Reward-guided cognitive resource allocation: a possible mechanism underlying cognitive deficits in Parkinson's disease

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Abstract

It is now recognized that Parkinson's disease causes both motor and non-motor symptoms. Cognitive symptoms, in particular those that relate to executive dysfunction, are highly prevalent (Foltynie et al., 2004), even at the earliest stages of disease. Attention and working memory deficits have been extensively characterized in Parkinson's disease but the mechanisms underlying these impairments remain largely unknown and effective therapies are lacking. Meanwhile, it has been suggested that reward signals help the brain to triage and prioritize incoming information, which has implications across both attention and working memory processing (Anderson, 2013; Gong & Li, 2014; Infanti et al., 2015). For instance, recent findings have suggested that reward signaling plays an important role in helping to allocate attention resources (Anderson et al., 2011). Critically, dopamine release in the striatum has been correlated with how much a previously-rewarded stimulus can capture attention (Anderson et al., 2017). In addition to executive function deficits, it is well documented that Parkinson's disease patients have reward-processing impairments (Bódi et al., 2009; Muhammed et al., 2016). Whether the reward deficits in patients directly contribute to poor attention, and more specifically, whether Parkinson's patients suffer from a dopamine-dependent inability to use reward to selectively allocate their attention resources is not known. The goal of this thesis is to address this gap by exploring the role of reward-driven attention selectivity in Parkinson's disease and how it may provide a framework for understanding executive function deficit as a whole in the disease.

Résumé

Il est reconnu que la maladie de Parkinson provoque à la fois des symptômes moteurs et non moteurs. Les symptômes cognitifs, en particulier ceux liés à un dysfonctionnement exécutif, sont très répandus (Foltynie et al., 2004) même dès le début de la maladie. Même si les déficits d'attention et de mémoire ont été décrit de manière compréhensive chez ceux avec la maladie de Parkinson, il manque de traitement efficace pour ces déficits et leurs mécanismes sous-jacents restent inconnus. Cependant, les signaux de récompense aident le cerveau à trier et à hiérarchiser les informations entrantes, impliquant les processus d'attention et de la mémoire (Anderson, 2013; Gong et Li, 2014; Infanti et al., 2015). Par exemple, des résultats récents suggèrent que la signalisation des récompenses aide à allouer les ressources attentionnelles (Anderson et al., 2011). Entre autre, la quantité dont un stimulus précédemment récompensé est capable de capter l'attention a été corrélé avec la libération de dopamine dans le striatum (Anderson et al., 2017). En plus des déficits des fonctions exécutives, plusieurs patients atteints de la maladie de Parkinson présentent également des troubles impliquant le système de récompense (Bódi et al., 2009; Muhammed et al., 2016). Il est inconnu si les déficits du système de récompense contribuent directement à leur faiblesse attentionnelle et si un mécanisme sous-jacent à ces déficits serait leur incapacité à utiliser la récompense pour allouer de manière sélective leurs ressources d'attention, dépendamment de leur niveau de dopamine. Le but de cette thèse est d'explorer le rôle de la récompense à sélectionner les contenus de la mémoire dans la maladie de Parkinson et comment la sélectivité attentionnelle biaisée par la récompense pourrait encadrer la compréhension le déficit de la fonction exécutive dans son ensemble dans la maladie.

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Contributions of Authors

Matthew Pilgrim partially created the dataset, performed the analyses, interpreted the results, drafted the manuscript and designed the follow-up experiments presented in Chapter 3.

Andu Ou was responsible for the initial implementation of the experiment design, piloting and contributed to the early stages of data collection.

Dr. Madeleine Sharp contributed to the design of the main study and the follow-up experiments, aided in the interpretations of the results and provided critical feedback and revisions at every step.

Chapter 1: General Introduction

The study of Parkinson's disease has evolved over the past several decades with increasing attention paid to non-motor symptoms, especially cognitive impairments in executive functions. Though many studies have characterized these impairments, their frequency, relationships to brain function and structure, our understanding of the mechanisms that bring about these impairments and how they relate to the underlying disease pathology is still lacking. The work presented in this thesis is an attempt to approach the study of cognition in Parkinson's disease from a more mechanistic standpoint by drawing from ideas in the cognitive neuroscience literature to test a specific mechanistic hypothesis of executive function impairment. The first chapter will give a broad overview of the relevant bodies of literature that influence the work including: an overview of Parkinson's disease, patient cognition with a focus on working memory and attention, reward mechanisms in cognition and will culminate in a set of research questions and hypotheses. The second chapter is the manuscript of a study conducted to address our questions. Finally, the third chapter is a general discussion, broader than the one included in the manuscript, which relates the work back to the field and takes an in-depth look at our future directions, with special attention paid to studies we are in the process of designing.

Overview of Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative condition caused by the early death of dopamine neurons in the substantia nigra (Kalia & Lang, 2015; Lang & Lozano, 1998). The resulting reduction of dopamine in the basal ganglia leads to the motor impairments that the disease is known for including resting tremor, bradykinesia, rigidity and loss of postural reflexes (Jankovic, 2008). Importantly, neuronal loss occurs in other brains regains as well, including the locus coeruleus, raphe nuclei, amygdala and hippocampus (Dickson, 2012), which has implications for

the role of multiple neurotransmitter systems in the disease's symptoms. Parkinson's disease is characterized by the presence of Lewy bodies, aggregates of misfolded α-synuclein proteins, that appear in neurons (Spillantini et al., 1997). As the disease progresses, Lewy pathology spreads from the brain stem to the basal forebrain and substantia nigra and then on to the cortex (Braak et al., 2003; Goedert et al., 2013).

Parkinson's disease is the second most common neurodegenerative disorder, second to Alzheimer's disease (Dorsey et al., 2007). It has a prevalence of 0.3% but 1% in individuals over 60 years of age (de Lau & Breteler, 2006) and an incidence of 13.4 per 100,000 person years when adjusted for age and sex (Van Den Eeden et al., 2003). Sex and age are both strong risk factors for the disease, with a higher prevalence in men than woman and an exponential prevalence increase from 40 (41 per 100,000) to 80 (1,903 per 100,000) years of age (Pringsheim et al., 2014).

Non-motor symptoms such as insomnia, REM sleep behavior disorder, constipation, urinary tract dysfunction and cognitive impairment are also highly prevalent in PD with over 90% of patients reporting at least one symptom (Barone et al., 2009; Martinez-Martin et al., 2007). Such symptoms occur early on in PD progression, even before the onset of the dominant motor symptoms (Kalia & Lang, 2015; Khoo et al., 2013). Additionally, it has been demonstrated that non-motor symptoms, especially cognitive symptoms, have a larger impact on patient quality of life than motor symptoms and contribute substantially to quality of life decline as the disease progresses (Karlsen et al., 1998; Martinez-Martin et al., 2011; Schrag, 2000).

Cognitive impairments are among the most impactful of the non-motor symptoms in Parkinson's disease and range from deficits in one or several executive domains to global impairment that declines to dementia (Dirnberger & Jahanshahi, 2013; Kudlicka et al., 2011).

When measured individually, cognitive impairments have been detected even in the earliest stages of the disease with prevalence estimates ranging from 18-36% in recently-diagnosed, untreated PD (Aarsland et al., 2009; Foltynie et al., 2004) and one group reporting up to 55% in certain cognitive domains for an early PD sample (Khoo et al., 2013). Mild Cognitive Impairment (MCI), a condition which can broadly be defined as impairment in memory, executive function, attention or speed of processing, perceptual-motor abilities, and language (Gauthier et al., 2006), is a common feature of PD progression and a thorough review reports a mean prevalence of 26.7% with a range of 18.9%–38.2% (Litvan et al., 2011). As the disease progresses, dementia also becomes common with 50% of patients presenting with dementia after 10 years and 80% after 20 years (Hely et al., 2008).

Cognitive challenges in Parkinson's disease can be roughly partitioned into two components: a series of executive function deficits that appear early on in the disease and a slower progressing dementia syndrome. This *Dual Syndrome Hypothesis* (Kehagia et al., 2012) purports that the early cognitive impairments in patients are mechanistically distinct from the development of dementia with disease progression. From this perspective, fronto-striatal executive functions such as set shifting, attention, working memory, planning and delayed response inhibition are thought to be due to dopaminergic loss and the slowly progressing dementia symptoms in patients, including lowered semantic fluency, reduced auditory and visuospatial skills, hallucinations, and memory loss, to the spread of Lewy body load throughout the cerebral cortex (Kehagia et al., 2012; Robbins & Cools, 2014). The work in this thesis is focused on the first of these two categories, the early executive function deficits, and aims to provide evidence for a dopamine-dependent cognitive mechanism that may play a role in their development.

