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The effects of clinical motor variables and medication dosage on working memory in Parkinson's disease

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ABSTRACT

In this study, we investigate the interrelationship between clinical variables and working memory (WM) in Parkinson's disease (PD). Specifically, the aim of the study was to investigate the relationship between disease duration, dopaminergic medication dosage, and motor disability (UPDRS score) with WM in individuals with PD. Accordingly, we recruited three groups of subjects: unmedicated PD patients, medicated PD patients, and healthy controls. All subjects were tested on three WM tasks: short-delay WM, long-delay WM, and the *n*-back task. Further, PD encompasses a spectrum that can be classified either into akinesia/rigidity or resting tremor as the predominant motor presentation of the disease. In addition to studying medication effects, we tested WM performance in tremor-dominant and akinesia-dominant patients. We further correlated WM performance with disease duration and medication dosage. We found no difference between medicated and unmedicated patients in the short-delay WM task, but medicated patients outperformed unmedicated patients in the long-delay WM and *n*-back tasks. Interestingly, we also found that akinesia-dominant patients were more impaired than tremor-dominant patients at various WM measures, which is in agreement with prior studies of the relationship between akinesia symptom and basal ganglia dysfunction. Moreover, the results show that disease duration inversely correlates with more demanding WM tasks (long-delay WM and *n*-back tasks), but medication dosage positively correlates with demanding WM performance. In sum, our results show that WM impairment in PD patients depend on cognitive domain (simple vs. demanding WM task), subtype of PD patients (tremor- vs. akinesia-dominant), as well as disease duration and medication dosage. Our results have implications for the interrelationship between motor and cognitive processes in PD, and for understanding the role of cognitive training in treating motor symptoms in PD.

1. Introduction

Parkinson's disease (PD) is a neurological disorder, associated with motor dysfunction (Kish, Shannak, & Hornykiewicz, 1988). The main motor symptoms in PD are rigidity, bradykinesia, and resting tremor. The primary neural dysfunction in PD is reduction of dopamine levels in the basal ganglia (Kish et al., 1988). Accordingly, PD patients are prescribed dopaminergic medications, including levodopa and dopamine agonists, to treat their motor symptoms. In addition to motor dysfunction, PD patients also show cognitive impairment (Amos, 2000; Charbonneau, Riopelle, & Beninger, 1996; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Gabrieli, Singh, Stebbins, & Goetz, 1996; Hodgson, Dittrich, Henderson, & Kennard, 1999; Lees & Smith, 1983; Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, 2004; Owen, Doyon, Dagher, Sadikot, & Evans, 1998; Partiot et al., 1996; Taylor, Saint-Cyr, & Lang, 1986). In this study, we investigate the interrelationship between motor and cognitive variables in PD, and how these measures are affected by dopaminergic medications.

PD is a heterogeneous disorder that encompasses a spectrum of motor symptoms. Some patients present with severe resting tremor (and mild akinesia), while others mainly show severe rigidity and akinesia (Jankovic et al., 1990; Zaidel, Arkadir, Israel, & Bergman, 2009). It has been argued that the different motor symptoms in PD are associated with dysfunction to dissociable neural structures. For example, akinesia and bradykinesia are arguably associated with basal ganglia (and corticostriatal circuits) dysfunction, while tremor is perhaps associated with cerebellar, thalamic, and subtha-

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lamic nucleus abnormalities (Kassubek, Juengling, Hellwig, Spreer, & Lucking, 2002; Mure et al., 2011; Probst-Cousin, Druschky, & Neundorfer, 2003; Weinberger, Hutchison, Lozano, Hodaie, & Dostrovsky, 2009; Zaidel et al., 2009). Importantly, studies also suggest that the severity of akinesia symptoms is a risk factor for the development of dementia and mild cognitive impairment in PD patients (Poletti & Bonuccelli, in press; Poletti, Emre, & Bonuccelli, 2011)

In the current study, we test whether different subgroups of PD patients (based on severity of motor symptoms) might show dissociable cognitive performance. While prior research has investigated cognitive dysfunction in subtypes of PD patients (Poletti & Bonuccelli, in press; Poletti, Frosini, Pagni, Baldacci, Nicoletti et al., 2012; Poletti et al., 2011; Vakil & Herishanu-Naaman, 1998), to our knowledge, no study has tested WM function in relation to motor and clinical variables in PD, including disease duration and dopaminergic medication dosage.

1.1. Neural substrates of WM

An extensive body of literature show that the basal ganglia and prefrontal cortex are involved in WM performance. For example, for many decades, animal and human studies found a strong relationship between the prefrontal cortex and WM (Barch et al., 1997; Castner & Goldman-Rakic, 2004; Gazzaley, Rissman, & Desposito, 2004; Goldman-Rakic, Muly, & Williams, 2000; Perlstein, Carter, Noll, & Cohen, 2001). For example, Brozoski Brown, Rosvold, and Goldman (1979) found that dopamine depletion in the prefrontal cortex impairs WM performance in monkeys. Studies have also reported an inverted-U relationship between dopamine levels and working memory performance, such that insufficient or excessive dopamine can impair performance (Cools & D'Esposito, 2011; Kwak et al., 2013).

