 receptor antagonist sulpiride in human volunteers. *Psychopharmacol* 2004;176:331–342.
15. Cohen JD, Braver TS, Brown JW. Computational perspectives in dopamine function in prefrontal cortex. *Curr Opin Neurobiol* 2002;12:223–229. [PubMed: 12015241]
16. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev* 2006;30:1–23. [PubMed: 15935475]

Figure 1.

a) Comparison of response latencies after L-DOPA for closely related, distantly related, and unrelated word pairs. b) Comparison of response latencies after D2/D3 drugs for closely related, distantly related, and unrelated word pairs. (*= $p < 0.05$ as compared to closely related).