Executive Function in Parkinson's Disease

A variety of executive function deficits have been described in Parkinson's disease using both classical neuropsychological tests and more recently, specifically developed computer-based laboratory tasks. Early studies identified executive deficits on commonly used tasks such as the Wisconsin Card Sorting Task (WCST) (Cooper et al., 1991), the Trail Making Test (TMT) (Ann E. Taylor et al., 1986), the Stroop Task (Gotham et al., 1988) and the Tower of London/Toronto Task (A. E. Taylor & Saintcyr, 1995). More recently, a meta-analysis conducted on cognitive deficits in Parkinson's disease showed a range of executive function deficits among Parkinson's patients including verbal fluency, working memory, set-shifting, rule formation, selective attention, resistance to distraction and cognitive flexibility deficits (Dirnberger & Jahanshahi, 2013; Kudlicka et al., 2011).

In addition to impairments in classical executive tasks, Parkinson's patients have been tested on a variety of other cognitive tasks designed to target specific functions. Working memory and attention in particular have been heavily studied. For example, Parkinson's patients are impaired at: shifting their attention between tasks or rule sets within tasks (Brown & Marsden, 1988; Cameron et al., 2010; Cools et al., 2009; Cronin-Golomb et al., 1994; Dujardin et al., 2013; Fallon et al., 2015, 2016; Gerrits et al., 2015; Hochstadt, 2009; Lewis et al., 2005; Moustafa et al., 2008; Rustamov et al., 2014; Sawada et al., 2012; Woodward et al., 2002; Zhou et al., 2012), having their attention captured by salient information (Alonso-Recio et al., 2014; Grande et al., 2006; Slagter et al., 2016; Verleger et al., 2014), visual search accuracy (Buhmann et al., 2015), and resisting distraction (Fallon et al., 2017; Kim et al., 2017; Lee et al., 2010), (though this seems sensitive to dopamine level (Cools et al., 2010)). Additionally, patients have displayed deficits with regards to: working memory capacity (Grogan et al., 2018; Lee et al.,

2010; Liozidou et al., 2012; Merkl et al., 2017), encoding items into working memory (Fallon et al., 2017; Uitvlugt et al., 2016; Wiesman et al., 2016; Zokaei et al., 2014), maintaining items in working memory (Liozidou et al., 2012; Rottschy et al., 2013; Sawamoto et al., 2008; Ventre-Dominey et al., 2014), working memory updating (Alonso-Recio et al., 2014; Beato et al., 2008; Moustafa et al., 2013; Simioni et al., 2017; Torta et al., 2009), and manipulating items in working memory (Bublak et al., 2002; Lewis et al., 2003, 2005).

There have been several efforts to link the documented executive dysfunction displayed by patients to the known dopamine pathology. This question has been investigated using medication manipulation studies in which patients are tested on a given cognitive task either after having taken dopaminergic medication (ON) or after an overnight withdrawal from it (OFF). While some cognitive domains show improvement, there is substantial variation in the effects of dopaminergic drugs on cognitive performance (Cools, 2006) where in some cases Patients are benefitted by the administration of medication (Fallon et al., 2017) and in other cases hindered by it (Cools et al., 2010). One proposed explanation is that while dopamine medications replenish levels in brain areas more heavily affected by the disease (ie. the dorsal striatum) they possibly "overdose" areas that are relatively intact early on in disease progression such as the ventral striatum (Gotham et al., 1988; Swainson et al., 2000). In line with this, Parkinson's patients show improved performance on cognitive tasks that leverage the dorsal striatum more than the ventral striatum when ON medication, but poorer performance on tasks that typically recruit the ventral striatum more than the dorsal striatum; the reverse is seen when patients are OFF medication (Cools et al., 2001; Cools & D'Esposito, 2011; Meder et al., 2019). It should be pointed out however, that at the current moment the specific distribution of dopamine in the striatum due to L-DOPA medication is purely speculative.

Despite ample studies identifying and characterizing early executive function impairments in Parkinson's disease, decisive therapies are lacking (Hindle et al., 2013; Mohlman et al., 2011). This could be due partially to the fact that the vast majority of studies focus on the *abilities* of patients on a given task or measure and do not attempt to tease apart the mechanisms underlying the impairments. An alternative way of conceptualizing the problem of executive dysfunction in Parkinson's disease is in terms of the allocation of cognitive resources (Brown & Marsden, 1988; Dujardin et al., 2013). It is widely accepted that the brain has limited resources with which to approach problems in the environment and handle incoming information (Franconeri et al., 2013; Scalf et al., 2013). Working memory capacity and attention span are examples of such limitations. It is possible in Parkinson's disease that early executive impairments stem partially from an inability to properly *allocate the cognitive resources* that are available instead of from a general *lack* of those resources. This implies that at least one of the mechanisms which guides the allocation of our limited cognitive abilities is impaired in Parkinson's disease. What such a deficient mechanism might be and how it operates in Parkinson's patients is currently an open question.

Reward Guided Cognition: Selective Attention and Working Memory

The use of reward signals in the environment by the brain to adapt behavior is crucial for the survival of any biological agent (Schultz et al., 1997; Schultz, 2000). While reward is often thought in terms learning and habit formation, studies from the past decade indicate that it has a role in guiding cognitive processes, particularly in the domains of attention and working memory.

Selective attention can broadly be defined as mechanisms which help to orient our focus on one piece of information rather than another (Driver, 2001), explaining why some details in

our environment capture attention when others do not. Past work has shown that attention resources can be guided by current, task-related goals (Baluch & Itti, 2011; Folk et al., 1993a, 1993b; Folk & Remington, 2006, 2008; Hopfinger et al., 2000), the physical salience of a stimulus (eg. brightness) (Itti & Koch, 2001; Theeuwes, 2004, 2010; Yantis, 1993, 1996) as well as the emotional and threatening content (Hodsoll et al., 2011; Sato & Kawahara, 2015; Schmidt et al., 2015b). A series of clever experiments have additionally demonstrated that reward influences attention selectivity when task goals and physical salience are controlled for (Anderson et al., 2011; Anderson, 2013; Anderson & Halpern, 2017; Anderson & Yantis, 2013; Bourgeois et al., 2017; Donohue et al., 2016; Gong & Liu, 2018; Hickey et al., 2010; Hickey et al., 2015; Itthipuripat et al., 2015; Jahfari & Theeuwes, 2017; Theeuwes & Belopolsky, 2012; Wang et al., 2013). This phenomenon is referred to as *value-driven attentional capture* (Anderson et al., 2011). A typical experimental design begins with subtle instrumental conditioning in the first phase of the task to associate different levels of reward to a stimulus feature (e.g. a large reward to the color green). In the second phase of the task, which measures attention, the previously rewarded features (e.g. color) are no longer relevant for the task but are still present on screen acting as "distractors". As the subject searches for a target amongst several stimuli, some of the stimuli will bear previously rewarded features (e.g. the color green). Value-driven attentional capture occurs when subjects are slower to respond to targets on trials where there is a distractor with a stimulus feature that was previously highly rewarded compared to trials where the distractor bears a stimulus feature that was associated with lower reward. In this way their attention is "captured" in a value-dependent manner.

There have also been a handful of studies using a similar concept to extend the idea of reward guided cognition to the domain of working memory. Gong and Li (2014) used a

paradigm similar to Anderson et al. (2011) to show that subjects better remembered the orientation of stimuli when those stimuli were presented in colors that were previously rewarded (Gong & Li, 2014). This finding has been replicated using a couple of different experimental designs (Infanti et al., 2017; Klink et al., 2017). In a similar vein Infanti et al. (2015) have shown that previously rewarded stimulus features can act as distractors during working memory encoding that impair recall performance (Infanti et al., 2015).

