MOTIVATIONAL MODES AND LEARNING IN PARKINSON'S DISEASE

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ABSTRACT

Learning and motivation are intrinsically related and both have been linked to dopamine. Parkinson's disease results from a progressive loss of dopaminergic inputs to the striatum and leads to impairments in motivation and learning from feedback. However, the link between motivation and learning in Parkinson's disease is not well understood. To address this gap, we leverage a well-established psychological theory of motivation, regulatory mode theory, which distinguishes between two functionally independent motivational concerns in regulating behavior: a concern with having an effect by initiating and maintaining movement (Locomotion) and a concern with establishing what is correct by critically evaluating goal pursuit means and outcomes (Assessment). We examined Locomotion and Assessment in patients with Parkinson's disease and age-matched controls. Parkinson's disease patients demonstrated a selective decrease in Assessment motivation but no change in Locomotion motivation, suggesting that Parkinson's disease leads to a reduced tendency to evaluate and monitor outcomes. Moreover, weaker Assessment motivation was correlated with poorer performance on a feedback-based learning task previously shown to depend on the striatum. Together, these findings link a questionnaire-based personality inventory with performance on a well-characterized experimental task, advancing our understanding of how Parkinson's disease affects motivation with implications for well-being and treatment outcomes.

KEYWORDS:

INTRODUCTION

Adaptive behavior relies on learning in order to improve choices based on experiences, but motivation to do so is of equal importance. From a neurobiological perspective, learning and motivation have both been linked to dopamine. Numerous studies have linked firing of dopaminergic neurons or activity in brain regions that receive dopaminergic input to learning from reinforcement (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Schultz, Dayan, & Montague, 1997), and dopamine has been shown to play a critical role in motivated behavior, such as choosing to expend greater effort or wait longer in order to obtain larger rewards (Niv, Joel, & Dayan, 2006; Salamone & Correa, 2012; Wang, Miura, & Uchida, 2013).

Parkinson's disease is characterized by a progressive loss of dopaminergic inputs to the striatum that leads to impaired motor control, often considered a core symptom of the disease. The past decade has seen mounting evidence that learning and reward processing also are compromised in Parkinson's disease, consistent with the proposed role of dopaminergic signals in learning (Foerde & Shohamy, 2011b; Frank, Seeberger, & O'Reilly, 2004; Schultz, 1998; Shohamy et al., 2004). Additionally, it has long been speculated that Parkinson's disease is associated with a general motivation deficit (Dagher & Robbins, 2009; Glosser et al., 1995; Menza, 2000; Todes & Lees, 1985). The prevalence of depression and apathy in the disease, along with reduced novelty seeking and reported decreases in susceptibility to addiction (Glosser et al., 1995; Menza, 2000), is thought to result from a general depletion in dopaminergic circuits prior to diagnosis with Parkinson's disease (Aarsland, Pahlhagen, Ballard, Ehrt, & Svenningsson, 2012). The dorsolateral striatum, which is the most severely affected region early in Parkinson's disease, is thought to be most directly related to the motor dysfunction, whereas motivational functions are more commonly associated with the ventral striatum (Liljeholm & O'Doherty, 2012). However, subtle deficits associated with less affected

ventral striatal circuits may still give rise to affective, cognitive, and behavioral changes. It is assumed that this wide variety of deficits in Parkinson's disease share a single initial cause, and there is an emerging understanding that dopaminergic dysfunction and related striatal dysfunction has multifarious effects involving learning (Dagher & Robbins, 2009; Shohamy & Adcock, 2010), motivation (Niv et al., 2006; Salamone & Correa, 2002), and performance (Smittenaar et al., 2012). These wide-ranging effects highlight the need for a better understanding of how dopaminergic deficits in Parkinson's disease manifest in motivational and cognitive changes and, in particular, of the interrelation of these effects, both at the neural and psychological level.

