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Research report

Cognitive states influence dopamine-driven aberrant learning in Parkinson's disease

James F. Cavanagh [a,*], Andrea A. Mueller [a], Darin R. Brown [a], Jacqueline R. Janowich [a], Jacqueline H. Story-Remer [a], Ashley Wegele [b] and Sarah Pirio Richardson [b]

[a] Department of Psychology, University of New Mexico, USA
[b] Department of Neurology, University of New Mexico, USA

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ABSTRACT

Individual differences in dopaminergic tone underlie tendencies to learn from reward versus punishment. These effects are well documented in Parkinson's patients, who vacillate between low and high tonic dopaminergic states as a function of medication. Yet very few studies have investigated the influence of higher-level cognitive states known to affect downstream dopaminergic learning in Parkinson's patients. A dopamine-dependent cognitive influence over learning would provide a candidate mechanism for declining cognitive integrity and motivation in Parkinson's patients. In this report we tested the influence of two high-level cognitive states (cost of conflict and value of volition) that have recently been shown to cause predictable learning biases in healthy young adults as a function of dopamine receptor subtype and dopaminergic challenge. It was hypothesized that Parkinson's patients OFF medication would have an enhanced cost of conflict and a decreased value of volition, and that these effects would be remediated or reversed ON medication. Participants included $N = 28$ Parkinson's disease patients who were each tested ON and OFF dopaminergic medication and 28 age- and sex-matched controls. The expected cost of conflict effect was observed in Parkinson's patients OFF versus ON medication, but only in those that were more recently diagnosed (<5 years). We found an unexpected effect in the value of volition task: medication compromised the ability to learn from difficult a-volitional (instructed) choices. This novel finding was also enhanced in recently diagnosed patients. The difference in learning biases ON versus OFF medication between these two tasks was strongly correlated, bolstering the idea that they tapped into a common underlying imbalance in dopaminergic tone that is particularly variable in earlier stage Parkinsonism. The finding that these decision biases are specific to earlier but not later stage disease may offer a chance for future studies to quantify phenotypic expressions of idiosyncratic disease progression.

* *Corresponding author*. Department of Psychology, University of New Mexico, Logan Hall, 1 University of New Mexico, MSC03 2220, Albuquerque, NM, 87131, USA.
E-mail address: jcavanagh@unm.edu (J.F. Cavanagh).
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1. Introduction

Dopaminergic neurodegeneration in Parkinson's disease not only manifests in difficulties with motor execution, but also in related problems with volitional action selection, high-level cognition, motivation and mood. Each of these related symptoms can cause understated but significant distress. In this report we describe how some of these related symptoms could be exacerbated by subtle but pervasive learning biases caused by low dopaminergic tone. This aberrant learning may have implications in the day-to-day quality of life of patients, and as it may differ depending on disease duration it may open novel avenues to quantify disease progression.

1.1. *Aberrant learning in Parkinson's disease*

Dopaminergic tone influences the sensitivity of the competing cortico-striatal action selection pathways. Phasic dopamine bursts in the cortico-striatal D1 receptor-mediated direct pathway underlie the ability to learn from and seek reward, whereas dopamine dips in the D2 receptor-mediated indirect pathway underlie the ability to learn from and avoid punishment (Kravitz et al., 2010; Kravitz, Tye, & Kreitzer, 2012; Porterstransky, Seiler, Day, & Aragona, 2013; Tai, Lee, Benavidez, Bonci, & Wilbrecht, 2012). Reduced tonic dopamine in Parkinsonism causes a lower dynamic range of phasic signaling and a loss of synaptic plasticity in the direct pathway (Frank, 2005; Frank, Seeberger, & O'Reilly R, 2004), as well as opposite effects of more effective phasic signaling and enhanced long term potentiation in the indirect pathway (Beeler et al., 2012; Wiecki & Frank, 2010). The outcome of these systemic alterations include impaired reward-related learning and motivation for action selection (diminished D1 effects) (Voon et al., 2010) but also paradoxically boosted learning of active inhibition (enhanced D2 effects) (Kravitz et al., 2012). This phenotype can be reversed with levodopa (L-dopa) treatment, causing hypersensitivity to rewards and inability to learn from punishments (Cools, 2006; Frank, Samanta, Moustafa, & Sherman, 2007; Frank et al., 2004). Given that L-dopa remains the prevailing treatment for PD, there are clear clinical benefits for understanding how striatal D1/D2 balance affects day-to-day life in Parkinson's patients, in particular understanding the emergence of gambling and impulse control disorders in some patients (Molina et al., 2000) due to L-dopa "overdosing" of the ventral striatum (Cools, 2006; Ryterska, Jahanshahi, & Osman, 2013).