Given the prevalence of reward driven cognition effects, recent work has sought to characterize the underlying neural mechanisms. Qi et al. (2013) have shown that previously rewarded stimulus features that are task irrelevant evoke the N2pc event-related potential (ERP) (Qi et al., 2013), a neural marker of attention capture (Hickey et al., 2006). It has been demonstrated with frontal lesion patients that the ventromedial frontal cortex (VMF) is critical for the presence of a strong reward-guided attention capture effect (Vaidya & Fellows, 2015). Itthipuripat et al. (2019), using an inverted encoding model, found that the fidelity of distractor representations in the early visual cortex for task-irrelevant stimulus features previously associated with reward was increased for distractors associated with higher reward compared to lower reward (Itthipuripat et al., 2019). Finally, and most interestingly in the context of Parkinson's disease, the strength of value-driven attentional capture in a given individual is correlated with the reward-related dopamine release in the right anterior caudate nucleus (Anderson et al., 2017) and with distractor-evoked dopamine release in the right caudate nucleus and the right posterior putamen (Anderson et al., 2016). Anderson et al. (2017) used [^{11}C] raclopride imaging to detect changes in reward-related dopamine release by measuring the density of available D_2/D_3 receptors during rewarded versus unrewarded visual search conditions. This was then correlated with individual differences in the amount which previously-

rewarded but task irrelevant distractors captured attention in the following test phase. Anderson et al. (2016) used a similar paradigm but measured dopamine release in test phase during trials with previously rewarded distractors present.

Studies from the past ten years have shown in multiple domains that reward signals can guide the allocation of cognitive resources. Additionally, there is emerging evidence that the nigrostriatal dopamine system plays a role in this selective mechanism. From the perspective of Parkinson's disease, dopamine-dependent reward-guided selectivity provides an interesting candidate for a deficient mechanism underlying cognitive impairments.

Reward Processing Deficits in Parkinson's Disease

The discovery that dopamine signaling codes for reward prediction error signals (Hollerman & Schultz, 1998; Pessiglione et al., 2006; Schultz et al., 1997; Schultz, 2000) has had a large impact on Parkinson's disease cognition research. Due to the known dopaminergic pathology in Parkinson's disease, numerous studies have investigated reward-related cognition in Parkinsonian patients. Initial studies that looked at patients under different conditions of dopamine replacement (using medication manipulation designs) revealed differences in the abilities of Parkinson's patients to learn from rewards and losses (Cools et al., 2006; Frank et al., 2004) and since then several other reward processing deficits have been identified (García-García et al., 2017; Perry & Kramer, 2015).

Many studies have demonstrated that reward learning deficits are present in Parkinson's disease, some comparing patients to controls others comparing patients when they took their dopamine replacement medication to when they were withdrawn from it (Bódi et al., 2009; Frank et al., 2004; Freedberg et al., 2017; Maril et al., 2013; Palminteri et al., 2009; Rutledge et al., 2009; Skvortsova et al., 2017; van Wouwe et al., 2012). Beyond reward learning, disrupted

reward processing is also behaviorally evidenced by a devaluation of future or expected rewards (Evens et al., 2015; Kapogiannis et al., 2011) as well as reduction of the motivating effect of rewards on other cognitive tasks (Aarts et al., 2012; Torta et al., 2009).

In addition to behavioral studies, there is evidence of reward processing abnormalities seen using functional neuroimaging and other physiological measures. Pupillary responses to reward, which are thought to index reward sensitivity (Murphy et al., 2011), are diminished in Parkinson's patients in a dopamine depleted state (Manohar & Husain, 2015; Muhammed et al., 2016). Additionally, ERPs related to reward prediction errors (Brown et al., 2020) and the anticipation of rewards (Mattox et al., 2006) have been shown to be blunted in Parkinson's patients. Studies looking and brain activity in response to rewards using a variety of tasks have shown abnormal reward related functional activity in the striatum(du Plessis et al., 2018; Schonberg et al., 2010), anterior cingulate cortex (Rowe et al., 2008), the cerebellar vermis (Goerendt et al., 2004) and the orbital frontal cortex (du Plessis et al., 2018). For example, Schonberg et al. (2010) compared model-derived prediction error signals in the striatum of Parkinson's disease patients to healthy controls during a procedural reward-learning choice task. They found that compared to healthy controls, patients had impaired error signals in the dorsal striatum but preserved signals in the ventral striatum and conclude that this may offer an explanation to the multitude of reward learning findings using similar tasks.

There is clear evidence for a series of reward processing deficits in Parkinson's disease patients, some of which are modulated by dopamine replacement. However, the extent to which these impairments relate to the early executive dysfunction that is also prevalent in the disease or other documented symptoms is currently unknown. The growing body of literature documenting

the effects of reward on the allocation of executive resources explored above had turned this into a pressing question.

Rationale

Executive dysfunction is highly prevalent in Parkinson's disease and effective treatments are lacking. Most work to date has measured patients in terms of their cognitive abilities relative to controls in various domains of function such as attention and working memory, but few studies have looked at potential mechanisms that underlie these deficits. An alternative way to conceptualize the problem of executive impairments is in terms of the allocation of available cognitive resources. From this frame of reference, cognitive deficits in Parkinson's could be the result of an impaired cognitive resource allocation mechanism. Research in the non-clinical literature has shown that reward signals in the environment can be used to guide the allocation of both attention and working memory resources, with emerging evidence suggesting a role of striatal dopamine. Reward selectivity is a good candidate for a potentially impaired executive resource allocation mechanism due to the fact that Parkinson's patients suffer from a variety of reward processing deficits, some of which have been shown to be dopamine-dependent. This thesis begins to address the hypothesis that **executive impairments in Parkinson's disease, especially attention and working memory deficits, are in part due to a dopamine-dependent inability to use reward signals in the environment to selectively allocate cognitive resources when engaging in typical executive function**. We addressed this by designing a series of attention and working memory experiments that test the role of reward in selective attention and working memory processing, using Parkinson's disease patients under different dopamine medication conditions. The next chapter in this thesis represents a pre-publication manuscript

detailing the first of these experiments and showcases the results. Two other experiments are still ongoing but their design and theoretical backing are explored in the third and final chapter.

Chapter 2: Influence of reward on attention selectivity in Parkinson's disease

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Abstract

Patients with Parkinson's disease suffer from a series of attention impairments. However, relatively few studies have investigated how this aspect of executive dysfunction relates to the dopamine-dependent reward processing deficits that are well known to occur in the disease. Recent work has shown that reward can guide the allocation of attention resources, and this mechanism is thought to rely on striatal dopamine. Whether Parkinson's patients, due to their striatal dopamine loss, suffer from an inability to use reward information to guide the allocation of their attention resources is unknown. To address this gap, we tested Parkinson's patients ON and OFF their dopamine replacement medication, as well as older controls. We used a standard two-phase attention capture task in which subjects were first implicitly trained to make colour-reward associations. Then, in the second phase, the previously reward-associated colours were used as distractors in a visual attention task. We found that patients did not use reward information to modulate their attention; they were similarly distracted by the presence of low and high-reward distractors. However, contrary to our predictions, we did not find evidence that dopamine modulated this inability to use reward to guide attention allocation. We found a trend for greater distractibility overall in Parkinson's patients compared to older controls, but interestingly, the degree of distractibility was not influenced by dopamine replacement. Our results suggest that loss of reward-guided attention allocation may contribute to executive deficits in Parkinson's disease, and that this aspect of attention impairment is due to the involvement of non-dopaminergic pathways.

Introduction

Early executive function deficits in Parkinson's disease are common and have been well documented (Kudlicka et al., 2011). However, despite several decades of work attempting to characterize these cognitive impairments, effective treatments are still lacking (Hindle et al., 2013; Mohlman et al., 2011). Attention deficits in particular are quite prevalent in Parkinson's patients but research from a mechanistic perspective has remained primarily focussed on attention set-shifting and related paradigms (Dirnberger & Jahanshahi, 2013). One mechanism currently unexplored in Parkinson's is the prioritization of attention based on reward, a process which is thought to depend on dopamine (Anderson et al., 2011; Anderson et al., 2016, 2017). This bears particular relevance to Parkinson's disease where dopamine-dependent reward processing is disrupted (Bódi et al., 2009; Frank et al., 2004; Maril et al., 2013; Palminteri et al., 2009; Rutledge et al., 2009; Skvortsova et al., 2017).

