CRITICAL REVIEW

The basal ganglia circuits, dopamine, and ambiguous word processing: A neurobiological account of priming studies in Parkinson's disease

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Abstract

Research into the processing of lexical ambiguities has provided a valuable paradigm for investigating the functional architecture of the language processing system in normal and neurologically impaired populations and specifically, how basal ganglia circuits and the neurotransmitter dopamine may act to enhance and/or suppress various meanings relative to the context in which the lexical ambiguity appears. In this review, we develop the hypothesis that an integrated basal ganglia thalamocortical circuit linking the striatum and inferior frontal cortex is involved in the enhancement and suppression of ambiguous word meanings when a lexical ambiguity is presented within a linguistic context. Reference to behavioral, neurophysiological, and neurochemical studies of subcortical function in both healthy populations and people with Parkinson's disease will be used to provide further support for the proposal that the subcortex is integrally involved in ambiguous word processing. (*JINS*, 2008, *14*, 351–364.)

Keywords: Dopamine receptors, Idiopathic Parkinson's disease, Linguistics, Prefrontal cortex, Semantics, Ventral striatum

INTRODUCTION

Research into the processing of lexical ambiguities (words with a single word form and more than one independent meaning) has provided a valuable paradigm for investigating the functional architecture of the language processing system in normal and neurologically impaired populations and specifically, how basal ganglia circuits and the neurotransmitter dopamine may act to enhance and/or suppress various meanings relative to the context in which the lexical ambiguity appears. When we read the sentence "*The man bought a pen,*" it is likely that we have formed a mental picture of a man in a stationery shop making a decision about red or blue ink. However, if the text goes on to say "*Finally the chickens would be safe from that nuisance fox,*" we are able to retrieve the alternate meaning of *pen* that is relevant to the sentential context. What is it in terms of the neurobiological processes underpinning ambiguous word processing that enables us to rarely be confused when we read or hear ambiguous words, yet which causes people with damage to basal ganglia structures to show impaired performance in comprehending sentences containing lexical ambiguities (Copland et al., 2000a) and to show altered patterns of ambiguity processing when tested in priming tasks (e.g., Copland, 2003; Copland et al., 2000b)?

In this review, we shall develop the hypothesis that the processing of ambiguous words is subserved by several non-motor basal ganglia thalamocortical circuits and that the nature of the task involving the lexical ambiguity (e.g., how much context is provided before encountering the ambiguous word) determines the relative contribution of these multiple circuits. We suggest that the influence of dopaminergic dysregulation such as in Parkinson's disease (PD), has an effect on the direct and indirect microcircuitry of the basal ganglia thalamocortical circuits leading to disturbances in enhancement and suppression mechanisms that subsequently

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disrupt the processing of ambiguous words. Before turning to the neuroanatomical and neurochemical contributions to ambiguous word processing, we present a brief review of psycholinguistic models of ambiguity processing.

MODELS OF AMBIGUOUS WORD PROCESSING

Various theories of lexical ambiguity resolution have been developed around the issue of how lexical access is influenced by the nature of context, meaning frequency, and temporal constraints. These three variables interact in predicting, first, which meaning of an ambiguous word is enhanced and when this enhancement might occur, and second, when and how other meaning/s of the ambiguity are suppressed during the course of ambiguity processing.

According to the exhaustive access model, the occurrence of an ambiguous word in contextually loaded discourse (e.g., sentences or paragraphs) automatically activates all possible meanings in memory for a brief initial period, until the appropriate meaning is selected on the basis of integrated contextual constraints and the inappropriate meaning is rendered inactive through attentional withdrawal, active suppression, or decay (Simpson, 1984). The postlexical stage of meaning selection and inhibition may occur through strategic/controlled processing whereby limited-capacity attention is allocated solely to the contextually appropriate meaning (Simpson, 1984) or the inappropriate meaning is actively suppressed (Gernsbacher, 1990).

In contrast, the selective access or interactive model of lexical ambiguity processing holds that only the contextually appropriate meaning of the ambiguity is selected upon its presentation, through the sensitivity of lexical access procedures to contextual constraints. The finding that only the contextually appropriate meaning for an ambiguity is active immediately following its presentation in a sentence supports this selective position (Glucksberg et al., 1986; Paul et al., 1992; Simpson, 1981; Simpson & Krueger, 1991).

More recently, the exhaustive/selective dichotomy has been reconceptualized in terms of hybrid models that assert the joint influence of context and meaning frequency on lexical ambiguity resolution. Whereas there is still considerable evidence of multiple meaning activation under certain conditions, the original conception of autonomous exhaustive access has been superseded by the view that the relative activation levels of different meanings may be modulated as a function of meaning frequency and the strength and nature of the context (Simpson, 1994). A meta-analysis of 25 studies of ambiguity resolution (Lucas, 1999) found that task, timing of target presentation, meaning frequency, type of target, and type of context all acted as potential moderator variables during ambiguity processing.

While studies of lexical ambiguity priming have focused predominantly on issues of contextual influence and lexical access, the priming of lexical ambiguities presented in isolation (i.e., without context) has also provided valuable information concerning the time course of lexical acti-

vation, the influence of meaning frequency, and the contribution of fast, automatic, enhancement mechanisms. Simpson and Burgess (1985) presented nonequibiased lexical ambiguities with associates related to the dominant (more frequent) or subordinate (less frequent) meaning of the ambiguity (e.g., *bank-money, bank-river*), in addition to unrelated word pairs that acted as controls (e.g., *calf-money, calf-river*). Subjects made lexical decisions on visually presented targets with a wide range of prime-target intervals being tested. At 16-ms stimulus onset asynchronies (SOA), only the dominant meaning showed facilitation relative to unrelated words, whereas both dominant and subordinate meanings appeared active at intermediate SOAs of 100 ms and 300 ms. At longer SOAs of 500 and 750 ms, the advantage for the dominant meaning was reestablished, as the subordinate meaning was no longer facilitated relative to unrelated words. This pattern of results suggested that when lexical ambiguities are encountered in isolation, both meanings are activated; however, the speed with which each meaning is retrieved, and the strength and duration of its activation, varies as a function of its relative frequency.

Simpson and Burgess (1985) also used a neutral prime condition to demonstrate that the process by which dominant meanings are selectively facilitated at longer prime target intervals involves an active direction of attention toward the dominant meaning and inhibition (suppression) of the subordinate meaning. Importantly, the attention-based process of meaning facilitation and inhibition appears particularly robust in normal subjects, as this pattern of priming was maintained when the proportion of dominant and subordinate biased pairs was manipulated and when subjects were instructed to focus on less frequent meanings. This view is supported by Gorfein et al. (2000) who reported that, when opposing semantic contexts are presented before an ambiguous word, a primacy effect is attained whereby processing of one meaning of an ambiguous word results in the inhibition of alternative meanings.

