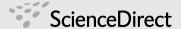
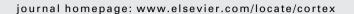


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Semantic activation in Parkinson's disease patients on and off levodopa

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ABSTRACT

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

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1. Introduction

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

Semantic priming refers to the faster recognition of a target word when it is preceded by a related prime word (tiger – stripe)

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

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

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

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

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

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

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