Recent work has demonstrated that the magnitude of reward associated with a distractor can enhance the degree to which it causes distraction, such that distractors associated with high reward are more distracting that those associated with low reward, even when these distractors are completely irrelevant to the task at hand (Anderson et al., 2011; Anderson, 2013; Anderson & Halpern, 2017; Anderson & Yantis, 2013). One interpretation of these findings is that reward signals in the environment can orient attention towards stimuli in a manner that is distinct from top-down or bottom-up control. Importantly, studies looking to uncover the neural correlates of this process have shown that the striatum, and more specifically, dopaminergic pathways, are involved in this process (Anderson, 2017; Anderson et al., 2014, 2016, 2017). Functional neuroimaging work has shown that activity in the striatum increases with the presence of a previously reward-associated distractor (Anderson et al., 2014). Additionally, using multivoxel

pattern analysis, it has been shown that increases in stimulus-category information in the object-selective visual cortex caused by prior reward association are predicted by dopaminergic midbrain activity (Hickey & Peelen, 2015). Evidence for the specific role of striatal dopamine in supporting reward-guided attention allocation comes from human studies using positron emission tomography with [C^{11}] raclopride to measure striatal dopamine. These studies found that dopamine release, both during the initial learning of the reward associated with the distractor (Anderson et al., 2017), and at the time of the presentation of the reward-associated distractor (Anderson et al., 2016) was correlated with the extent to which reward-associated distractors slowed response times (i.e. the extent to which attention was allocated towards rewarded distractors instead of targets).

It is well established, across a number of different paradigms, that Parkinson's patients show evidence of dopamine-dependent reduced reward sensitivity. Much of this work has focused on how this manifests as reduced learning from reward (Bódi et al., 2009; Cools et al., 2006; Frank et al., 2004; Palminteri et al., 2009; Rutledge et al., 2009; Skvortsova et al., 2017). Interestingly, however, reward sensitivity measured in a more isolated way, i.e., independently of any particular downstream cognitive process, is also reduced in Parkinson's patients. This has been shown by measuring reward-related pupillary reactivity, and this reward sensitivity has also been shown to be dopamine-sensitive (Manohar & Husain, 2015; Muhammed et al., 2016).These findings raise the possibility that altered reward signaling could have consequences on cognitive processing *beyond* its effect on learning and motivation, in areas of cognition where reward is perhaps less integral to the cognitive process itself. Indeed, there is recent evidence that the use of reward information to guide the prioritization of episodic memories for long-term storage is impaired in Parkinson's patients (Sharp et al., in press). Whether the reward-guided allocation of

attention resources is similarly impaired in Parkinson's disease in a dopamine-dependent manner is not known.

To address this question, we used a standard two-stage attention capture task, which has been previously used to show the role of reward in guiding attention (Anderson et al., 2011; Anderson, 2017; Anderson et al., 2016, 2017; Anderson & Halpern, 2017; Anderson & Yantis, 2013). The first phase is a reward-association paradigm where different stimuli are paired with either a low or a high reward. The second phase is an attention test where the stimuli previously associated with reward now act as goal-irrelevant distractors to draw attention away from targets. To assess the role of dopamine, we tested patients with Parkinson's disease in a within-subject design, both ON and OFF dopaminergic medication, and compared them to older controls. We found that attention in Parkinson's patients was not influenced by reward magnitude; patients were distracted by both the high-reward and the low-reward distractors to a similar degree. Contrary to our predictions, however, we did not find that dopamine modulated the effect of reward on attention, nor the overall distractibility; patients both ON and OFF performed similarly. These findings suggest that while Parkinson's patients lose the ability to use reward to guide attention allocation, this impairment is not dopamine-sensitive. These results extend our understanding of the mechanisms underlying attention deficits in Parkinson's disease and suggest that dopamine may not uniformly play a role across cognitive processes in the prioritization of resource allocation.

Methods

Patients and control subjects

Forty-three Parkinson's disease patients (13 females, mean ± SD age = 63.8 ± 6.4) and 31 control subjects (21 females, mean ± SD age = 63.8 ± 7.9) were recruited to participate in our study. Patients were recruited from the Movement Disorders Clinic at the Montreal Neurological Institute, community groups and the Parkinson Quebec Network, a registry of Parkinson's patients interested in research who have been referred by movement disorder specialists. Control subjects were recruited from spouses and friends of patients, community groups and social media posts. Controls had no major health issues or current neurological diagnoses. All subjects gave informed written consent and were compensated for their participation. Disease duration ranged from 0.42 -14.25 years (Mean years = 4.75 (3.25). All patients were taking levodopa, 6 patients were additionally taking a dopamine agonist (either pramipexole or rotigotine). See Table 1 for detailed demographic and clinical information. Comparing demographics with Welch-approximated two-sample T-tests (Welch, 1947) and Chi-squared tests we note that patients had fewer years of education than controls ($p = 0.031$) and that there were fewer women in the Parkinson's group than in the control group ($p = 0.003$). To control for these differences, we included sex and education as covariates in our analysis.

General procedure and medication manipulation

All subjects came to the lab for two sessions and, to minimize practice effects, the interval between sessions was at least one and a half months. At both sessions, subjects completed the full neuropsychological battery (described below) and a behavioral task which was divided into two phases: the reward association phase and the attention test phase (described in detail below).

All sessions were conducted in the morning, starting between 9 and 10 AM to allow us to more easily control the timing of medications and to control for circadian factors. For Parkinson's disease patients, one session was conducted after an overnight withdrawal (minimum 15 hours) from dopamine medications (OFF state) while the other session was conducted with patients having taken their medication one hour prior to the start of testing (ON state). The order of these sessions was counterbalanced across subjects. Fifteen Parkinson's patients did not complete their second session: eight missed their OFF session and seven missed their ON session. Three older controls did not complete their second session. All of these subjects were still included in the analysis such that we have 28 patients and 28 controls with both sessions, and 15 patients and 3 controls with only one session. See **Supplementary Table 1** for demographic comparisons between the ON and OFF samples.

Measure	**Parkinson's patients (N = 43)**	**Controls (N = 31)**	**P-Value**
Age	63.8 (6.4)	63.8 (7.9)	.996
Education, years	15.2 (3.5)	17.1 (2.7)	.009 **
Disease duration, years	4.8 (3.3)	NA	NA
Percent Female	30%	68%	.003 **
MoCA	26.7 (2.6)	27.8 (1.5)	.031 *
Verbal Fluency (MoCA)	12.4 (4.2)	13.8 (3.4)	.100
Digit Span Test	11.2 (2.3)	12.1 (2.0)	.077
Symbol Digit Modalities Test	40.1 (10.7)	47.4 (8.5)	.002**
Geriatric Depression Scale	8.6 (6.1)	5.4 (5.4)	.114
Apathy Evaluation Scale	58.4 (8.2)	58.9 (12.2)	.825

Table 1. Demographic and neuropsychological information. MoCA = Montreal Neurological Assessment, Verbal Fluency is taken from the Language section of the MoCA. Values presented are mean (SD). * $p<0.05$, ** $p<0.01$.

Neuropsychological battery

All subjects were administered a neuropsychological battery to establish baseline cognitive functioning. This battery included the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), the Digit Span (Lezak et al., 2004) and the Symbols Digit Modalities Test (SDMT) (Smith, 1973). Subjects were also administered the Geriatric Depression Scale (Yesavage, 1988) and the Apathy Evaluation Scale (Marin et al., 1991). Patients and controls were compared on their various neuropsychological scores using Welch- approximated two-sample T-tests (Welch, 1947). Patients scored 1.1 points lower on the MoCA ($p = 0.031$) and 7.3 point lower on the SDMT ($p = 0.002$). To account for potential biases in cognitive ability we included SDMT scores as a covariate in our models. The SDMT has been used in other neurodegenerative disorders as an overall marker of cognitive ability that is sensitive to decline (Lemiere et al., 2004; Rodrigues et al., 2009). We chose to include it instead of the MoCA, because the intended use of the MoCA is as a screening tool for dementia (Nasreddine et al., 2005). Scores for the neuropsychological battery can be found in Table 1.

Task

We made minor adjustments to a task commonly used to measure the influence of reward on attention (Anderson et al., 2011; Anderson, 2013; Anderson et al., 2014, 2016, 2017; Anderson & Halpern, 2017; Anderson & Yantis, 2013) in order to make it more suitable for an older population. At each session, subjects performed a task with two phases: the reward association phase and the attention test phase (**Figure 1**).

Reward association phase: during this phase, subjects gradually learned to associate different colors with different levels of reward. Subjects were instructed to search for a red or

green target circle (blue and yellow were used for each subject's other session and the order was counter balanced) on a screen with five other non-target circles (2.3° x 2.3° visual angle) present surrounding a white fixation cross (0.5° x 0.5° visual angle). The stimuli were arranged in a large circle around the center of the screen with an approximate radius of 5°. Subjects were asked to report the orientation of a white bar that was inside the target circle as either vertical or horizontal using a key press. They were told to press the "z" key if the bar was vertical and the "m" key if the bar was horizontal. The bars inside the targets were always vertical or horizontal while the bars in the non-target circles were tilted at 45° to the left or right. Every trial had *either* a red or a green circle.