The key points for the current review are the reference to fast, automatic enhancement and slower, later stage contextual integration encompassing selection and suppression mechanisms. Of interest, is how various brain regions may subserve these critical factors in ambiguity processing; namely, the influence of context, meaning frequency and the temporal sequence of enhancement and suppression.

FUNCTIONAL NEUROIMAGING STUDIES OF AMBIGUOUS WORD PROCESSING

The handful of studies that have measured functional brain activation during ambiguity processing provide us with evidence as to the possibility of multiple neural regions contributing to the processing and resolution of lexical ambiguities. Indeed, considering the complexity of processing involved across the range of tasks in which ambiguous word resolution has been tested using functional magnetic resonance imaging (fMRI), it seems likely that the process would

be associated with activation of multiple neural regions. Even given the variety of tasks used to measure lexical ambiguity processing in the neuroimaging literature (refer Table 1 for summary), it is possible to make some assumptions about the multiple brain regions involved and what their specific function may be.

The temporal lobe and left inferior prefrontal cortex (LIPFC) appear strongly implicated in the representation and processing of ambiguous words presented in a task that does not encourage or require integration with preceding context. Copland et al. (2003b) used a two-word semantic priming task where participants made lexical decisions on real word or nonword targets. The word pairs of interest comprised an ambiguous prime word (e.g., *bank*) followed by its dominant related meaning (e.g., *money*), its subordinate related meaning (e.g., *river*), and an unrelated word. The time interval between the prime and target was very brief (150 ms), which does not give the participant sufficient processing time to integrate the target within the context established by the preceding prime. Reduced BOLD signal proposed to represent automatic neural priming was found for the dominant meaning in the left middle temporal gyrus (BA 21) and the subordinate related meaning in the left inferior prefrontal cortex (BA 11/47).

These exact stimuli were presented in a parallel study (Copland et al., 2007) with a time interval between prime and target of 1000 ms, encouraging the use of postlexical meaning integration processes and prime-generated expectancies, whereby the target has sufficient processing time to be integrated into the context established by the related prime. Copland et al. (2007) reported greater activation for the primed dominant meaning of the ambiguity compared with a baseline control word in left inferior frontal gyrus (LIFG) operculum, right anterior cingulated, and right superior temporal gyrus. The unrelated condition evinced greater activation than the dominant condition in the region of the right supramarginal gyrus, which Copland et al. (2007) interpreted as signaling an expectancy-based mechanism (the greater activity for the unrelated target arises as the result of a mismatch between the target that is expected and that which actually appears). The subordinate meaning was associated with reduced BOLD signal primarily in the occipitotemporal regions associated with word recognition, suggesting frequency-based suppression of word forms. The study by Copland et al. (2007) raises the possibility that a different functional anatomy is engaged when controlled processes are invoked during the integration of a target word into the context established by an ambiguous prime. The neural regions comprise the LIFG, the right anterior cingulated, and the right superior temporal gyrus.

Although direct comparisons between fMRI studies are problematic due to differences in both the nature and complexity of the tasks and the response parameters used, Rodd et al. (2005) observed greater frontal and temporal cortex activation in their participants who heard high and low ambiguity sentences (refer Table 1 for stimulus examples and summary). The crucial distinction between the study of automatic ambiguity processing by Copland et al. (2003b) and that reported by Rodd et al. (2005) lies with the emphasis on contextual integration in the latter; participants were only able to understand a sentence involving multiple lexical ambiguities by developing an integrated, congruent sentential context (e.g., in the sentence "*The shell was fired towards the tank*" the three ambiguous words can only form a plausible interpretation if the contextually appropriate meanings are activated and integrated and the contextually inappropriate meanings suppressed). In the study reported by Rodd et al. (2005), the heightened activation was located more posteriorly in the left temporal cortex than that reported by Copland et al. (2003b), specifically, posteriorly in the inferior temporal cortex, in the middle temporal gyrus and in the superior temporal sulcus. Greater activation was also reported for high ambiguity compared with low ambiguity sentences in the lateral frontal cortex, centered on the inferior frontal sulcus bilaterally, although the activation was greater in the left than the right hemisphere. In the left inferior frontal cortex, the activation was greatest in the LIFG pars triangularis (BA 45) and more posterior portions of the left inferior frontal sulcus (LIFS), extending onto the surface of the middle frontal gyrus (BA 9/46, 8).

More recently, Zempleni et al. (2007) largely replicated the findings of Rodd et al. (2005) in a task where sentences were congruent with either the dominant or the subordinate meaning of a sentence-initial ambiguous word. Zempleni et al. (2007) found greater activation in the left inferior frontal gyrus (BA 45/44) and in the left inferior/middle temporal gyri (BA 20/37). Also present were significant activations in the right hemisphere, specifically, the right inferior frontal gyrus (BA 47) and the right inferior/middle temporal gyri (BA 20). Note the overlap with the activated region in the LIFG operculum (study by Copland et al., 2007) and the greater signal in the study by Zempleni et al. (2007) in BA 44. Collectively, the three studies of Rodd et al. (2005), Copland et al. (2007), and Zempleni et al. (2007) begin to build a picture of activation in the left inferior frontal gyrus (BA 44 and/or 45) in ambiguity processing tasks that engage contextual integration and updating and associated enhancement and suppression of contextually appropriate and inappropriate meanings, respectively.

The studies reviewed so far collectively suggest that a bilaterally distributed network subserves context-driven lexical ambiguity resolution. Left hemisphere activation dominates particularly in the inferior frontal gyrus (BA 45/44) and in the left inferior/middle temporal gyri. The right hemisphere also contributes to ambiguity processing and, although the picture is not quite so clear, the areas involved have been reported to include the right inferior frontal gyrus (BA 47) and the right inferior/middle temporal gyri (BA 20; Zempleni et al., 2007) or the right opercular inferior frontal gyrus and the right IFG (pars triangularis; Rodd et al., 2005). It is not surprising that activation in the right cerebral hemisphere has been reported in lexical ambiguity resolution tasks. Investigations of language processing in healthy adults using divided visual field methodology have suggested that