Dopamine operates in both tonic and phasic modes, resulting in signals that convey distinct kinds of information. Phasic dopamine signals carry temporally specific learning signals (Glimcher, 2011; Schultz, 2000) and are commonly associated with reward. Notably, dopamine is associated with expectation and instrumental aspects of pursuing rewards (or wanting) rather than consummatory or hedonic aspects (liking) (see Salamone & Correa, 2012 for review). Tonic dopamine signals, according to recent proposals, may instead carry information about overall rates of responding or "response vigor" that may be related to overall levels of reward available (Beierholm et al., 2013; Niv, 2007; Wang et al., 2013). That is, in a context where rewards are plentiful, it is advantageous to work vigorously to obtain as much reward as possible. Dopaminergic dysfunction should affect functions relying on both phasic and tonic signaling, and there is substantial evidence that this is the case in Parkinson's disease. Impaired learning from rewards has been widely documented (Foerde & Shohamy, 2011a; Frank et al., 2004; Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004; Knowlton, Mangels, & Squire, 1996), and individuals with Parkinson's disease exhibit decreased movement vigor, even when they are able to accurately execute movements (Mazzoni, Hristova, & Krakauer,

2007). Thus, Parkinson's disease appears to affect multiple aspects of motivation, perhaps

through dysfunction in both phasic and tonic signaling (Dayan & Balleine, 2002; Niv et al.,

2006).

Additionally, dopamine neurons arise from two main clusters in the midbrain, the substantia

nigra pars compacta and the ventral tegmental area, which project to distinct anatomical targets.

Parkinson's disease progresses from primary involvement of substantia nigra neurons that

project to dorsolateral striatum in the early stages of disease, towards also affecting neurons

projecting to the ventral striatum (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, &

Seitelberger, 1973; Cools, 2006; Hornykiewicz, 1989; Kish, Shannak, & Hornykiewicz, 1988).

Together, these aspects of dopaminergic function suggest that dopamine can be involved in

different forms of motivation characterized by neuroanatomical specificity and distinct signaling

modes, thereby accounting for the varied deficits stemming from dopamine dysfunction. Paired

with a stereotypical disease progression in Parkinson's disease from dorsolateral to

ventromedial degeneration of midbrain and striatum function, some specificity in the effects of

Parkinson's disease on motivation should be expected and these effects are likely to change

with disease progression.

As outlined above, important progress has been made in understanding distinctions between

different forms of motivation and learning based on computational and neurobiological models.

By contrast, psychological and personality level theories targeting motivation have not generally

been sensitive to such distinctions. Instead, broad measures of apathy and depression have

been used to demonstrate differences in Parkinson's disease patients, but these measures may

not always have the resolution to provide tighter links across neural, computational, and

psychological levels of analysis. Linking self-report measures of motivation with experimental

tasks that have been characterized in terms of their computational or neural underpinnings could provide the initial steps needed to bridge across levels of analysis.

Recent work has explored the interface of motivation and cognition in healthy individuals by linking psychological theories of motivation with classification learning and decision making (Maddox, Baldwin, & Markman, 2006; Maddox & Markman, 2010; Markman, Baldwin, & Maddox, 2005; Otto, Markman, Gureckis, & Love, 2010; Worthy, Maddox, & Markman, 2007). A similar approach might illuminate the interplay of motivation and cognition in Parkinson's disease. One promising source of insight into understanding motivation and learning in Parkinson's disease comes from regulatory mode theory (Higgins, Kruglanski, & Pierro, 2003; Kruglanski et al., 2000). Regulatory mode theory describes two functionally independent motivational concerns in regulating behavior. One mode, termed "Locomotion", involves a concern with having an effect by initiating and maintaining movement, regardless of whether all alternatives have been fully considered ("get going"). A distinct and independent, and potentially complementary, motivational concern termed "Assessment", involves establishing what's right and correct through critical evaluation and comparison of all possibilities. Assessment entails an emphasis on discovering and precisely understanding the relative worth of alternative goal pursuit means and outcomes, and, as a consequence, involves a desire to carefully observe feedback from the environment to stay in line with norms and goals ("get it right") (Kruglanski et al., 2000). Given this distinction, locomotion motivation should be most strongly related to "movement vigor" or the "energizing" functions described for dopamine above, whereas Assessment motivation should be most strongly related to the learning functions of dopamine. Regulatory mode has been characterized extensively in healthy populations (Higgins et al., 2003; Kruglanski et al., 2000), where it has shed light on motivational processing and

performance. Yet it remains unknown whether, and how, regulatory modes are altered in Parkinson's disease.

We sought to address this gap by studying how Parkinson's disease affects Locomotion and Assessment *and* by determining how motivational modes in Parkinson's disease are related to the well-characterized learning deficits in this population. We focused on two main questions: First, does the dopaminergic dysfunction, as seen in Parkinson's disease, affect the motivational modes of Locomotion and Assessment uniformly? Second, are changes in motivational modes in Parkinson's disease related to striatal-dependent feedback learning?