Reward was given for correct answers according to a specific formula. The high reward colour (counterbalanced between red and green (or blue and yellow depending on the session) across subjects) yielded 10 cents on 80% of the trials and only 1 cent on 20% of the trials upon a correct response. The low reward colour led to a reward of 10 cents on only 20% of the trials and 1 cent on 80% of the trials for a correct answer. For incorrect answers, subjects were notified in red text that their answer was "Incorrect!" and earned "0 cents". Subjects were told that they would receive a cash bonus equivalent to the winnings from 100 randomly selected trials. Subjects had 1200 milliseconds to make a response and were asked to fixate on a white cross in the center of the screen for 2000 milliseconds between each trial. If they did not respond before the time limit, they heard a loud beep and the text "Too slow!" was presented in white on the screen. Subjects performed 240 trials and 20 practice trials, and they were given the possibility of taking a break after 120 trials.

Attention test phase: during this phase the previously rewarded colors were used as distractors in an attention test to probe the influence of reward on attention. This phase was

structurally similar to the previous phase but subjects were specifically told that colours no longer mattered and that they should instead focus on shapes. Subjects were required to report the orientation of a white bar in a target shape as either horizontal or vertical by pressing the "z' key if the bar was vertical and "m" if the bar was horizontal. The target shape was identified as the unique shape, e.g., the diamond among circles or the circle among squares. On every trial, one target shape and five non-targets were arranged in a circle around the center of the screen. Non-target shapes also contained white bars but these were diagonally oriented at 45°. Subjects were notified if they were "Correct" or "Incorrect" with white text after making a response. Subjects had 1500 milliseconds to make a key response and if they failed to they were given the feedback "Too Slow!" in white text accompanied by an audible beep from the computer. They were asked to fixate on a white cross in the center of the screen for 2000 milliseconds between each trial. Critically, there were three types of trials: trials that included a high reward distractor, a low reward distractor and trials where no distractor was present. On high reward trials, the colour of one of the non-target shapes corresponded to the high reward colour from the reward association phase the subject had just completed. On low reward trials, the colour of one of the non-target shapes corresponded to the low reward colour for the reward association phase. Finally, on trials where no distractor was present, the colours of the non-targets did not correspond to either of the rewarded colours. The remaining shapes (i.e. those that were not the distractor) were never coloured with one of the previously-rewarded colours. Following 10 practice trials there were 240 trials: one half of the trials included a distractor (one quarter were high reward and one quarter were low reward), and the other half did not include a distractor. The order of these trials was randomized. Subjects were offered a break after 120 trials.

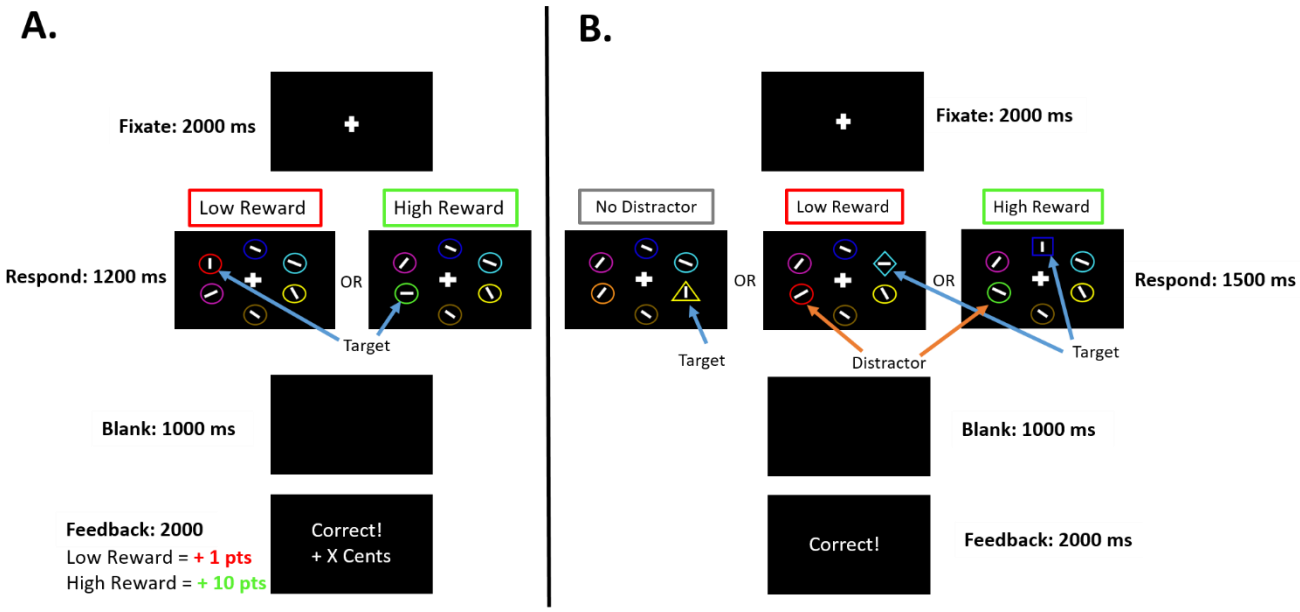


Figure 1. Trial sequence for the two phases of the task. A) Reward association phase: Targets in the reward association phase were defined by a pre-specified color (e.g., red and green). Subjects reported the horizontal or vertical orientation of the white bar inside the target by pressing one of two keys. Correct answers were differentially rewarded based on the color (e.g., 10 cents for green and 1 cent for red). B) Attention test phase: Here subjects were told to ignore the colours. Targets were identified as the unique shape. Once again, subjects reported the orientation of a white bar inside the target by pressing one of two keys. Half of the trials contained a distractor, i.e. a non-target shape in a colour previously associated with a reward (e.g., green for the low reward distractor and red for the high reward distractor). The other half of the trials did not include a distractor.

Analysis

To compare performance across groups and conditions, statistics were computed using mixed effects linear and logistics regressions (R lme4 package; (Bates et al., 2015)), performed in R version 3.6.3 (R Core Team, 2020). The general approach to model specification was as follows: we included random intercepts for subjects and included random slopes for all within-subject variables included in the model as well as interactions that were fully within subject (e.g., medication*reward_condition) (Barr et al., 2013; Meteyard & Davies, 2020). Because the maximally specified models failed to converge, we removed modelling of the correlation

between random intercepts and slopes as well as random effects that prevented a given model from converging.

For the reward association phase, to compare performance between reward conditions and groups, we performed logistic regressions with probability of a correct response on each trial as the dependent variable. We ran three separate models: one in controls only, which included only reward level (low or high) as our main experimental variable; one in Parkinson's patients which included reward level, medication state (OFF of ON) and their interaction; and one in all subjects that included reward level, disease (control or Parkinson) and their interaction. This third model, by including disease state as an independent predictor, allowed us to specifically model the effect of disease on behaviour; therefore, in the case of PD patients, data from both the ON and the OFF session were included, and in the case of the controls, both sessions were also included. All models included session (first or second), and Symbol Digit Modalities Test performance as covariates to control for learning and cognitive ability. The model with all subjects also included education as a covariate to account for sample differences. Sex was not included as a covariate because its inclusion caused a convergence failure.

Analyses for the attention test phase followed a similar approach except that reaction time was the main dependent variable, which, for the sake of normality, was transformed using base-ten logarithm. We ran three separate models: one in controls only, which included only distractor type (no distractor, low reward or high reward) as our main experimental variable; one in Parkinson's patients which included distractor type, medication state (OFF of ON) and their interaction; and one in all subjects which, similarly to above, was intended to investigate the role of disease. This third model included distractor type, disease (control or Parkinson) and their interaction. As above, all models included session (first or second), and

Symbol Digit Modalities Test performance as covariates to control for learning and cognitive ability. The model with all subjects also included education and sex as a covariates to account for sample differences.

Because the categorical variable distractor type has three levels (high reward, low reward, and no distractor), and because we were principally interested in the differences *between* these levels, it was coded using two vectors, each with 3 levels: V1 (1=low reward, 0=high reward, -1=no distractor) and V2 (0=low reward, 1 = high reward, -1 = no distractor). As a result, the regression coefficient for V1 represented the difference in logRT between the low reward condition and the grand mean and the regression coefficient for V2 represented the difference between the high reward condition and the grand mean. In order to test all three possible contrasts between the distractor levels (no distractor vs. low reward, no distractor vs. high reward, and low reward vs. high reward) we used the esticon function in R (Hojsgaard, 2007) to compute weighted sums of the relevant coefficients as follows: no distractor vs. low reward = $2*\beta V1 + \beta V2$; no distractor vs. high reward = $\beta V1 + 2*\beta V2$; low reward vs. high reward = $\beta V1 - \beta V2$. We applied the same approach to test the contrasts between the condition*variable interactions.

