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Research report

Effects of levodopa on corticostriatal circuits supporting working memory in Parkinson's disease

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ABSTRACT

Working memory dysfunction is common in Parkinson's disease, even in its early stages, but its neural basis is debated. Working memory performance likely reflects a balance between corticostriatal dysfunction and compensatory mechanisms. We tested this hypothesis by examining working memory performance with a letter *n*-back task in 19 patients with mild-moderate Parkinson's disease and 20 demographically matched healthy controls. Parkinson's disease patients were tested after an overnight washout of their usual dopamine replacement therapy, and again after a standard dose of levodopa. FMRI was used to assess task-related activation and resting state functional connectivity; changes in BOLD signal were related to performance to disentangle pathological and compensatory processes. Parkinson's disease patients off dopamine replacement therapy displayed significantly reduced spatial extent of task-related activation in left prefrontal and bilateral parietal cortex, and poorer working memory performance, compared to controls. Amongst the Parkinson's disease patients off dopamine replacement therapy, relatively better performance was associated with greater activation of right dorsolateral prefrontal cortex compared to controls, consistent with compensatory right hemisphere recruitment. Administration of levodopa remediated the working memory deficit in the Parkinson's disease group, and resulted in a different pattern of performance-correlated activity, with a shift to greater left ventrolateral prefrontal cortex activation in patients on, compared to off dopamine replacement therapy. Levodopa also significantly increased resting-state functional connectivity between caudate and right parietal cortex (within the right fronto-parietal attentional network). The strength of this connectivity contributed to better performance in patients and controls, suggesting a general compensatory mechanism. These findings argue that Parkinson's disease patients can recruit additional neural resources, here, the right fronto-parietal network, to optimize working memory performance despite impaired corticostriatal function. Levodopa seems to both boost engagement of a task-specific prefrontal region, and strengthen a putative compensatory caudate-cortical network to support this executive function.

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1. Introduction

Working memory refers to maintaining, manipulating and updating information online, processes that are key for higher-order, goal-directed behaviour. Its neural basis has been studied extensively: neuroimaging studies consistently show that working memory tasks engage a subcortical–cortical network including bilateral caudate, dorsal and ventrolateral prefrontal and parietal cortex in healthy people (Owen, McMillan, Laird, & Bullmore, 2005). Lesion studies have shown that lateral frontal and parietal cortex and the basal ganglia are necessary for working memory tasks requiring manipulation and updating (Barbey, Colom, Paul, & Grafman, 2014; Tsuchida & Fellows, 2009; Voytek & Knight, 2010).

People with Parkinson's disease have impairments in working memory, but the neural basis of the deficit is unclear. Parkinson's disease is characterized by a loss of midbrain dopamine neurons with consequent dopamine depletion of the striatum, including the caudate nucleus, even in the early stages of the disease (Hornykiewicz & Kish, 1987; Kordower et al., 2013). Optimal dopamine signaling is thought to be critical for effective information processing in corticostriatal circuits (Bell et al., 2015; Hazy, Frank, & O'Reilly, 2007). Pharmacological manipulation of dopamine modifies resting-state corticostriatal functional connectivity in people with Parkinson's disease (Bell et al., 2015; Cole et al., 2013; Kwak et al., 2010; Simioni, Dagher, & Fellows, 2016). Striatal dopamine release has been related to working memory performance in healthy subjects (Backman et al., 2011), and may act by gating the updating of information represented in cortex (Frank, Loughry, & O'Reilly, 2001).

However, dopamine also directly modulates prefrontal cortical function in Parkinson's disease (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Mattay et al., 2002), and Parkinson's disease may lead to frontal cortical neuronal loss (Dickson, 2012). Furthermore, dopamine replacement therapy is usually titrated to motor symptoms, related to dopamine depletion in the putamen (Galvan, Devergnas, & Wichmann, 2015), which is more severe than in the caudate, at least in the early stages of the disease (Kish, Shannak, & Hornykiewicz, 1988; Kordower et al., 2013). This has led to the idea that dopamine replacement therapy may 'overdose' relatively less affected corticostriatal circuits important for cognition (Gotham, Brown, & Marsden, 1988).

Further complicating the picture, the slowly progressive nature of Parkinson's disease makes it likely that neural compensatory processes are engaged to preserve function. Working memory impairment in Parkinson's disease may only manifest with advancing disease (Owen, Iddon, Hodges, Summers, & Robbins, 1997), which is consistent with engagement of compensatory processes, eventually overwhelmed by disease progression. Studies of the impact of normal ageing on executive functions report that older adults tend to show less prefrontal cortical asymmetry during higher-level cognitive tasks, compared to younger adults, and that increased bi-hemispheric recruitment is associated with better performance (Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz et al., 2000; Rosen et al., 2002). Compensatory changes in the motor system in Parkinson's disease have been detected with fMRI in the pattern of activation seen with motor tasks (Palmer, Ng, Abugharbieh, Eigenraam, & McKeown, 2009) and in the strength of putamen functional connectivity at rest (Simioni et al., 2016), but neural mechanisms that might be engaged to preserve working memory performance in mild-moderate Parkinson's disease have not been clearly defined.

There is some evidence that dopamine depletion in the caudate may contribute to working memory impairment in Parkinson's disease. Positron emission tomography has shown reduced regional cerebral blood flow in the caudate and output nuclei of the basal ganglia during working memory performance in patients with Parkinson's disease compared to healthy controls (Owen, Doyon, Dagher, Sadikot, & Evans, 1998). Similarly, reduced task-related BOLD signal measured with fMRI has been detected in caudate in Parkinson's disease patients with executive dysfunction (Lewis, Dove, Robbins, Barker, & Owen, 2003) and mild cognitive impairment (Ekman et al., 2012), compared to Parkinson's disease patients without such symptoms, during working memory tasks. Further, Lewis et al. (2003) found that lower activity in the caudate in Parkinson's disease correlated with poorer working memory. However, alterations in striatal activity in Parkinson's disease have also been reported in the face of intact working memory performance (Marklund et al., 2009; Poston et al., 2016). For example, Marklund et al. (2009) detected diminished transient activity in caudate and its main output relay, the globus pallidus internal segment, during a working memory task in Parkinson's disease patients compared to healthy controls, with no difference in performance. This could reflect effective compensation. Trujillo et al. (2015) provided evidence for compensatory activity in the prefrontal cortex, finding increased task-related engagement of the left dorsolateral prefrontal cortex in Parkinson's disease patients with only trend-level poorer working memory performance and decreased task-related functional connectivity between the dorsolateral prefrontal cortex and superior and inferior frontal gyri, compared to healthy controls. Evidence for compensation remains indirect however, because correlations between performance and these neural measures were not reported (Trujillo et al., 2015). A recent study by Poston et al. (2016), using different methods, provided evidence for a compensatory role for the putamen in faster reaction times in a working memory task in Parkinson's disease.

Resting state fMRI may provide additional evidence as to the circuits involved in working memory. Studies using this method in healthy subjects have shown that the dorsal caudate is functionally connected to the dorsolateral and ventrolateral prefrontal cortices, as well as parietal association areas (Choi, Yeo, & Buckner, 2012; Di Martino et al., 2008; Helmich et al., 2010; Kelly et al., 2009; Kwak et al., 2010), all regions implicated in working memory. At least some of these connectivity patterns are functionally relevant: Gordon, Devaney, Bean, and Vaidya (2015) reported the strength of functional connectivity between dorsal caudate and left anterior middle frontal gyrus predicts working memory accuracy in healthy young adults. Thus, changes in caudate connectivity could be the basis for working memory dysfunction in Parkinson's disease. The small existing