We used the Regulatory Mode Questionnaire (Kruglanski et al., 2000) to measure chronic motivation and computed scores on the Locomotion and Assessment scales. Importantly, the Regulatory Mode Questionnaire consists of questions whose content does not overlap with diagnostic interviews for diagnosis of Parkinson's disease, and it has been used to predict performance and decision making across a range of settings in healthy individuals (see Higgins et al., 2003; Kruglanski, Pierro, Mannetti, & Higgins, in press; Kruglanski et al., 2000).

In order to measure striatal-dependent feedback learning deficits, we used a probabilistic learning task where feedback was delivered either immediately or after a delay. Previously, we found that the timing of feedback modulates whether learning depends on the striatum (for immediate feedback) or on the hippocampus (for delayed feedback) (Foerde, Race, Verfaellie, & Shohamy, 2013; Foerde & Shohamy, 2011a; see also Maddox, Ashby, & Bohil, 2003; Maddox & Ing, 2005). Thus, this task provides a *within-subject* measure of the selective impairment of learning that depends on the striatum, which is the region most compromised in Parkinson's disease.

Guided by current understanding of motivation in Parkinson's disease, we considered several different relations between Parkinson's disease and regulatory mode. Given that Parkinson's disease is associated with loss of motor control and changes in the computations underlying the exertion of movement vigor (even in PD patients on dopamine replacement therapy; Mazzoni et al 2007), one possibility was that Locomotion—the motivation to move from state to state, manage to make things happen, or "get going"—would be weaker in Parkinson's disease patients. However, given that Parkinson's disease is also associated with intrinsic monitoring problems (e.g. enhanced walking when externally cued by painted footsteps or an auditory beat), another possibility was that Assessment—the motivation to establish what's correct, critically evaluate alternatives, or "get it right"—would be weaker among Parkinson's disease patients. Finally, both Locomotion and Assessment, although functionally independent, could be weaker among Parkinson's disease patients.

Additionally, in order to begin understanding whether dopaminergic dysfunction exerts independent influences on learning and motivation, we sought to determine whether differences in regulatory mode motivation are linked to those specific learning deficits that are associated with dopaminergic dysfunction in the striatum. We reasoned that if learning deficits associated with striatal dopamine dysfunction were associated with motivational mode scores, this would point to a link between striatal dopamine dysfunction and motivational changes.

MATERIALS AND METHODS

Participants

Fifty-seven participants with a diagnosis of idiopathic Parkinson's disease were recruited from the Center for Parkinson's Disease and Other Movement Disorders at the Columbia University Medical Center Department of Neurology with the assistance of Dr. Lucien Cote and through

online databases for volunteers interested in participating in research on Parkinson's disease (Fox Trial Finder, PDtrials). Only patients in mild or moderate disease stages (Hoehn & Yahr stage 1-3) were recruited. Seventy healthy controls, matched to the Parkinson's disease patients on age and education, were recruited from Columbia University and the community surrounding Columbia University (see **Table 1**). All participants provided informed consent in accordance with the guidelines of the Institutional Review Board of Columbia University and were paid $12/hour for their participation.

Participants were excluded if they had suffered brain injury, were diagnosed with neurological or psychiatric disorders other than Parkinson's disease, or were on antidepressant, antipsychotic or anxiolytic medication. All participants completed a battery of neuropsychological tests and were excluded if they exhibited general cognitive impairment [scoring 27 (2.5 SD below the mean) or below on the Mini-Mental State Exam, MMSE] or showed signs of depression [scoring 7 (2.5 SD above the mean) or above on the cognitive subscale of the Beck Depression Inventory, BDI]. This left 42 Parkinson's disease patients and 53 older adult controls. The Parkinson's disease and healthy control groups did not differ in age, education, or neuropsychological assessments (ps > 0.25). Parkinson's disease patients were tested either on medication (ON state: n=27), or off medication [OFF state: n=15; either withdrawn from medication (n=10) or not yet receiving dopaminergic treatment (n=5)]. Withdrawal from medication entailed omission of medications taken for Parkinson's disease in the morning such that withdrawal had occurred overnight (approx. 16 hours), as is common practice in the field (Cools, Barker, Sahakian, & Robbins, 2001b; Frank et al., 2004; Shohamy, Myers, Geghman, Sage, & Gluck, 2006).