Table 1. Summary of studies investigating ambiguity processing using fMRI

Task	Authors	Participants	Details of the methodology	Results
Two-word automatic priming task with ambiguous word as prime followed by related or unrelated target	Copland, de Zubicaray, McMahon, Wilson, Eastburn, and Chenery (2003b)	12 right-handed participants (6 female) with mean age of 25 years	Unbalanced homophones followed by either the dominant related meaning or the subordinate related meaning or an unrelated word, e.g., *bank-money* and *bank-river* and *bank-table*. Interstimulus interval of 150 ms	When the unrelated condition was contrasted with the combined related conditions, decreased BOLD signal was noted in the left middle temporal gyrus (BA 21) and the LIPC (BA 11). Within these regions, decreased activity for dominant *versus* unrelated meanings was found in the left middle temporal gyrus (BA 21). The comparison between subordinate *versus* unrelated targets revealed decreased BOLD signal in the LIPC (BA 11/47).
Two-word controlled priming task with ambiguous word as prime followed by related or unrelated target	Copland, de Zubicaray, McMahon, and Eastburn (2007)	14 right-handed participants (6 female) with mean age of 26 years	Unbalanced homophones followed by either the dominant related meaning or the subordinate related meaning or an unrelated word, e.g., *bank-money* and *bank-river* and *bank-table*. Interstimulus interval of 1000 ms	Significant BOLD signal changes between the dominant and unrelated conditions were noted in the left inferior frontal gyrus (LIFG: pars operculum), right superior temporal gyrus (BA 21), and the right anterior cingulate. Comparisons between the dominant and subordinate conditions showed decreased subordinate-related activity in the lingual gyrus bilaterally, the left fusiform and insular and the middle occipital gyrus bilaterally. Relative to the unrelated condition, there was increased activity for the subordinate condition in the left middle occipital gyrus and decreased activity in the pre–supplementary motor area and the middle occipital gyrus bilaterally, and the right precuneus and fusiform cortex.
Sentence context loaded with multiple ambiguous words compared with low ambiguity sentence context	Rodd, Davis, and Johnsrude (2005)	15 right-handed individuals (10 females) aged 18–40 years	Participants heard sentences that contained two or more ambiguous words (e.g., "*The shell was fired towards the tank.*") or that contained minimal semantic ambiguity (e.g., "*Her secrets were written in her diary.*"). Participants were asked to judge whether a word, presented visually after the sentence, was semantically related to the sentence's meaning. In a second study, no secondary task was performed, with participants instructed to listen attentively without making any response. These sentences were compared with a baseline noise condition.	High ambiguity sentences produced greater activation than low ambiguity sentences in the lateral frontal cortex, centered on the inferior frontal sulcus bilaterally but greater in the left than the right. Within the left inferior frontal activation, significant peaks were observed in BA 45 and more posterior portions of the left inferior frontal sulcus, extending onto the surface of the middle frontal gyrus (BA 9/46,8). The left temporal region also recorded greater activation in inferior temporal cortex, middle temporal gyrus, and superior temporal cortex.
Ambiguous words were presented in a sentence context that was congruent with the dominant or the subordinate meaning of the ambiguity.	Zempleni, Renken, Hoeks, Hoogduin, and Stowe (2007)	16 right-handed participants (8 female) with average age of 32.5 years	The ambiguous word occurred early in the sentence and was biased toward one particular meaning by the final word/s of the sentence, e.g., *de advocaat* translated as either the lawyer or the egg liqueur was followed by a sentence ending in either *benaderd* (approached) or *ingeschonken* (poured out). Participants simply had to read and comprehend the sentences silently.	A bilaterally distributed neural network was activated with the majority of activation in the left inferior frontal gyrus (BA 45/44) and the left inferior/middle temporal gyri (20/37). Right hemisphere activation was also seen in the inferior frontal gyrus (BA 47) and the inferior/middle temporal gyri (BA 20).
Word generation paradigm using both semantically precise and semantically ambiguous words	Chan, Liu, Yip, Fox, Gao, and Tan (2004)	8 male right-handed volunteers aged between 29 and 39 years	Participants were asked to covertly produce a word that was semantically related to a viewed target word. Target words were either semantically precise or had several frequently used meanings.	Compared with words without semantic ambiguity, semantically ambiguous words showed significant activation in the left mid-superior frontal gyrus (BA 9, 46, and 10) and the right mid-superior frontal gyri (BA 46, 9, and 10), inferior parietal lobe (BA 39) and cuneus (BA 17). Anterior cingulate cortex (BA 32) was also strongly activated.

Note. fMRI = functional magnetic resonance imaging.

the right hemisphere may contribute significantly to the process of ambiguity resolution, as evidenced by an increased sensitivity to the activation of subordinate meanings in the right hemisphere (Coney & Evans, 2000; Titone, 1998). Similar research has also indicated that the right hemisphere may play a significant role in the comprehension of metaphors (Anaki et al., 1998; Kacinik & Chiarello, 2007). Investigations of language processing in people with unilateral damage to the right cerebral hemisphere lend additional support to such findings. For instance, research has demonstrated that people with a unilateral lesion to the right hemisphere experience significant difficulty using contextual information to assist with ambiguity resolution (Grindrod & Baum, 2003, 2005; Klepousniotou & Baum, 2005), and experience difficulties comprehending humor and metaphors (Bihrle et al., 1986; Brownell et al., 1990). For the present review, our attention will be directed to the specific functional neuroanatomy that involves the left inferior frontal gyrus and inferior/middle temporal gyri in lexical ambiguity resolution.

Several other imaging studies also report activation in the left inferior frontal gyrus in tasks that have investigated contextual integration. For example, Baumgartner et al. (2002) reported activation in the left inferior frontal and left posterior middle temporal gyri when participants were presented with sentence endings that were expected, unexpected, and that violated contextual constraints, lending support for the hypothesis that the LIFG contributes to contextual upgrading and/or integration.

Also of interest is that activation in the LIFG during ambiguity processing tasks is reported coincident with reports of greater signal in the middle and/or posterior temporal cortex (as in Rodd et al., 2005 and Zempleni et al., 2007), leading to speculation that these cortical regions may coassociate to form parts of a semantic processing network or loop that is involved in understanding lexical ambiguities by means of contextual updating/integration.

The story is not quite complete, however. In addition to the activation of multiple temporal and inferior frontal regions during contextually loaded ambiguity processing tasks, other frontal regions located more dorsally have been identified. In a study of words without semantic ambiguity *versus* words with high semantic ambiguity, Chan et al. (2004) asked participants to covertly produce a word that was semantically related to a viewed target word with items presented in a blocked design. A region-of-interest analysis showed strong BOLD activity in the left mid-superior frontal gyrus (Brodmann's areas 9, 10, and 46), and their right hemispheric homologues. Further right hemisphere activation was noted in the inferior parietal lobe and cuneus. The anterior and posterior cingulate cortices were also strongly activated. The areas of activation in the study by Chan et al. (2004) in the dorsolateral prefrontal cortex (DLPFC specifically BA 9 and 46) resemble those identified by Rodd et al. (2005) and have been implicated in a large literature investigating goal-directed selection, manipulation, and monitoring of maintained representations (Fletcher & Henson, 2001).