Furthermore, numerous imaging studies with healthy subjects report basal ganglia activity during WM task performance (Chang, Crottaz-Herbette, & Menon, 2007; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Along the same vein, lesion (Battig, Rosvold, & Mishkin, 1960; Divac, Rosvold, & Szwarcbart, 1967) and neurophysiological (Hikosaka, Sakamoto, & Usui, 1989; Kawagoe, Takikawa, & Hikosaka, 1998; Ljungberg, Apicella, & Schultz, 1992) studies with nonhuman primates also support a role of the basal ganglia in WM. For example, Collins, Wilkinson, Everitt, Robbins, and Roberts (2000) found that Parkinsonian monkeys were significantly more impaired than controls at performing a spatial delayed-response (WM) task, suggesting a key role for striatal dopamine in WM. Further, neuroimaging studies reveal, across a range of tasks, that WM impairment in PD patients is associated with decreased activity of the basal ganglia (Lewis et al., 2003; Postle, Jonides, Smith, Corkin, & Growdon, 1997). Taken together, the above studies suggest that, among other brain areas, the basal ganglia and prefrontal cortex play an important role in WM performance in healthy subjects and PD patients.

Further, prior studies reported an inverted-U relationship between dopamine levels and WM performance in PD patients and healthy controls (see Fig. 1, Cools & D'Esposito, 2011). For example, some studies reported that increase of dopamine levels enhances WM in PD patients (Moustafa, Sherman, & Frank, 2008). This is different from results in healthy adults,where an increase in dopamine levels can impair WM performance (Frank & O'Reilly, 2006). These prior results are explained by the inverted-U relationship between WM performance and dopamine levels: PD patients are located more toward the left hand side of the curve (Fig. 1), and thus dopaminergic medications increase dopamine levels to sufficient levels to enhance WM, but healthy controls are located at the top of the curve, and an increase in dopamine levels impairs WM performance (see Fig. 1).

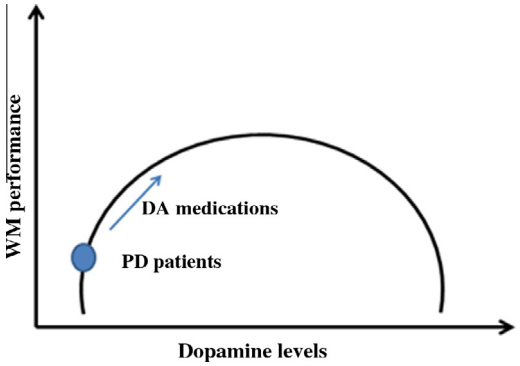

Fig. 1. An inverted-U relationship between dopamine levels and working memory performance. Our data suggest that given PD patients lie at the far left side of the curve, dopamine (DA) medications perhaps pushes performance towards the top of the curve, and this ameliorate WM deficits.

1.2. Clinical variables in PD: links to cognition

There are individual differences among PD patients in terms of the severity of their motor symptoms, the duration of their PD symptoms, and their dopaminergic medications dosage. Each of these variables might have different effects on the brain and cognition in PD patients.

As mentioned above, clinical research has shown that motor abnormalities differ among individual PD patients, such that some patients have severe tremor, while others have severe akinesia (Jankovic et al., 1990; Lee et al., 2012; Mure et al., 2011; Schillaci et al., 2011; Zaidel et al., 2009). For example, Schillaci et al. (2011) found that PD patients with akinesia and rigidity as the predominant symptoms have significantly more widespread dopamine loss in the striatum than PD patients with tremor as the predominant symptom. Along the same lines, studies found PD patients with predominant tremor are less cognitively impaired than patients with bradykinesia (Jankovic et al., 1990). Similarly, models of the basal ganglia and corticostriatal circuit function have been able to explain the occurrence of akinesia and bradykinesia, but not tremor (Obeso et al., 2008).

In addition, PD is a progressive disorder. As the disease progresses, neural dysfunction encompasses many cortical and subcortical structures (Agid et al., 1993; Kish et al., 1988; Sawamoto et al., 2008). These findings suggest that disease duration might correlate with cognitive function in PD patients. Specifically, we hypothesize that WM performance might worsen as the disease progresses.

Furthermore, studies found that the administration of dopaminergic medications to PD patients either enhances (Beato et al., 2008; Costa et al., 2003; Fernandez-Ruiz, Doudet, & Aigner, 1999; Lange et al., 1992; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Marini, Ramat, Ginestroni, & Paganini, 2003), impairs (Brusa et al., 2003), or has no effect (Brusa et al., 2003; Costa et al., 2003) on WM performance. These differential effects of dopaminergic medications on WM could be related to the use of variable medication dosages across different studies, the differential effects of levodopa and dopamine agonists on the brain and cognition, or the different disease stages (early or mild vs. advanced PD) (for discussion see, Owen et al., 1992; Poletti, Frosini, Pagni, Baldacci, Giuntini et al., 2012; Poletti, Frosini, Pagni, Baldacci, Nicoletti et al., 2012).

Given these findings, we argue that there is a relationship between WM performance and the dosage of dopamine medications administered to PD patients. The standard method of calculating the dosage of dopaminergic medications is the levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010). In the present study, we