Procedure

Participants filled out the Regulatory Mode Questionnaire to assess motivation, and completed a neuropsychological battery to assess overall cognitive function and mood (MMSE, North American Adult Reading Test (NAART), Controlled Oral Word Association Test (COWAT), Digit Span, and the BDI). A subset [n=48: PD n=24 (11 ON and 13 OFF medication), Control n=24] of participants also completed a computerized feedback-learning task. Some participants did not complete the feedback-learning task as they were recruited to participate in other tasks not reported here.

Locomotion and Assessment scales

The Regulatory Mode Questionnaire comprises the Locomotion and Assessment scales (see Kruglanski et al., 2000) and requires participants to determine how much they agree with each of 30 statements. An example statement associated with the Assessment scale is 'I often critique work done by myself and others.' An example item from the Locomotion scale is 'By the time I accomplish a task, I already have the next one in mind'. Agreement with these statements is indicated on a 6-point scale ranging from 1 (strongly disagree) to 6 (strongly agree). Scores for Assessment and Locomotion were computed across appropriate items for each scale.

Feedback learning task

Forty-eight of the participants completed a probabilistic learning task, which previously has been shown to be sensitive to striatal function in humans and is known to be sensitive to learning impairments in Parkinson's disease (Foerde, Knowlton, & Poldrack, 2006; Foerde & Shohamy, 2011a; Knowlton et al., 1996; Poldrack et al., 2001; Shohamy et al., 2004). Note that the majority of these data, with the exception of four Parkinson's patients, have been reported previously in Foerde & Shohamy (2011) and Foerde, Race, Verfaellie, & Shohamy (2013). In

this type of task, participants learn to associate cues with outcomes through trial and error. Because there is no one to one mapping between cues and outcomes, optimal learning involves the use of response-contingent feedback across multiple trials to incrementally learn the most probable outcome.

We used a version of the task with two *within-subject* conditions that differed in the timing with which feedback was delivered during probabilistic learning: feedback was either immediate or delayed by a few seconds (Immediate vs. Delayed Feedback conditions). In previous work we have shown that Immediate Feedback learning depends on the striatum and is impaired in Parkinson's disease, whereas Delayed Feedback learning depends on the hippocampus and is spared in Parkinson's disease (Foerde, Race, et al., 2013; Foerde & Shohamy, 2011a).

On each trial, participants saw a cue (one of four different butterflies) and had to predict which of two outcomes (different colored flowers) that cue was associated with (see **Figure 1A**). Each butterfly was associated with one flower on 83% of trials and with the other flower on 17% of trials (**Figure 1B**). Response-contingent feedback was presented after a fixed delay of either 1 second (Immediate condition; striatal-dependent) or 7 seconds (Delay condition; striatal-independent), such that two butterflies were associated with each feedback timing condition. Participants' choices remained on the screen during the delay in order to minimize working memory demands. The assignment of cues to outcomes and conditions was counterbalanced across participants. Immediate and Delayed feedback trial types were interleaved throughout training. Feedback consisted of a verbal response ('CORRECT' or 'INCORRECT') presented on the screen for 2 seconds (Foerde & Shohamy, 2011a). A 7 second response deadline was imposed, and a reminder to respond appeared after 4 seconds.

Participants completed a short practice to ensure that they understood the task and were able to respond in the allotted time. Next they completed 96 learning trials of the task (Learning phase), followed by a Test phase with 24 trials, in which participants saw the butterflies from the Learning phase and were told to continue performing based on what they had learned. The Test phase structure resembled the Learning phase, with the exception that no feedback was given and the timing of all trial parts was equivalent across trial types.

Performance on the feedback learning task was assessed in terms of making optimal choices—the degree to which participants selected the most likely outcome for each cue. Thus, regardless of the feedback outcome (correct vs. incorrect) on each trial, a participant was scored as making a correct response if the flower associated with a butterfly on 83% of trials was selected. The overall optimal proportion correct was calculated separately for the Immediate and Delayed feedback conditions for both the learning and test phases.