In the task of Chan et al. (2004), the activation of the left mid-superior frontal cortex and involvement of its right hemisphere homologue was presumed to reflect the extensive search and selection processes involved in generating a single lexical meaning of an ambiguous word when multiple meanings are activated.

The function of the DLPFC is controversial; however, Badre and Wagner (2004) suggested that this area guides response selection under conditions of response conflict, whereas Cohen and Servan-Schreiber (1992) suggested that the DLPFC serves to represent the context of a task by providing a bias signal that favors a task relevant response over other (particularly prepotent) competitors. Cohen and Servan-Schreiber's (1992) work was based on computational modeling of the effects of dopamine on ambiguity resolution (among other cognitive tasks) and dopamine's resultant impact on the internal representation of context in the prefrontal cortex. More recently, various neuroimaging studies have also implicated DLPFC in tasks involving a cognitive control component (Cabeza & Nyberg, 2000), especially tasks that call on working memory (D'Esposito et al., 1998). In an item-recognition task in which the number of to-be-remembered letters was manipulated, Narayanan et al. (2005) found that the dorsolateral and the ventrolateral PFC exhibited linearly increasing activation in response to increasing working memory load. They proposed that the DLPFC was more directly involved in maintaining information relevant to response selection and execution at retrieval. Miotto et al. (2006) investigated semantic organizational strategy application after cognitive training and found bilateral DLPFC and orbitofrontal cortex activation after training. It is difficult to evaluate the studies of Chan et al. (2004) and Rodd et al. (2005) against the requirements for working memory or semantic strategy application given that these tasks did not explicitly test for these effects. There are important avenues for further investigation as to whether DLPFC activation in ambiguity processing tasks is associated with additional memory and strategic processing. If this turns out to be the case, DLPFC activation may represent a further thalamocortical circuit recruited for ambiguity processing which involves additional cognitive and strategic processes. It remains, however, that a possible role for the DLPFC in ambiguity processing is not likely to be specific for this one task, but that ambiguity resolution is but one of many cognitive tasks that call upon the function of the DLPFC.

It is acknowledged that working memory capacity influences lexical ambiguity processing and resolution, however, the exact nature of this relationship in healthy individuals is unclear at present. For instance, Miyake et al. (1994) observed that individuals with high working memory spans were more able to maintain alternative meanings of lexical ambiguities. Other findings suggest that a higher working memory capacity results in more efficient inhibition of non-selected or subordinate meanings (Gadsby et al., in press; Gunter et al., 2003).

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is associated with additional memory and strategic processing. If this turns out to be the case, DLPFC activation may represent a further thalamocortical circuit recruited for ambiguity processing which involves additional cognitive and strategic processes. A role for the DLPFC in ambiguity processing is not likely to be specific for this one task, but rather that ambiguity resolution is but one of many cognitive tasks that call upon the function of the DLPFC.

Also noteworthy was the reporting of cortical activity in the anterior cingulate cortex in the processing of ambiguous words (Chan et al., 2004). The anterior cingulate is thought to play a prominent role in executive control and the online monitoring and evaluation of performance through detecting response competition (Carter et al., 1998). When processing ambiguous words, the increased demand in meaning manipulation and a double check procedure to verify meanings against orthography may call on brain function associated with the anterior cingulate. Indeed, Posner and DiGirolamo (1998) suggest that the anterior cingulate and other midline frontal areas act to produce a form of local amplification in neural activity that accompanies the top-down selection of ambiguous words. Specifically, the anterior cingulate is responsible for the top-down effects whereby a prime word such as tree provides a boost in activation to items associated with the expectation (the appropriate meaning of palm). Interestingly, Copland et al. (2007) observed increased anterior cingulate activity for primed dominant ambiguity meanings and decreased anterior cingulate or pre–supplementary motor area activity for suppressed subordinate meanings of ambiguities, further implicating this region in ambiguity processing and meaning selection. The recent proposed functional separation of the anterior cingulate into dorsal (attentional) and ventral (emotional) components (Bush et al., 2000) suggests that future studies may allow finer distinctions regarding the role of the anterior cingulate in ambiguity resolution and language processing more generally.

Whereas the available functional imaging data on ambiguous word processing is relatively sparse, it does raise some interesting hypotheses. Processing in both middle temporal and inferior prefrontal cortex might represent some fundamental processes involved in automatic ambiguous processing with this neural network processing ambiguous words on the basis of meaning frequency and not on the basis of contextual appropriateness. Regions activated during ambiguous word processing that require contextual integration and suppression of inappropriate meanings are located both temporally and in the left inferior frontal gyrus. The dorsolateral prefrontal cortex may be activated during the goal-directed search and selection processes implicit in other more complex ambiguous word processing tasks or when extensive search and selection processes are required. Finally, anterior cingulate cortex is called into play during the semantic selection and manipulation required in some ambiguity processing tasks.

Of interest to the present review are those studies that highlight the inferior frontal cortex during ambiguity processing. We have selected this region for particular atten-

tion as the majority of fMRI studies on contextually dependent ambiguous word processing have found activation in this area. Interestingly, it is also proposed to be involved in an as-yet unconfirmed basal ganglia thalamocortical circuit (Ullman, 2006). We take the inferior frontal area (and its hypothesized role in a basal ganglia thalamocortical circuit) as a template for the hypothesis we wish to explore; namely, that the microcircuitry of the proposed inferior frontal basal ganglia circuit and the modulatory role of dopamine are crucial factors in the processing of ambiguous words in healthy people. One consequence of dopamine dysregulation such as in PD is a deficit in ambiguity processing. Before developing the argument further, various studies reporting ambiguity processing deficits on behavioral tasks in brain damaged populations will be reviewed as they provide further evidence to support the existence of multiple thalamocortical circuits subserving ambiguity processing.

LANGUAGE PROCESSING IN INDIVIDUALS WITH DAMAGE TO THE BASAL GANGLIA AND FRONTAL CORTEX

The literature investigating people with damage to the basal ganglia and frontal cortex has involved populations with focal, acute lesions such as stroke, and degenerative conditions such as PD and Huntington's disease (HD). A recurring theme from these behavioral studies is that impairments in inhibition are associated with basal ganglia and frontal cortex damage and these deficits in inhibition may affect both linguistic and other cognitive functions, for example, attentional processing. Longworth et al. (2005) investigated inflectional morphology in people with focal damage to the striatum resulting from stroke, and in people with PD and people with HD. They suggested that the striatum is primarily involved in the inhibition of competing alternatives that arise during later integrational stages of language comprehension. These later integrational stages are typically thought to occur after initial lexical access and reflect the processes that serve to integrate this initial phase of processing into the sentential context as a whole. Longworth et al.'s view was consistent with the results of a study by Filoteo et al. (2002) who found participants with PD did not display a normal pattern of negative priming, consistent with the proposal that the striatum is involved in inhibitory deficits at the level of response selection.