We conducted follow-up analyses to evaluate overall distractibility where the three-level distractor type variable was collapsed into a new variable with only two levels (distractor present vs. absent). As above, we ran three separate models, which other than the new two-level distractor variable, were identical to the ones detailed above.

Hardware and Software

All computerized tasks were conducted on a MacBook Air (13-inch, 2017) with a 13.3-inch screen (diagonal) a 1440 x 900-pixel resolution and a 60Hz refresh rate. Responses were collected with the device's built-in keyboard. Subjects sat approximately 50 cm from the display though they were instructed to take a "comfortable position". Our behavioral task was coded in Python Version 2.7.

Results

Performance in the reward association phase for both disease groups and medication conditions can be found in **Figure 2** and model estimates are presented in **Supplementary Table 2**. Generally, as expected, Parkinson's patients ON, OFF, and controls performed well. Reward magnitude of the feedback associated with the two target colours did not affect accuracy in neither the controls (β_{HC} = 0.006, p=0.907) nor the patients (β_{PD} = 0.019, p= 0.553). Controls generally performed better than patients (β_{HCvsPD} = -0.289, p < 0.001), but the influence of reward on performance was not different between the two groups ($\beta_{disease*reward}$ = 0.029, p = 0.136). Dopamine medications did not influence performance ($\beta_{ONvsOFF}$ = 0.005, p = 0.938) nor did they alter the influence of reward magnitude on performance ($\beta_{med*reward}$ = 0.021, p = 0.368). The absence of a difference between groups for the effect of reward on performance is important for the interpretation of the second phase of the task as it indicates that patients (in both medication conditions) and controls had similar experiences during the reward training.

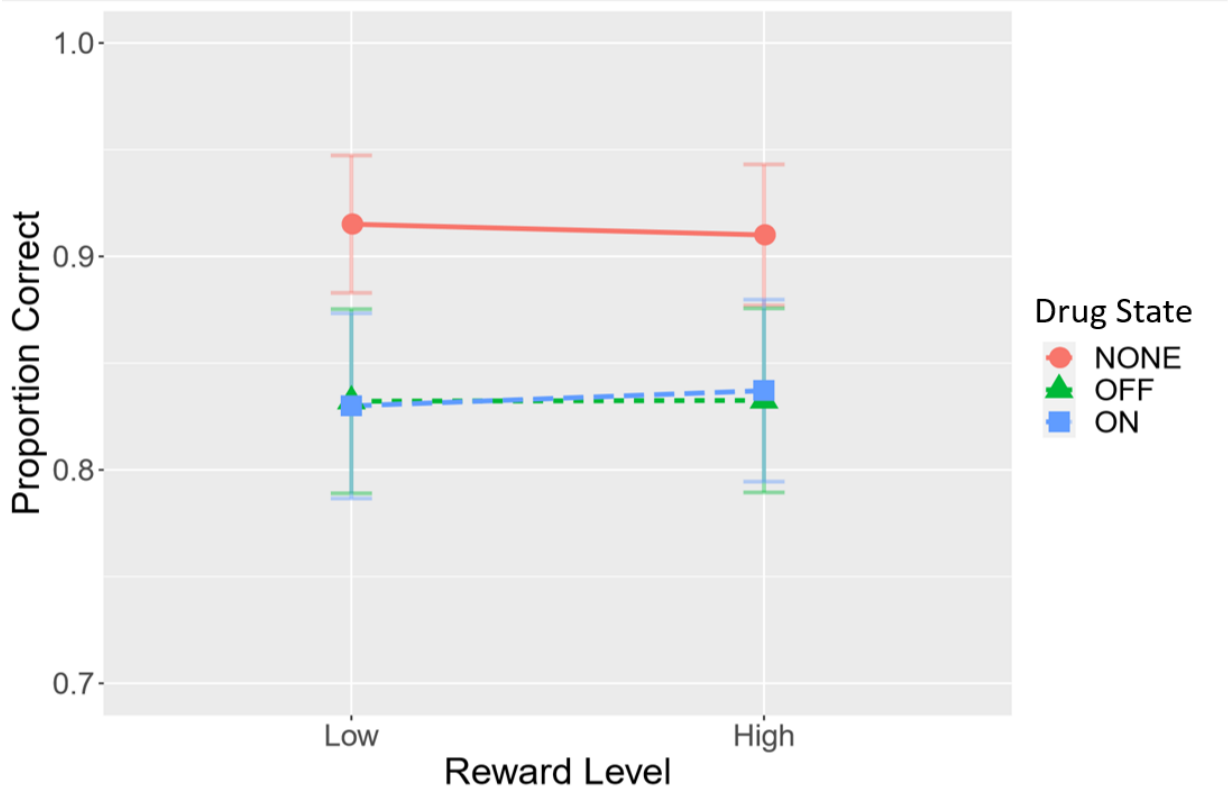


Figure 2. Performance during the initial colour-reward association phase.
Performance on the initial learning phase of the task shown separately for trials where the target colour was associated with low reward feedback 80% of the time versus trials where the target colour was associated with high reward feedback 80% of the time. Controls performed better than Parkinson's patients ($p < 0.001$) but importantly the effect of reward magnitude on performance did not differ between groups ($p = 0.136$) or drug states ($p = 0.368$). There was no effect of dopamine state on overall performance ($p = 0.938$). Error bars represent the standard error of the mean.

Results from the attention test phase are presented in **Figure 3**, model estimates are shown in **Supplementary Table 3** and weighted sums are shown in **Supplementary Table 4**. We were principally interested in the effects of rewarded distractors and dopaminergic medications on attention (measured with reaction time) in Parkinson's disease patients. We found that Parkinson's patients were slowed by both low and high reward distractors (low reward vs. no distractor difference estimate = 0.010, $p < 0.001$; high reward vs. no distractor difference estimate = 0.006, $p = 0.007$), but there was no difference in slowing between low and high

reward distractors (low vs. high difference estimate = 0.004, p = 0.170). These findings indicate that the effect of reward on attention cannot be uncoupled from an effect of distraction in our case. Surprisingly, dopamine medications did not influence attention in patients. Specifically, there was no difference between ON and OFF patients in the effect of low vs. high reward distractors (difference estimate= -0.002, p = 0.543), low reward vs no distractor (difference estimate = 0.001, p = 0.752), or high reward vs. no distractor (difference estimate = 0.002, p = 0.313). The only difference between patient ON and OFF was that patients ON were slower, across all three trial types, than patients OFF ($\beta_{ONvsOFF}$ = 0.008, p = 0.006), indicating that the effect of medication was not selective to distraction. Given the absence of an effect of medication on attention, we also compared patients (collapsing across medication state) to controls. Overall patients were not slower than controls (β_{HCvsPD} = 0.001, p = 0.863). With respect to the effects of interest, Parkinson's patients were more distracted than controls by the presence of a low reward distractor (low vs. no distractor difference estimate = 0.004, p = 0.012) but were not more distracted than controls by the presence of a high reward distractor (high vs. no distractor difference estimate = 0.001, p = 0.425). To better understand these differences, we also examined the effect of reward on attention within each group. We found that in healthy controls, though the effect of reward level on attention did not reach statistical significance (difference estimates: low vs no distractor = 0.001, p = 0.590; high vs. none = 0.004, p = 0.121, low vs. high = -0.002, p = 0.411), the overall direction of the effect was as expected: they were slowest on the trials that included a high reward distractor (881ms ± 235), compared to the trials with a low reward distractor (875ms ± 233) and those without a distractor (871ms ± 230), and the degree of slowing induced by the highly rewarded distractor was comparable to that reported previously in young controls (Anderson, 2013). In contrast, the Parkinson's patients OFF were

significantly slowed only by the low reward distractor (low vs. none difference estimate = 0.009, p=0.005) and patients ON were slowed by both but the degree of slowing between the two reward levels did not differ (difference estimates: low vs. none = 0.01, p=0.001; high vs. none = 0.009, p=0.012; low vs. high = 0.002, p=0.6). See **Supplementary Table 5** for raw reaction time scores across all groups.