RESULTS

Regulatory mode

First, we tested whether Locomotion differed between Parkinson's disease patients and healthy controls (matched to the Parkinson's disease patients on age and education). Although Locomotion and Assessment are considered independent constructs, they were significantly, moderately correlated in our sample (r=0.28, p=0.003). Thus, we compared Locomotion between groups in a Univariate ANOVA with Assessment as a covariate. Parkinson's patients (PD) and age-matched controls (AC) did not differ on the Locomotion scale (AC: $M_{adjusted}$=4.47, SE=0.10; PD: $M_{adjusted}$=4.50, SD=0.12; $F(1,92)$=0.06, p=0.81; **Figure 2A**). Second, we tested whether Assessment differed between Parkinson's disease patients and healthy controls. We compared Parkinson's disease patients and controls using a Univariate ANOVA with

Locomotion as a covariate. We found that Parkinson's disease patients scored significantly lower on the Assessment scale (AC: $M_{adjusted}$=3.64, SE=0.11; PD: $M_{adjusted}$=3.12, SE=0.12; $F(1,92)$=10.58, p=0.002; **Figure 2B**). Thus, Parkinson's disease patients differed from controls on Assessment specifically, and not generally in how they answered the questionnaire.

In order to determine whether age affected responses, we also compared Locomotion and Assessment scores of the healthy controls to a sample of young adults. The regulatory mode scales have been used extensively in young adult and middle-aged adult populations, but not in older populations (50-85 years) such as our sample. We found no differences between young and old adults on either Assessment ($t(102)$= -1.42, p=0.16) or Locomotion ($t(102)$= 0.37, p=0.71), suggesting that differences between Parkinson's disease patients and age-matched controls in assessment were not due to age-related differences. Additionally, scores on the built-in "Lie" scale did not differ between groups overall (One-way ANOVA: $F(2,143)$=0.22, p=0.80; M_{YOUNG}=2.4+/-0.78 M_{AC}=2.4+/-0.80; M_{PD}=2.3+/-0.80).

Although the study was not designed to compare Parkinson's patients ON and OFF medication, we report this comparison for completeness. Most of the Parkinson's patients were tested while ON their regular dopamine replacement medication (n=27), whereas some were tested while OFF dopaminergic medication (n=15). ON vs. OFF patients did not differ in Assessment scores ($t(40)$=-0.67, p=0.51). Comparing only the patients ON dopaminergic medication to age-matched controls, the difference in Assessment was still significant: $F(1,77)$=6.45, p=0.013, suggesting that remediation with dopamine replacement therapy did not strengthen Assessment motivation.

Relation between regulatory mode and feedback learning

Next, we sought to determine whether differences in regulatory mode motivation were linked to

learning deficits previously associated with dopaminergic dysfunction in the striatum (Foerde,

Race, et al., 2013; Foerde & Shohamy, 2011a; **Figure 3**; the majority of the data included here

were reported previously). In order test the link between Assessment and striatal-dependent

learning, we focused on a subset of our participants (n=48) who completed the immediate vs.

delayed feedback-learning task described above. If Assessment is related to the striatal

dysfunction underlying Parkinson's disease, then Assessment would be expected to be related

specifically to learning from immediate feedback (shown previously to depend on the striatum)

but not to learning from delayed feedback (shown previously to depend on the hippocampus).

Therefore, we planned to test correlations between immediate and delayed feedback learning

and Assessment scores.

Across groups, Assessment and Immediate feedback learning were positively correlated

(r=0.32, p=0.028; **Figure 4A**). By contrast, there was no correlation between Assessment and

Delayed feedback learning (r=-0.07, p=0.66; **Figure 4B).** The difference between these two

correlations was borderline significant (p=0.036, one-tailed test for dependent correlations; Lee

& Preacher, 2013). Thus, scores on the Assessment scale were specifically related to learning

from immediate feedback, which has been shown to depend on the striatum (Foerde, Race, et

al., 2013; Foerde & Shohamy, 2011a).

Given the relationship between Parkinson's disease and both Assessment and Immediate

feedback learning, we tested whether Assessment motivation mediated the Immediate feedback

learning performance through a series of regression analyses (**Figure 5**). First, disease status

(Group: AC/PD coded -1/+1) significantly affected Immediate feedback learning (β=0.29,

t(46)=2.08, p=0.043). Second, disease status was marginally associated with Assessment scores in the reduced subset sample that completed the feedback learning task (β=0.25, t(46)=1.72, p=0.09). Finally, there was a near significant association between Assessment and Immediate feedback learning when controlling for disease status (β=0.23, t(45)=1.85, p=0.07) and the association between disease status and Immediate feedback learning was non-significant when controlling for Assessment (β=0.23, t*45)=1.61, p=0.11). To test the indirect effect, we used the Hayes and Preacher SPSS macro implementing the bootstrapping method (Preacher & Hayes, 2008); the 95% confidence interval was obtained using 5000 resamples. Results indicated a significant mediating role of Assessment on the relation between disease status and Immediate feedback learning (β =0.0092, 95% CI=0.0002 to 0.0262).