A more general impairment of inhibition following striatal dysfunction is also suggested by Grossman et al. (2002) who measured comprehension of complex syntax and processing speed for planning and inhibition in people with PD. They found a significant correlation between these two measures. Of interest, the striatum is also implicated in inhibitory processes in motor control (Mink, 1996). Thus, the role of the striatum in language processing may relate to a more generalized role in suppressing competing alternatives in the late integrational processes of language comprehension.

Inhibitory deficits in patients with LFC damage are a recurring theme in the literature and are referred to again in studies of patients with PD and patients with nonthalamic subcortical (NS) vascular lesions (Copland, 2003). In a word pair priming task containing ambiguous words as primes, the NS and PD groups continued to prime both the dominant and subordinate meanings of an ambiguous word at a long interval between prime and target. Copland (2003) interpreted the findings as reflecting a deficit in selective attentional engagement possibly implicating deficits in frontal–subcortical systems related to inhibitory semantic mechanisms.

These few studies have reported processing difficulties by patients with subcortical pathology related predominately to deficits in inhibitory processing, whereby the meaning to be inhibited because of conflict with context or weaker meaning frequency, remains activated. It has been proposed that there are distinct microcircuits within the basal ganglia thalamocortical loops whose function it is to suppress activation and whose actions are modulated by the neurotransmitter dopamine. These additional themes will be explored in the following sections.

FRONTAL BASAL GANGLIA CIRCUITS AND THEIR POTENTIAL ROLE IN AMBIGUITY PROCESSING

Neurophysiological Framework

The functional imaging and behavioral studies reviewed above provide evidence for a role for the temporal cortex (middle and/or posterior), the inferior frontal cortex, the DLPC, the anterior cingulate, and the striatum in ambiguity processing. The hypothesis we wish to develop relates to the left inferior frontal cortex in particular and its potential involvement in a closed basal ganglia thalamocortical circuit that contributes to contextually loaded ambiguity processing. Of interest also is the dorsolateral prefrontal area and its proven involvement in a specific nonmotor circuit. We develop our hypothesis relating to dopaminergic modulation of ambiguity processing using the proposed left inferior frontal circuit as a template as there is greater consensus about its action on inhibitory/suppression mechanisms. The arguments may be equally developed in the future to extend to the dorsolateral prefrontal circuit if greater consensus is reached about its role in ambiguity processing.

The classic view of the basal ganglia was that they acted as very efficient funnels. Information from the cerebral cortex was gathered and directed through various input structures (the caudate nucleus, putamen, and ventral striatum) before being directed back to the cortex by means of output structures (the internal segment of the globus pallidus, substantia nigra pars reticulate, the ventral pallidum) by means of the thalamus. The thalamus was thought to project to a single cortical area, the primary motor cortex thus accounting for many decades of research that investigated the motor

functions of the subcortical circuits (Alexander & Crutcher, 1990). Around this time, an additional three cognitive circuits were also described: a DLPFC circuit, a lateral orbital cortex circuit, and an anterior cingulate cortex circuit (Alexander et al., 1986).

The last 15–20 years of advancement in anatomical, physiological, and neurochemical techniques have helped us to greatly redefine this view and we know that there are possibly another nine cortical areas in addition to the motor cortex that are the targets of basal ganglia output (see Middleton & Strick, 2000a,b, for summaries). These other cortical areas include subdivisions of premotor, oculomotor, prefrontal, and inferotemporal cortex. In a series of elegant experiments, Middleton and Strick injected McIntyre-B strain of herpes simplex virus type 1 (HSV1) into areas of monkey cortex knowing that the virus is transported transneuronally in the retrograde direction. Thus, after initial cortical injection, the virus then travels "backward" to label first-order neurons in the thalamus that innervate the injection site. The virus then continues to travel transneuronally in the retrograde direction to identify second-order neurons in the output structures of the basal ganglia.

Middleton and Strick (2000b) review these studies and provide evidence that three regions of prefrontal cortex (areas 9, 12, and 46) are the target of output from the basal ganglia as well as projecting to the input structures of the basal ganglia. Similarly, an area of inferotemporal cortex, area TE, also receives basal ganglia output. For those neurons injected in the inferotemporal (TE) cortex, the sequence was TE → magnocellular part of ventral anterior nucleus of the thalamus (VAmc) → caudodorsal substantia nigra pars reticulata (SNpr) → TE. The function of this TE circuit is largely unexplored, but it is thought to serve aspects of visual recognition and discrimination.

To our knowledge, no specific studies have charted the potential connectivity of the left inferior frontal gyrus with subcortical structures, although in the studies of nonhuman primates conducted to date, all frontal regions examined have been found to be targets of basal ganglia thalamocortical outputs (Middleton & Strick, 2002). Ullman (2006) suggests that, like other areas of cortex, the LIFG is "likely to be highly interconnected with both cortical and subcortical structures" (p. 480). We take the hypothesized left inferior frontal circuit and its role in the processing of lexical ambiguities as a starting point to develop the hypothesis that dopaminergic modulation contributes to the enhancement and suppression mechanisms involved in ambiguity processing. To further this argument, we provide a more detailed review of the microcircuitry of the basal ganglia (and in particular the prefrontal) circuits and their neurophysiology.

Microcircuitry of the Basal Ganglia Loops

It is known that prefrontal cortical areas also form a closed loop with each of these nonmotor areas being the target of topographically organized output from the basal ganglia.

Figure 1 shows the basic circuitry of the basal ganglia circuits using the dorsolateral prefrontal circuit as an exemplar as most is known about this nonmotor circuit.