All models controlled for session and score on the Symbol Digit Modalities Test: across groups and conditions, overall responses were faster on the second session ($\beta_{session}$ = -0.006, p=0.021), and better Symbol Digit Modality scores were associated with faster responses (β_{SDMT} = -0.002, p<0.001).

We were also interested in the effect of disease and dopaminergic medications on overall distractibility, i.e., collapsing across reward levels and comparing performance on trials with a distractor to those without a distractor (**Supplementary Table 6.**). We found that there was a trend for the influence of disease ($\beta_{disease*distraction}$ = 0.001, p = 0.053) such that patients were more distractible than controls. We did not find an effect of medication on overall distractibility ($\beta_{drugs*distraction}$ = 0.001, p = 0.417).

Finally, there are known links between apathy and reward sensitivity deficits in Parkinson's disease (Muhammed et al., 2016), and there is clinical interest in understanding the extent of the relationship between dopamine-linked apathy symptoms and executive dysfunction in patients. To this end, we looked at correlations between individual scores on the Apathy Evaluation Scale/Geriatric Depression Scale and the extent to which reward magnitude slowed reaction time (**Supplementary Figure 1.**). We did not see any significant relationships between apathy and reward driven attentional slowing for controls or patients OFF medication ($\rho_{Controls}$=0.20, p = 0.287; ρ_{OFF}=0.15, p = 0.385) though there was a trend for a negative

relationship in patients ON medication (ρ_{ON}=-0.28, p = 0.077). There were no significant relationships present between depression and reward driven attention slowing ($\rho_{Controls}$=0.07, p = 0.707; ρ_{ON}=0.12, p = 0.463; ρ_{OFF}=-0.09, p = 0.598).

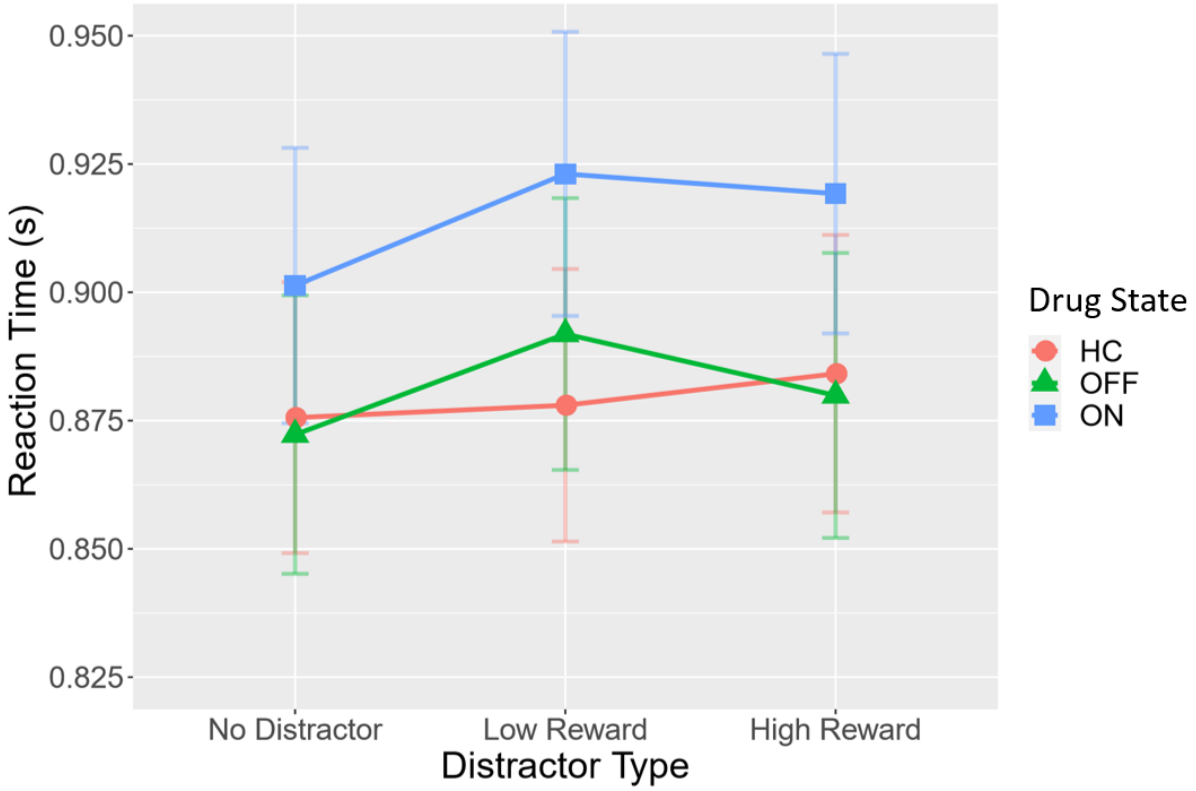


Figure 3. No influence of reward or dopamine on attention in Parkinson's disease. Reaction time on the attention task shown for trials where no distractor was present, and for trials where either a low-reward or high-reward-associated distractor was present. Performance (reaction time in sec) is shown for patients ON, OFF and for healthy controls. Parkinson's patients were slowed (i.e., distracted) by the presence of both low and high-reward distractors (low: p < 0.001, high: p = 0.007). There was a trend for greater overall distractibility in the patients compared to the controls (p = 0.053). Attention in patients was not sensitive to the difference in reward magnitude nor to dopamine state, though across all conditions, patients ON were slower than patients OFF (p = 0.006). Error bars represent standard error of the mean (SEM).

Discussion

Reward is known to orient the allocation of attentional resources and this process is thought to be dopamine-dependent (Anderson, 2013; Anderson et al., 2017). In Parkinson's disease, both

dopamine-dependent reward signaling deficits (Bódi et al., 2009; Frank et al., 2004; Muhammed et al., 2016) and attention impairments are well established (Dirnberger & Jahanshahi, 2013; Robbins & Cools, 2014). However, little is known about whether the reward deficits in patients directly contribute to poor attention, and more specifically, whether Parkinson's patients suffer from a dopamine-dependent inability to use reward to selectively allocate their attention resources. Using a task where the presence of distractors was used to probe reward-driven attention allocation, we found that Parkinson's patients were insensitive to reward information in the allocation of their attention; they were similarly distracted by the presence of low and high-reward distractors. However, contrary to our predictions, we did not find evidence that dopamine modulated this inability to use reward to guide attention allocation. We found a trend for greater distractibility overall in Parkinson's patients compared to older controls, but interestingly, the degree of distractibility was not influenced by dopamine replacement.

Our results advance our understanding of the ways in which reward deficits in PD contribute to attention impairments. We found that patients with Parkinson's disease were insensitive to the level of reward associated with a distractor – whether high or low, the distracting effect was comparable. This is generally consistent with studies using this task that have found a relationship between striatal function and reward-guided attention selectivity (Anderson, 2017; Anderson et al., 2014). However, this body of work also shows evidence, though indirectly, of a role of dopamine in driving the reward-guided attention allocation (Anderson et al., 2016, 2017). Surprisingly, we did not find that dopamine replacement restored reward sensitivity in patients. One possible explanation for these results stems from the body of research investigating a somewhat different aspect of attention impairments in Parkinson's patients – the formation of attentional sets. Across a number of studies, it has been shown that

Parkinson's patients are generally inflexible in their ability to shift their attentional focus (Fallon et al., 2016; Slabosz et al., 2006) though the exact nature of this inflexibility seems to depend on dopamine state: when dopamine levels are low, they tend to perseverate on previously relevant features of the environment (Fallon et al., 2013), and when dopamine levels are higher, they tend to have difficulty shifting their attention to previously irrelevant features (Owen et al., 1993). It is possible, given the two-phase structure of our task, that both of these types of inflexibility may have contributed to our reward-independent finding, and in particular, to the absence of reward-sensitivity in the ON patients. More specifically, the first phase required subjects to attend to the colour of stimuli whereas the second phase required subjects to attend to the shape of stimuli, thereby requiring that subjects shift their attention from one feature to another. It is therefore possible that patients ON may have been unable to shift their attention to the newly relevant stimulus feature, and therefore unable to benefit from the reward information associated with those colours to help guide their attention allocation. In this case, there may be more than one attention mechanism operating – reward selectivity and top-down attentional set formation – and it is possible that, depending on the medication state, the latter is over-riding the former.