DISCUSSION

Aspects of both learning and motivation are thought to depend on striatal dopamine function and multiple neurobiological mechanisms underpinning such effects on learning and motivation have been posited. Yet little is known about how this relates to broader psychological theoretical frameworks and personality-based measures of motivation. Here, we determined whether questionnaire-based measures of chronic goal pursuit motivations, related to either movement (Locomotion) or monitoring (Assessment) functions, were affected by Parkinson's disease and were related to performance on an experimental task known to depend on the striatum.

Our results suggest that Parkinson's disease differentially affects Assessment motivation. Patients with Parkinson's disease had lower Assessment scores than healthy controls, but they did not differ in Locomotion. Additionally, the self-reported Assessment scores were correlated specifically with the ability to learn from immediate response-contingent feedback, a form of learning previously shown to depend on the striatum (Foerde, Race, et al., 2013; Foerde &

Shohamy, 2011a). The relation between these two separate measures suggests a link between the differences in Assessment in Parkinson's disease and the known feedback-based learning disruption in the disease. Such a link could tie Assessment motivation to the functioning of phasic dopamine signals that are critical for learning in the striatum.

It is increasingly clear that Parkinson's disease involves cognitive and motivational deficits as well as motor deficits, even in the early stages of the disease (Cools, Barker, Sahakian, & Robbins, 2001a; Frank et al., 2004; Jahanshahi, Wilkinson, Gahir, Dharmarinda, & Lagnado, 2010; Shohamy et al., 2004; White, 1997), and the present results are consistent with such findings. Indeed, the lower scores on the Assessment scale, which captures a self-reported reduced motivation to "get it right", are consistent with a substantial body of research demonstrating selective deficits in feedback-driven learning in Parkinson's disease (Cools, 2006; Foerde & Shohamy, 2011a; Frank et al., 2004; Shohamy et al., 2004).

Interestingly, recent theoretical (Daw, Niv, & Dayan, 2005) and empirical (Daw, Gershman, Seymour, Dayan, & Dolan, 2011; Yin & Knowlton, 2006) work points to an important distinction between habitual vs. goal-directed behavior. Feedback learning is often thought to be habitual in nature, but in past work we have found that feedback learning tasks may invite contributions from both habitual and goal-directed forms of learning (Foerde et al., 2006). The feedback learning task used in the current study manipulated the timing of feedback, which we have shown determines whether learning depends on the striatum or the medial temporal lobes (Foerde, Race, et al., 2013; Foerde & Shohamy, 2011a). In this previous work we also found that learning that relied on the striatum was related to poorer memory of trial outcomes, which could suggest that such learning may be less goal-directed. However, recent work has shown that it may be difficult to distinguish between habitual vs. goal-directed learning at the level of

the striatum (Daw et al., 2011), and we cannot preclude the possibility that goal-directed

learning played a role even when learning from immediate feedback. Given the characterization

of the Assessment scale, it is tempting to speculate that it is more related to goal-directed

responding. Although it is often assumed that PD patients suffer primarily from deficits in

habitual learning, there is some evidence suggesting this may not be the case (de Wit, Barker,

Dickinson, & Cools, 2011; Sharp, Foerde, Daw, & Shohamy, in preparation) and that dopamine

dysfunction may also affect goal-directed learning (de Wit et al., 2012). Moreover, it has been

proposed that energizing functions of motivation may be most relevant for habitual responding

(Niv et al., 2006). In future work it would be important to further characterize the links between

self-reported motivation and habitual vs. goal-directed learning.