Activation from prefrontal areas (BA 9, 46, and 10) leads to increased firing of the neurons of the dorsolateral head of the caudate nucleus and throughout a continuous expanse that extends to the tail of the caudate. The caudate nucleus is itself inhibitory and sends inhibitory neurons to the SNpr and the internal segment of the globus pallidus (GPi; the output nuclei) by means of two pathways, the direct and the indirect pathways. Figure 1 describes in further detail the microcircuitry of the direct and indirect pathways. The functional outcome of the dual pathways to the output nuclei (SNpr/GPi) is that their effects are functionally opposite; the direct pathway enhances thalamic activation back to the cortex and the indirect pathway suppresses activation. Although the projections from the caudate nucleus are viewed as the primary means by which cortical information is transferred to the basal ganglia, there is in fact a third pathway which projects directly from the cortex to the sub-
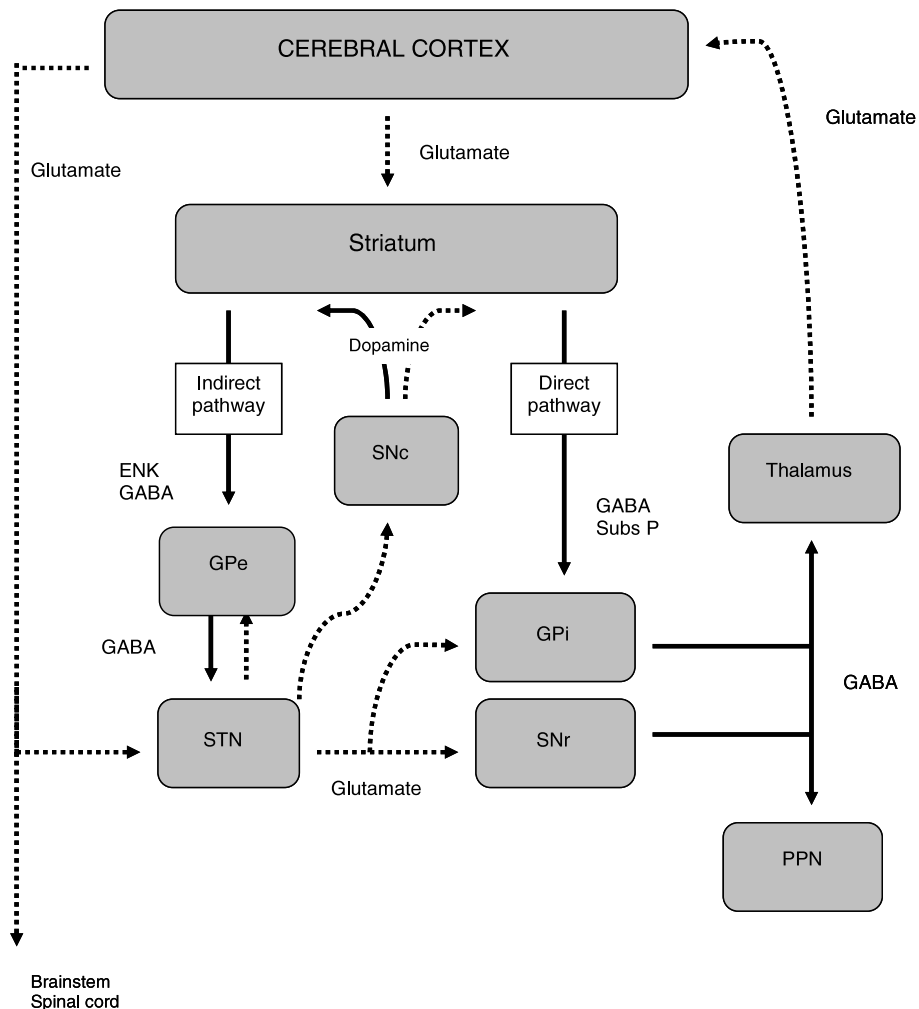

Fig. 1. Intrinsic microcircuitry of the basal ganglia thalamocortical circuit (adapted from Alexander & Crutcher, 1990 and Smith et al., 1998). Inhibitory projections are shown as block lines and excitatory projections as dashed lines. According to this model developed by Smith, Bevan, Shink, and Bolam (1998), cortical information that reaches the striatum, is then conveyed to the basal ganglia output structures (GPi/SNr) by either a direct or an indirect pathway. There is a direct inhibitory projection from the striatum to the GPi/SNr and an indirect pathway. The indirect pathway involves an inhibitory projection from the striatum to the GPe, an inhibitory projection from the GPe to the STN and an excitatory projection from the STN to the GPi/SNr. A relay via the thalamus then transmits the information back to the cerebral cortex or conveys it to various brain stem structures. There is a projection from the GPi and the SNr to the PPN.

The direct and indirect pathways preferentially express differing subclasses of dopamine receptors. The dopaminergic neurons of the SNc give rise to the direct pathway and exert a net excitatory effect on spiny neurons by the activation of D_1 receptors. These same SNc neurons exert a net inhibitory effect on spiny neurons giving rise to the indirect pathway by activation of D_2 receptors. DA, dopamine; enk, enkephalin; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulate; STN, subthalamic nucleus; subs P, substance P.

thalamic nucleus (STN). Being glutamatergic connections, this so-called hyperdirect pathway is excitatory to the GPi/SNpr and is derived predominantly from the primary motor cortex with a minor contribution from the prefrontal and premotor cortices. The prefrontal limbic cortices are topographically organized through the hyperdirect pathway to the medial-most tip of the STN. Whereas the hyperdirect pathway comprises excitatory output to the GPi/SNpr, it has been argued that its effect on action and cognition is one of suppression (Crosson et al., 2007).

Various studies investigating the intrinsic physiological properties of cells in the external segment of the globus pallidus (GPe), STN, and output nuclei in animal models (cited by Smith et al., 1998) have confirmed that the first response of GPe, STN, SNpr, and GPi to cortical stimulation is a brief period of excitation mediated by the hyperdirect pathway. Smith et al. (1998) describe this activation as affecting information flow through the basal ganglia and give examples citing motor but not cognitive information as being relayed. A more direct interpretation of the microcircuitry's effect on cognition is provided by Crosson et al. (2007). The conduction speeds of this system are very fast, and the net result on cognition is a suppression of function. The major route of DLPFC influence on the basal ganglia, however, is directly by means of the caudate nucleus and the D1 subtype of dopamine receptors. Its influence is facilitatory on cognition. The indirect pathway is thought to terminate on the same output nuclei targets as the direct pathway and is, therefore, likely to exert its suppression effects on cognition after the direct pathway. Thus, a wave of enhancement followed by a wave of suppression ensues, and, because we know that the neurons that are the targets of this direct and indirect pathway are identical, it appears intuitive that the two processes are sequential, although the proposed time interval is difficult to judge in behavioral terms.

All of the basal ganglia thalamocortical circuits share the intrinsic microcircuitry of direct, indirect and hyperdirect routes (Alexander & Crutcher, 1990). We elucidate further how this same basic microcircuitry from the hypothesized left inferior prefrontal circuit may contribute to the processing of ambiguous words, as a function of the complexity of the task in which they are embedded.

