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Reversal learning in Parkinson's disease depends on medication status and outcome valence

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Abstract

We investigated the role of dopamine in distinct forms of reversal shifting by comparing two groups of patients with mild Parkinson's disease (PD), one ON and one OFF their normal dopaminergic medication. In accordance with our previous work, patients ON medication exhibited impaired reversal shifting relative to patients OFF medication. The present results extend previous studies by showing that the medication-induced deficit on reversal shifting was restricted to conditions where reversals were signaled by unexpected punishment. By contrast, patients ON medication performed as well as patients OFF medication and controls when the reversal was signaled by unexpected reward. The medication-induced deficit was particularly pronounced in patients on the dopamine D3 receptor agonist pramipexole. These data indicate that dopaminergic medication in PD impairs reversal shifting depending on the motivational valence of unexpected outcomes.

Keywords: Dopamine; Cognition; Reward; Punishment; Flexibility; Ventral striatum

1. Introduction

The mesocortical and nigrostriatal dopamine (DA) systems are well known to play a role in cognitive and reward-related processing (Brozoski, Brown, Rosvold, & Goldman, 1979; Castner, Williams, & Goldman-Rakic, 2000; Goldman-Rakic, 1992; Hollerman & Schultz, 1998). Human disorders that implicate the DA system, such as Parkinson's disease (PD), attention-deficit/hyperactivity disorder (ADHD) and schizophrenia, are associated with a variety of cognitive deficits, ranging from impulsivity to inflexibility. Treatment with dopaminergic medication may alleviate some of these deficits. However, the relationship between DA and cognitive performance is complex (Arnsten, 1998; Williams & Goldman-Rakic, 1995; Zahrt, Taylor, Mathew, & Arnsten, 1997): Dopaminergic medication may improve or impair cognitive function depending on a number of factors, such as task demands and baseline DA levels in underlying neural circuitry (Arnsten, 1998; Cools, Barker, Sahakian, & Robbins, 2001; Kimberg, D'Esposito, & Farah, 1997; Mattay et al., 2003).

PD is associated with nigrostriatal, and to a lesser extent mesocorticolimbic DA depletion and subtle cognitive impairments even in the early disease stages (Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986). Recent evidence indicates that administration of dopaminergic medication, which is known to ameliorate the motor deficits in PD, has more complex effects on cognitive function: Both beneficial and detrimental effects have been observed (Cools et al., 2001; Cools, Barker, Sahakian, & Robbins, 2003; Frank, 2005; Frank, Seeberger, & O'Reilly, 2004; Shohamy, Myers, Geghman, Sage, & Gluck, 2005; Shohamy, Myers, Grossman, Sage, & Gluck, 2005; Swainson et al., 2000). It has been hypothesized that these contrasting effects reflect an imbalance of DA in distinct regions of the striatum (Cools et al., 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). In early PD, DA depletion is restricted to the dorsal striatum, whereas the ventral striatum is relatively intact (Farley, Price, & Hornykiewicz, 1977; Kish, Shannak, & Hornykiewicz, 1988). Thus, medication doses necessary to remedy depleted DA levels in the dorsal striatum may detrimentally 'over-dose' DA levels in the relatively intact ventral striatum. To test this, we have assessed performance of patients ON and

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OFF L-Dopa medication on two tasks associated with the dorsal and ventral striatum, respectively (Cools et al., 2001). Consistent with the hypothesis, we found that dopaminergic medication in mild PD remedied impairments in task-switching, associated with the lateral prefrontal cortex and its connections with the severely depleted dorsal striatum (Brass et al., 2003; Meyer et al., 1998; Sohn, Ursu, Anderson, Stenger, & Carter, 2000). Conversely, medication impaired probabilistic reversal learning (Cools et al., 2001; Swainson et al., 2000), associated with the relatively intact ventral striatum and its connections with the ventral prefrontal cortex (Cools, Clark, Owen, & Robbins, 2002; Dias, Robbins, & Roberts, 1996; Divac, Rosvold, & Szwarcbart, 1967; Iversen & Mishkin, 1970). A follow-up functional imaging study in mild PD patients has strengthened this 'over-dose' hypothesis by showing that dopaminergic medication modulated the ventral striatum (i.e. the nucleus accumbens), but not the dorsal striatum during the performance of a probabilistic reversal shifting paradigm (Cools et al., submitted for publication). The findings are consistent with observations from animal studies suggesting that the dopaminergic modulation of cognitive function adheres to an 'inverted U' function whereby excessive, as well as insufficient DA receptor stimulation impairs cognitive performance (Arnsten, 1998; Williams & Goldman-Rakic, 1995; Zahrt et al., 1997).