Notably, we did not find differences in Locomotion (nor any association with measures of

disease severity, e.g. UPDRS). Yet motor impairments and "energizing" deficits in PD are well

known (Mazzoni et al., 2007). We can speculate about several potential reasons such a

"disconnect" between symptoms and self-reported motivation might occur. One possibility is that

while Parkinson's patients may report that they still are motivated to take action, they are less

effective in doing so. This would be consistent with the idea that a key problem in Parkinson's

disease is the translation of internal motivation into selecting the appropriate action (Balleine &

O'Doherty, 2010; Mogenson, Jones, & Yim, 1980; Schmidt et al., 2008), and selection includes

making the right or correct choice, which would involve assessment motivation. Another

possibility is that the "implicitness" of Locomotion vs. Assessment differs, such that individuals

are less able to accurately report on some motivational functions than others (i.e. less able for

the locomotion function)—a possibility it could be fruitful to explore in future research in order to

better understand how to evaluate motivational changes in PD.

The current results extend previous work documenting cognitive and motivational deficits in Parkinson's disease by linking a questionnaire-based goal pursuit personality measure with performance on a well-characterized experimental task that measures striatal learning. A considerable body of research, largely separate from the experimental investigations of cognitive learning deficits in Parkinson's disease, has investigated the idea that those with a predisposition to develop Parkinson's disease share a distinct set of traits—the "parkinsonian personality" (Dagher & Robbins, 2009; Glosser et al., 1995; Menza, 2000; Todes & Lees, 1985). For example, patients with Parkinson's disease are described as rigid, introverted, and low in novelty seeking (Glosser et al., 1995; Menza, 2000); traits that have been thought to fit with the idea that damage to the dopaminergic system is present prior to the onset of motor illness and gives rise to a variety of symptoms (Aarsland et al., 2012; Menza, 2000). Thus, an open question is whether the differences in Assessment motivation that we found are the result of changes associated with the onset of Parkinson's disease or reflect stable differences in people who go on to develop Parkinson's disease.

Limitations and future directions

One limitation of the current work is that we lack direct measurements of striatal and dopaminergic functioning. Instead, by showing an association between questionnaire measures and an experimental task that was previously characterized in terms of its neural substrates (Foerde, Braun, & Shohamy, 2013; Foerde, Race, et al., 2013; Foerde & Shohamy, 2011a), we provide a strong indirect link to dopaminergic and striatal changes as the neurobiological underpinning of motivational changes in Parkinson's disease. Future neuroimaging and pharmacological investigations will be needed to address this directly.

Another limitation is that we did not have sufficient sample size to evaluate the role of

dopaminergic medication status by comparing patients tested ON vs. OFF medication. The absence of significant differences in motivation between Parkinson's disease patients ON or OFF medication is consistent with our previous reports of no differences in learning from immediate feedback between Parkinson's disease patients ON and OFF medication (Foerde, Braun, et al., 2013; Foerde, Race, et al., 2013; Foerde & Shohamy, 2011a), but due to the sample size, we interpret this null result with caution. Previous studies of cognition and learning have found effects of dopaminergic medication status on both learning and performance on a variety of tasks, such that medication sometimes helps and sometimes hurts performance (Cools et al., 2001a; Frank et al., 2004; Jahanshahi et al., 2010; Shohamy et al., 2006; Swainson et al., 2000). Separately, studies have reported effects of medication status on measures of motivation, such as the Starkstein Apathy scale (Czernecki et al., 2002; Czernecki et al., 2008; Rektorova et al., 2008; Starkstein, 2012; Thobois et al., 2010; Thobois et al., 2013). A question that arises is how pharmacological treatment aimed at alleviating motor symptoms affects motivation, which could be a critical issue in managing the care of patients with Parkinson's disease. Future studies should assess motivation in Parkinson's disease patients that are medication naïve to disentangle the effects of changes in dopaminergic medication once treatment is initiated from those of dopaminergic dysfunction in the striatum associated with the onset of Parkinson's disease.

Finally, a limitation that is shared by most studies attempting to systematically investigate motivation in Parkinson's disease is that we cannot determine whether Parkinson's disease changes motivational concerns or whether people who are diagnosed with Parkinson's disease fit particular profiles. In order to address these questions it will be necessary to track motivational changes longitudinally. It will be particularly useful to examine changes on well-characterized cognitive and motor tasks along with measures of motivation to understand how

the neurobiological changes in the disease affect these functions uniformly and/or selectively. Further work in this arena is of particular interest because it holds the promise of identifying personality inventory-based markers of the disease prior to the onset of motor illness.