Neurochemical Modulation of the Basal Ganglia Loops

The direct and indirect pathways are differentially modulated by two main groups of dopamine receptors. Thus, communication between neurons in the dopaminergic pathways is accomplished by dopamine interacting with its docking sites, the dopamine receptors. The D1 class of receptors modulates the direct (excitatory) pathway and the D2 class modulates the indirect (inhibitory) route (Gerfen, 1992). Thus, the two classes of dopamine receptors may act in a temporal gradient with the D1 class acting to enhance cognition before the D2 subgroup (acting on the indirect route) then suppress aspects of cognition. The D1 and D2 receptor

subtypes have also been linked to tonic and phasic actions of dopamine respectively. Grace (1991) suggested that dopamine in the striatum is regulated by two processes, namely (a) a high-amplitude phasic dopamine release that operates synaptically by burst firing in dopamine neurons and (b) a low level tonic dopamine that is governed by extrasynaptic levels of dopamine. The phasic dopamine is rapidly removed by reuptake by means of the dopamine transporters before it can escape the synaptic cleft. In contrast, the constant tonic dopamine are less influenced by reuptake but do control and thus oppose phasic dopamine responses with high levels of phasic dopamine stimulating highly sensitive autoreceptors on the dopamine terminals. The net result of these two antagonistic processes is the maintenance of a steady-state homeostasis. In summary, we know that the direct route operates quickly and leads to enhancement of information flow (and potentially cognitive functions) by means of tonic dopamine regulation. In contrast, the indirect route operates at a later stage and may suppress cognitive functions through the action of phasic D2 receptors.

How do these anatomical and neurophysiological properties influence cognition? A further clue to this question comes from Camps et al. (1990) who found that D2 receptors are more abundant in the striatum than in the prefrontal cortex with a preferential distribution of D1 receptors in the prefrontal cortex. Cools (2006) elaborated on this theme by proposing that dopamine D1 receptors in the PFC enhance stability and the maintenance of cognitive representations. This enhanced stability is apparent even in the face of competing distractors and is accomplished by making the representations more resistant to distraction. Evidence from computational models (Durstewitz et al., 2000) support the proposal that the D1 receptor subtype linked to the tonic action of dopamine by means of the fast acting direct striatal thalamic route, is beneficial for the stability of representations.

In contrast, administration of sulpiride, a D2 receptor agonist that modulates the striatum (Mehta et al., 2004), acted on cognitive flexibility during a spatial working memory task. Cognitive flexibility and adaptation are important when the demands from the environment are changed or when behavior needs to be guided by changing goals (Cohen et al., 2002). The phasic D2 receptors operate preferentially in the striatum by means of the indirect route and act after the first wave of direct enhancement by suppressing information flow (on both actions and cognition).

BASAL GANGLIA CIRCUITRY AND THE ACTIONS OF DOPAMINE IN PROCESSING AMBIGUOUS WORDS

To understand the potential role of basal ganglia thalamocortical circuits in processing ambiguous words, we propose that at least two circuits are involved most probably linked to the complexity of the task and to what extent it involves contextual upgrading and integration. For example, responding to a target word (e.g., *river*) some time after

viewing an ambiguous word presented as a prime (e.g., *bank*) will call into play, we propose, the inferior frontal circuit. Adopting Alexander and Crutcher's (1990) proposal that the fundamental architecture of the basal ganglia circuits comprise both direct, indirect, and hyperdirect routes, we contend that in the processing of a word pair *bank-money* with a long interval between prime and target, the direct pathway enhances the processing of both the dominant and subordinate meanings. The activation from the direct route operates equally on both meanings yet the dominate meaning, by virtue of its preferential representational status, will benefit to a greater degree by the enhancement from the direct route.

At some later stage, the indirect route sends a wave of excitation throughout the circuit, which results in a suppression of the subordinate meaning of the ambiguous word. The indirect route is thought to act upon the D2 receptors and leads to a suppression of the subordinate meaning as previous experience and representational strength (as determined by meaning frequency) would indicate that is more likely that the dominant meaning will be required in further processing.

This proposal receives support from an L-dopa challenge study (Copland et al., 2003a), where healthy university students were administered a capsule containing 100 mg of levodopa (L-dopa) and 25 mg of benserazide. The effect of L-dopa stems mainly from its ability to elevate dopamine levels (Maruyama et al., 1996) in the striatum (Hornykiewicz, 1974; Lloyd et al., 1975), with administration of L-dopa in rats generating 50–60 times more extracellular dopamine in the striatum than the PFC (Carey et al., 1995). Thus, L-dopa would presumably produce a greater effect on the phasic D2 indirect pathway leading to greater suppression of cognition. Indeed greater suppression of meanings was observed by Copland et al. (2003a), whereby subordinate meaning priming observed on placebo at a short SOA was absent on L-dopa and dominant meaning priming that was evident in the placebo group at a long SOA disappeared under L-dopa challenge. Thus, both subordinate and dominant meanings were suppressed and, therefore, susceptible to the increased levels of phasic dopamine in the striatum.

In a contextually loaded ambiguity processing task using sentential contexts to bias toward either dominant or subordinate meanings of an ambiguous word, we predict that the D1 direct pathway will operate initially to enhance the processing of both meanings of the ambiguous word, irrespective of context. At a later integrational stage, the indirect D2 pathway acts to suppress that meaning which is contextually inappropriate.

EVIDENCE FROM PEOPLE WITH PARKINSON'S DISEASE

PD is a progressive neurodegenerative disorder with the core neuropathology being degeneration of the dopamine cells in the midbrain leading to severe dopamine depletion in the striatum (Dauer & Przedborski, 2003). The most severe cell loss in PD is in the ventrolateral tier of the substantia nigra pars compacta, which projects to the dorsal striatum including the dorsal parts of the caudate nucleus. Cools (2006) provides evidence to suggest that the progression of PD follows a temporal–spatial procession of dopamine depletion with the dorsal striatum affected early in the disease course followed only later by ventral striatum dopamine depletion. It is argued that the cognitive deficits in mild PD may reflect disruption to a common updating mechanism subserved by phasic DA transmission in the striatum. This is followed only later in the progression of the disease by disruption to the ventral striatum and subsequent PFC function, specifically the maintenance function subserved by tonic DA release.

We offer a slightly alternative view that may not be entirely incompatible with the model proposed by Cools (2006). Suppose that the striatum and inferior frontal cortex participate in a reentrant cortico-subcortical circuit that both originates and ends in the LIFC and is involved in contextual upgrading/integration. It has been suggested that PD disrupts the phasic D2 indirect pathway (Frank, 2005; Gerfen, 2000) leading to alterations in the suppression of behavior. This change would only impact upon ambiguity processing tasks that depend on later stage contextual integration. Thus, PD, which is associated with a disruption to the phasic dopamine release in the striatum, will affect the suppression wave that occurs by means of the indirect route at later stage processing. The behavioral predictions would have patients with PD most affected on ambiguity processing tasks that require contextual integration and rely on the primary suppression mechanisms of the left inferior frontal circuit. What is needed to adjudicate on the proposals of Cools (2006) and Frank (2005) is a prospective study of ambiguity processing in PD that carefully measures increasing disease severity. On Cools' (2006) view, we should eventually witness D1 direct pathway involvement resulting in deficits in the enhancement of the contextually appropriate meanings of the ambiguity.