A recent study by Frank et al. (2004) extended the above-described contrasting effects of dopaminergic medication on cognitive flexibility to the domain of outcome-based learning.[1] Frank et al. (2004) showed that relative to PD patients ON medication, PD patients OFF medication were better at learning from negative outcomes than at learning from positive outcomes. Thus, patients OFF medication exhibited an increased tendency towards 'not-choosing' (i.e. avoiding) a previously punished stimulus (an increased 'NoGO' bias) relative to patients ON medication. By contrast, patients ON medication learned more from positive than negative outcomes and accordingly, exhibited an increased 'GO' tendency towards choosing a previously rewarded stimulus (Frank et al., 2004). This profile was predicted by their computational model, which simulated transient changes in DA following positive and negative outcomes, and subsequent contrasting effects on the direct and indirect pathways within the basal ganglia system: DA was thought to excite the direct or 'GO' pathway, which facilitates rewarded responding, while inhibiting the indirect or 'NoGO' pathway, which suppresses non-rewarded responding. It was proposed that DA bursts, which occur when animals receive unexpected reward, increase plasticity in the direct pathway (supporting 'GO' learning). Conversely, plasticity in the indirect pathway (supporting 'NoGO' or avoidance learning) was proposed to be increased by DA dips, which occur when an expected reward is omitted. In the model, elevated (tonic) levels of DA following dopaminergic medication blocked the effects of normal phasic 'DA dips', which are thought to occur following reward omission (i.e. a form of punishment) (Hollerman & Schultz, 1998). The medication-induced attenuation of phasic 'DA dips' impaired reversal learning by diminishing the normal 'NoGO' bias in learning from punishment (Frank, 2005). Although this model did not explicitly take into account the spatiotemporal progression of DA depletion from the dorsal to the ventral striatum in PD, it did provide a mechanistic account of the detrimental effect of dopaminergic medication on outcome-related functioning associated with relatively intact ventral fronto-striatal circuitry.

These data raise the question whether the previously observed medication-induced deficit on reversal shifting is valence-specific; that is, restricted to conditions where the reversal is signaled by an unexpected negative outcome. The specific aim of the present study was to examine the hypothesis that dopaminergic medication in mild PD impairs reversal shifting based on unexpected negative, but not positive outcomes. Such a selective punishment-based reversal deficit would support the existence of different representations of reward- and punishment-based learning signals (Daw, Kakade, & Dayan, 2002; Frank et al., 2004; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Seymour et al., 2005). We examined performance of 2 groups of 10 patients with mild PD, 1 ON medication and 1 OFF medication, as well as 12 control subjects using a novel paradigm that enabled the separate investigation of learning reversals, signaled by either negative or positive outcomes.

2. Methods

2.1. Patients

The study was approved by the UC Berkeley Committee for the Protection of Human Subjects and all subjects gave written informed consent.

Twenty-eight patients with mild PD were recruited from the movement disorders clinics at the Northern California Veterans Administration Medical Center and the University of California, San Francisco. All patients were diagnosed by a neurologist. Selected patients were contacted and a medical history was obtained. Patients with a significant neurological history not related directly to PD (e.g. stroke, head injury) as well as dementia (as measured with the Montreal Cognitive Assessment; MoCA; scores < 24; Nasreddine et al., 2005) or depression (as measured with the Beck Depression Inventory; BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) were excluded from the study. The MoCA and BDI were administered on the same test session on which the here-presented data were obtained (except for one patient from the ON group who was tested on a subsequent OFF session and one patient from the OFF group who tested on a subsequent ON session). Following MoCA and BDI testing, six patients were excluded based on MoCA scores below 24 and one patient based on an abnormally high BDI score (above 20). One additional patient, tested ON medication, was unable to understand the instructions of the task. The mean MoCA score of the remaining 20 patients was 26.4 (S.E.M. = 0.4) and the mean BDI score was within the normal range (mean = 8.0, S.E.M. = 0.9). The severity of clinical symptoms was assessed according to the Hoehn and Yahr rating scale (Hoehn & Yahr, 1967) and the Unified PD (44-item) Rating Scale (UPDRS; Fahn, Elton, & Members of the UPDRS Development Committee, 1987). Hoehn and Yahr ratings ranged between I and III. The average disease duration was 9.6 years (S.E.M. = 1.7). All, but two patients included in the study were receiving daily L-Dopa preparations. The two patients that were not receiving L-Dopa preparations were receiving mirapex only, a DA D3 receptor agonist. Other dopaminergic and non-dopaminergic medications are summarized in Table 1. All patients were on stable medication for at least 2 months prior to the study. Patients were

[1] The term cognitive flexibility refers here to the ability to rapidly change previously relevant responding in response to a change in the environment. Conversely, the term learning is used to refer to the ability to gradually acquire newly relevant responding in order to adapt to the environment.