Conclusion

We found that Parkinson's disease was associated with changes in motivational concerns, selectively in concerns with critical evaluation and comparison of goal pursuit means and outcomes (Assessment) rather than concerns with initiating and maintaining movement (Locomotion). Moreover, we found that scores of Assessment motivation were correlated with performance on a separate learning task, one that requires the use of immediate response-contingent feedback to drive learning and which has previously been shown to depend on the striatum. Understanding how distinct motivational concerns are affected by Parkinson's disease and how various treatments impact motivation may have implications for patients' well-being and engagement with treatment options (e.g. propensity to exercise, participation in therapy). A richer understanding of motivation in Parkinson's disease may also help identify markers of disease prior to the onset of motor illness.

Table 1. Demographic and neuropsychological characteristics of participants

| | Regulatory Mode participants | | | | Feedback learning participants[‡] | | | |
	AC (n=53)		PD (n=42)		CTRL (n=24)		PD (n=24)	
Age	65.2	*7.9*	64.1	*7.2*	63.3	*7.3*	65.2	*8.2*
M/F	14/39		17/25		6/18		11/13	
Education	16.3	*1.4*	16.6	*2.6*	16.2	*1.6*	16.1	*2.1*
MMSE	29.6	*0.7*	29.4	*0.8*	29.5	*0.6*	29.3	*0.8*
COWAT	46.9	*13.9*	46.5	*12.6*	45.3	*12.4*	43.9	*11.0*
NAART	15.5	*9.2*	15.2	*7.5*	15.2	*8.3*	17.0	*6.9*
Digit Span	12.3	*2.1*	12.0	*1.7*	12.3	*2.2*	12.0	*1.6*
BDI*	3.3	*2.9*	6.4	*5.1*	3.0	*2.0*	6.5	*5.3*
BDI cognitive	1.0	*1.2*	1.4	*1.5*	0.8	*1.2*	1.4	*1.5*
PD duration			6.4	*5.1*			6.7	*6.1*
UPDRS Motor			18.5	*11.1*			28.5	*14.2*
H-Y			1-3				1-3	

Table displays Mean *SD* of Age-matched controls (AC) and Parkinson's disease patients (PD).

[‡] Note that the Feedback learning participants are a subset of the Regulatory Mode Questionnaire participants.

* The PD group had significantly higher overall BDI scores (p=0.002) but did not differ significantly on the cognitive subscale (p=0.17). This was also the case for the Feedback learning participants (BDI: p=0.039; BDI cognitive subscale: p=0.25).

FIGURE CAPTIONS

Figure 1. Probabilistic learning with immediate and delayed feedback.

Participants completed a probabilistic learning task where feedback was delivered either immediately or delayed several seconds. On this task, learning with immediate feedback depends on the striatum and dopamine, whereas learning from delayed feedback depends on the hippocampus. **A)** In the Learning phase, participants used trial-by-trial feedback to learn which of two outcomes were associated with four different butterflies. On each trial, as soon as a response was made, participants' choices were displayed along with the cue stimulus until feedback was provided. For one pair of cues feedback was presented immediately (1 s) after the response was made, and for another pair of cues feedback was presented with a delay (7 s). Feedback timing (Immediate vs. Delayed) was manipulated within-subjects, and trial types were interleaved in randomized order during learning. **B**) The task required participants to learn which of two flowers four different butterflies preferred. Each butterfly was associated with one flower on 83% of trials and with the other flower on 17% of trials. Two butterflies were associated with each feedback timing condition and this association was counterbalanced across participants.

Figure 2. Regulatory mode in Parkinson's disease patients and healthy controls.

Parkinson's disease patients (PD) scored significantly lower than age-matched controls (AC) on the Assessment scale. Groups did not differ significantly on the Locomotion scale.

Figure 3. Performance on immediate and delayed feedback learning task.

PD patients were impaired in the Immediate feedback condition in learning and test phases. PD and AC did not differ in the Delayed feedback condition. Majority of data previously reported in Foerde & Shohamy (2013) and Foerde, Race, Verfaellie, & Shohamy (2013).

Figure 4. Relationship between Assessment scores on the Regulatory Mode Questionnaire and learning from immediate and delayed feedback.

A) Across groups, Assessment and Immediate feedback learning was positively correlated (r=0.32, p=0.028). **B)** By contrast, there was no correlation between Assessment and Delayed feedback learning (r=-0.07, p=0.66).

Figure 5. A mediation analysis testing the hypothesis that Assessment mediates the relationship between disease status group and learning from immediate feedback. Standardized beta coefficients are listed along with p-values. *p<0.1 **p<0.05.

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