While these overt biases to rewarded and punished outcomes are well defined, a tonic striatal D1/D2 imbalance can lead to other subtle behavioral and decision-making biases (Chong et al., 2015; Foerde et al., 2016; Sharp et al., 2015), suggesting valenced learning biases simply scratch the surface of aberrant learning in Parkinson's disease (Wiecki & Frank, 2010). In this report we examine two extrinsic factors that have been shown to influence cortico-striatal plasticity during learning: conflict costs and agency preferences. Similar to an effort cost, conflict induces a cognitive demand during learning. Agentic decisions similarly require higher-order decision making, yet this has a different influence on learning. Conflict costs and agency preferences reflect ecologically relevant situations that have recently been shown to contribute to learning biases as a function of striatal D1/D2 balance in healthy young adults (Cavanagh, Masters, Bath, & Frank, 2014; Cockburn, Collins, & Frank, 2014). We postulate that an understanding of the influence of dopaminergic tone on learning under the influence of these higher-level cognitive phenomena could lead to a better mechanistic understanding of cognitive, motivational, and mood symptoms in Parkinson's patients.

1.2. *Cost of conflict*

It was recently shown that cognitive conflict can act as an implicit cost during learning, similar to an effort cost (Cavanagh et al., 2014). Both effort and conflict costs are mediated by dopaminergic tone and are amplified by a striatal D2 > D1 imbalance (Cavanagh et al., 2014; Denk et al., 2005; Drew et al., 2007; Salamone, Correa, Farrar, Nunes, & Pardo, 2009; Simpson et al., 2011; Treadway et al., 2012). Cognitive conflict occurs when competing response options compete for control of behavior, and it acts as a trigger of the need for cognitive control (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Cavanagh & Frank, 2014; Shenhav, Botvinick, & Cohen, 2013). Since control is effortful, it acts as a cost when integrating action values in cortico-striatal circuits, and individuals with genetic striatal D2 > D1 sensitivities integrate these conflict-related action sequences with greater associated cost (Cavanagh et al., 2014). To note, this effect can also be induced in healthy young adults by administration of cabergoline, a selective D2 agonist which in low doses preferentially acts on striatal D2-autoreceptors to boost indirect pathway function (Cavanagh et al., 2014). This collective set of findings leads to the clear *a priori* hypothesis that Parkinson's patients off medication should have an enhanced cost of conflict effect due to striatal D2 > D1 imbalance caused by low dopaminergic tone. We think this phenomenon might be ecologically and clinically relevant, since an enhanced cost of conflict may act to increase the intrinsic cost of goal-directed actions (Kool, McGuire, Wang, & Botvinick, 2013; Shenhav et al., 2013). This would suggest a negative influence on the ability to instantiate higher cognition, leading to poor executive function and low motivation (apathy) in Parkinson's patients.

1.3. *Value of volition*

A different study recently explained why volitional choice can be associated with greater value than a-volitional or instructed choice (Cockburn et al., 2014). People prefer options based on previous volitional, agentic choices (Bown, Read, & Summers, 2003; Sharot, Velasquez, & Dolan, 2010), particularly when they may be rewarding (Leotti & Delgado, 2014). Imaging studies have indicated an important role of basal ganglia in this value of volition bias (Leotti & Delgado, 2014; Murty, DuBrow, & Davachi, 2015; Sharot, Shiner, Brown, Fan, & Dolan, 2009), and individuals with a genetic striatal D1 > D2 sensitivity show an enhanced value of volition for rewarded options (Cockburn et al., 2014). This latter study advanced the novel hypothesis that this value of volition is the result of a credit-assignment process in the basal ganglia,