In a series of studies investigating ambiguity processing in mild to moderate stage PD, Copland (2003) and Copland et al. (2000a) did indeed report greater difficulty with ambiguity tasks calling on contextual integration. The proposed tonic D1 early stage processes of the circuit, as predicted, were relatively spared. For example, in the contextual priming task using two words (*bank-river vs. bank-money* presented with a short interval between prime and target), which we hypothesize is subserved by the inferior prefrontal/temporal regions, the participants with PD showed equal priming of both meanings of the ambiguous word during early stage processing, suggesting that the direct pathway mediated by tonic dopamine release is intact. Their pattern of performance was not significantly different from that of healthy controls. In contrast, participants with PD showed clear disruptions to the later stage processing of ambiguous word pairs presented with greater reliance on contextual processing with both meanings of the ambiguous word

remaining active, in contrast to control participants, who had suppressed the subordinate meaning. Continuing the assumption that PD is associated with a disruption of D2 phasic dopamine mechanisms that support the suppression of representations, the disruption to the suppression of subordinate meanings at a longer SOA is exactly what would be predicted.

When participants with PD were presented with a sentence context with two target words either related to the dominant or the subordinate meaning of the sentence final ambiguity, PD participants enhanced all meanings in a similar pattern as control participants; the D1 direct enhancement pathway appears less compromised at this stage. At the later stage processing, however, where the D2 indirect pathway is called upon to suppress meanings that are contextually inappropriate, the subordinate related meaning of the sentence (a meaning that violated the context and in controls was suppressed) remained active in the PD group.

As noted previously, lexical ambiguity resolution appears influenced by working memory capacity, although this relationship is not clear. Given that PD individuals with poor working memory show impaired metaphor processing, compared with those with unimpaired working memory (Monetta & Pell, 2007), working memory capacity may also influence lexical ambiguity resolution in PD; however, this possibility has not been directly examined.

REMAINING QUESTIONS AND DIRECTIONS FOR FURTHER RESEARCH

The investigation of ambiguity processing using fMRI as a window to the neural regions involved remains largely unexplored. What is needed for progress in the area is a systematic series of investigations selectively targeting the component processes of ambiguity resolution from context free automatic processing through to ambiguous word tasks that present the homographs in either two-word, triplet, or sentence contexts. Variations in the influence of working memory, response conflict and response competition could be selectively manipulated to form a more comprehensive picture of neural activity that subserves the spectrum of ambiguity processing tasks. The activation of subcortical regions is difficult to capture with fMRI without a large number of participants and possibly different imaging analyses (Crosson et al., 2007) so future studies will need to consider the optimum sample size and analytic approach to test subcortical hypotheses. Given the emphasis in this review on neural circuits, there is the possibility that studies investigating correlations of activation may shed light on the cooccurrence of neural areas during specific task performance, thus contributing to our understanding of integrated neural circuitry. Recently, Booth et al. (2007) assessed the functional connectivity between the cerebellum and the basal ganglia during a rhyming judgment task using dynamic causal modeling techniques. Similarly, Stamatakis et al.

(2005) used interregional covariance analysis as a measure of functional connectivity in a judgment task for regularly and irregularly inflected word forms. These techniques and others like them that investigate the influence that one brain region has on another have the potential to add to our understanding of integrated neural circuitry.

Psychopharmacological studies that transiently manipulate the DA system in healthy individuals may also be used to investigate the cause of DA-related cognitive deficits. Frank and O'Reilly (2006) used either a D2 agonist (cabergoline) or D2 antagonist (haloperidol) and found that cabergoline impaired whereas haloperidol enhanced Go learning from positive reinforcement in tasks that assessed working memory and reversal and attentional shifting. In their tasks, Go learning was recorded as a button press that accurately responded to the instructions provided, whereas No-Go learning was measured by the subject correctly withholding their response postinstruction. Specifically, cabergoline resulted in overall reduced Go learning that was assumed to occur due to reduced DA bursts from presynaptic stimulation. The haloperidol group displayed enhanced Go learning that was assumed to arise from increased DA bursts affecting the direct pathway from autoreceptor antagonism. If this finding extends to the ambiguous word processing framework outlined here, administration of cabergoline would lead to enhanced suppression of the inappropriate and perhaps even the appropriate meanings of the ambiguous word presented in a contextually loaded environment. There should be no effect on the D1 direct pathway evidencing as normal enhancement mechanisms during contextually biased ambiguity processing. Haloperidol, on the other hand, which functions as a D2 antagonist, would show the reverse effect and lead to reduced suppression of inappropriate meanings with once again no effect on the enhancement function subserved by the D1 direct pathway. More direct measures of dopaminergic transmission associated with language processing (using positron emission tomography or single photon emission tomography techniques) would also allow further testing of these hypotheses.

Psychopharmacological studies directly targeting the action of dopamine on language processing in healthy individuals have also yielded important insights. For example, Kischka et al. (1996) used a semantic priming experiment to show that the ingestion of dopamine by healthy individuals resulted in an enhancement of the most salient signal (measured in their experiment by the priming between a directly related prime and its target) and a reduction in the salience of the less dominant signal (measured as priming between an indirectly related word and its target). Similarly, the results of the levodopa challenge study (Copland et al., 2003a) also suggested that the ingestion of dopamine by healthy individuals resulted in the enhancement of strong signals (as evidenced by increased dominant ambiguity meaning priming at a short SOA) and the dampening of weaker signals (as evidenced by reduced subordinate meaning priming at a short SOA). These results from hyperdopaminergic subjects broadly support the hypothesis put forward in this review relating to

hypodopaminergic states and further research to extend these efforts is clearly warranted.

There is also an opportunity to test the validity of the hypotheses developed in this review by conducting a prospective study of lexical ambiguity resolution in people with PD as the severity of the disease worsens. If, as suggested by Cools (2006), the disease progresses from dorsal to ventral striatum, then we should see a gradual progression of suppression difficulties early in the disease (with enhancement of appropriate meanings retained) to eventual involvement of both suppression and enhancement mechanisms. This evidence would provide further support for the early vulnerability of the indirect D2 pathway in PD followed later by involvement of the action of the direct D1 pathway.

In this review, we have provided a model of ambiguity processing that draws on neuroimaging, neurophysiological, and neurochemical data to account for behavioral data from both healthy populations and people with basal ganglia pathology. We have drawn on previous work describing the roles of the DLPFC and anterior cingulate circuits in ambiguity resolution and have proposed an additional frontal circuit linking the inferior frontal cortex with the basal ganglia. This interdisciplinary framework, although necessarily speculative, has the potential to lead to enhanced insights into the neurobiology of language and how it is affected by chronic neurodegenerative diseases.

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