Though the fact that we did not find an effect of dopamine on reward-driven allocation of attention diverges from PET studies where decreases in D2/D3 dopamine receptor availability in the striatum during reward-driven attention allocation (Anderson et al., 2016, 2017), it is important to note that these experiments did not manipulate dopamine directly, as was done in the present study, nor did they account for dopamine transmission outside of the striatum, either one of which could lead to the apparent inconsistency. With that in mind, one interpretation of our results is that dopamine function is not *necessary* for the reward-driven allocation process, nor for the presence of a selective attention deficit in Parkinson's disease. Indeed, selective

attention deficits in Parkinson's patients may arise from the dysregulation of other neuromodulator systems such as the noradrenergic, cholinergic and serotonergic pathways which are known to be disrupted in the disease (Bohnen et al., 2003; Bohnen & Albin, 2011; Kalia & Lang, 2015; O'Callaghan & Lewis, 2017). For example, cortical acetylcholine activity and cortical-cholinergic integrity correlate with general tests of executive function in Parkinson's patients such as the Trail Making Test and the Stroop Test (Bohnen et al., 2006; Kim et al., 2018). In a similar vein, preliminary evidence from noradrenergic and serotonergic medication manipulations suggests that these systems may play a role in Parkinsonian executive dysfunction (Kehagia et al., 2014; Ye et al., 2014, 2015). Perhaps most critically, other work using distraction-oriented paradigms has shown that cortical-cholinergic integrity but not striatal-dopaminergic integrity contributes to the ability of patients to resist distraction (Kim et al., 2017). When combined with initial evidence for deficits in top-down attentional control in Parkinson's disease (Cools et al., 2009), these findings challenge the typical assertion that the early executive dysfunction in the disease stem primarily from striatal dopamine loss. What is more likely, is that early executive deficits in Parkinson's disease, including impairments in attention allocation, stem from a combination of dopamine loss and disruption to multiple neuromodulatory systems.

We found that dopamine state did not influence attention capacity, measured here as overall distractibility. While this may seem surprising, dopaminergic manipulations on tasks that leverage distractibility have had mixed results with evidence of both improvement (Cools et al., 2010) and worsening (Fallon et al., 2017) of resistance to distractors after the withdrawal of dopamine medication from Parkinson's patients. It has been proposed that cognitive distractibility is primarily a function of dopamine signaling in the prefrontal cortex (Cools &

D'Esposito, 2011; Fallon & Cools, 2014). While we cannot be sure where in the brain our dopaminergic manipulation is acting, it is possible that we primarily replenished striatal dopamine, which is thought to be the main site of dopamine dysregulation in Parkinson's disease (Cools, 2006; Vaillancourt et al., 2013), as opposed to dopamine levels in other brain areas. If this is the case then the absence of a dopaminergic effect might indicate that prefrontal dopamine plays the greater role than the striatum in protection attention from distractors.

It is important to note that in our sample of older controls, we did not find the effect of reward magnitude that has been repeatedly shown with this task in younger controls (Anderson, 2013; Anderson et al., 2011; Anderson & Halpern, 2017; Anderson & Yantis, 2013); older controls did not show statistically significant slowing from the high reward distractor . However, it is also worth noting that the differences in slowing between conditions were in the expected direction, and the degree of slowing induced by the high reward distractor was of similar magnitude to that reported previously in young controls (Anderson, 2013; Anderson et al., 2011; Anderson & Halpern, 2017; Anderson & Yantis, 2013). However, as is often the case in samples of older adults, the variability was considerably higher, suggesting that our analysis was underpowered to detect the desired effects. It is possible that this somewhat weaker (and more variable) effect of reward could arise from two sources: age-related differences in the power of monetary rewards to act as incentives, and an age-related decline in dopamine function. We used monetary incentives to drive reward-colour associations in the initial phase of our task as has been done previously. However, there is evidence that older adults have reduced sensitivity to rewarding outcomes (Eppinger et al., 2011) and disrupted processing of monetary rewards in particular (Rademacher et al., 2014; Samanez-Larkin et al., 2007; Spaniol et al., 2015). Given that the mean age of both our patient and control samples was over 60, we cannot discount the

fact that a lack of an effect of reward might have arisen as a function of age itself or from a failure to incite the formation of reliable colour-reward associations. To our knowledge, common reward-driven attention capture paradigms have not been tested in aging populations so future work might shed light on this question. Normal aging is also associated with a decline of midbrain dopaminergic function (Kaasinen & Rinne, 2002). It is therefore also possible that this decline led to reduced learning of the colour-reward associations in the initial phase of our task, thereby weakening the intended reward-related manipulation of the following phase.

There are several limitations to our study. First, we are chiefly interested in if and how reward guides attention *towards* objects in the environment, in a goal-congruent manner, akin to the way it is thought to guide memory resources to enhance storage (Adcock et al., 2006; Gruber et al., 2016; Murty et al., 2017; Patil et al., 2017; Sharp et al., in press; Shohamy & Adcock, 2010). However, the task used here relies on the effect of distractors to measure attentional processes. Thus, we were in effect measuring how reward draws attention *away* from the task at hand, i.e. in a goal-*incongruent* manner. It is unclear whether these two sides of attention are identical and it would worth considering future experiments where the influence of reward on attention aligns with the task goals. Furthermore, this task, and others like it, tend to elicit relatively small effect sizes (Anderson, 2013; Anderson et al., 2011; Anderson & Halpern, 2017; Anderson & Yantis, 2013; Gong & Li, 2014; Klink et al., 2017). In our case, as in previous reports of this task, changes in reaction time were on the order of ten or twenty milliseconds. Effect sizes of this magnitude are difficult to detect in populations whose cognitive behavior is inherently noisy, such as older adults and neurological patient populations in particular (Burton et al., 2006; Hultsch et al., 2002). However, there is often a trade-off between the size of a task-elicited effect and a task's ecological validity and future work could incorporate peripheral

physiological measures such as eye-tracking to improve sensitivity of the outcome measures. Finally, there is no way to assess the strength of the reward-colour associations that are formed during the first phase of the task. As mentioned above, we compared accuracy between reward conditions across groups and found that neither patients nor controls performed differently on the different trial types. However, given the low level of difficulty of the task, this might not reveal subtle differences in the reward-association phase, which could potentially influence the degree to which the reward-associated colours subsequently modulate attention.

In summary, we found that Parkinson's patients did not use reward to guide the allocation of attention, but, contrary to predictions, that this impairment was not modulated by dopamine state. This extends previous attention work in Parkinson's by providing a novel mechanism underlying general attention impairments prevalent in patients. Our results also contribute to the growing recognition that, even in the earlier stages of Parkinson's disease, there are aspects of cognitive decline that cannot be directly attributed to dopamine neuron loss. Additionally, our experiment highlights the advantage of a mechanistic approach to Parkinson's disease cognition. By using a neurobiologically grounded approach to evaluate cognition, we focused on the role of dopamine in a reward-driven selective attention. Testing how specific cognitive mechanisms underlie well-known executive impairments allows us to advance our understanding of how such deficits arise. Future work will be required to determine if the loss of reward-sensitive attention allocation is related to extra-striatal loss of dopaminergic inputs, or whether, alternatively, it can be linked to neurodegeneration of other structures (the locus coeruleus, for instance, involved in the detection of novelty), and whether this pattern of impairment can also be seen across other cognitive processes ranging from perceptual processes to working memory.

Supplementary Material

Measure	Patients ON (N = 40)	Patients OFF (N = 35)	P-Value
Age	63.5 (6.4)	64.2 (5.9)	.636
Education, years	15.6 (3.2)	15.4 (3.3)	.813
Disease duration, years	4.8 (3.4)	5.1 (3.4)	.738
% Taking Dopamine Agonists	14%	17%	.999
% Female	23%	33%	.503
MoCA	27.1 (2.2)	27.0 (2.5)	.927
Verbal Fluency (MoCA)	12.4 (4.3)	12.6 (4.0)	.873
Digit Span Test	11.2 (2.3)	11.2 (2.1)	.961
Symbol Digit Modalities Test	40.9 (10.5)	40.7 (10.5)	.923
Geriatric Depression Scale	7.9 (6.1)	7.6 (5.8)	.815
Apathy Evaluation Scale	58.5 (8.01)	58.6 (7.9)	.945

Supplementary Table 1. Demographic and neuropsychological information for patients ON and OFF medication. MoCA = Montreal Neurological Assessment, Verbal Fluency is taken from the Language section of the MoCA. Values presented are mean (SD). * p<0.05.

Predictor	Model	Estimate (SE)	P-Value
Intercept	All Subs	0.073 (0.501)	0.885
Disease	All Subs	-0.289 (0.087)	<0.001 ***
Reward Level	All Subs	-0.004 (0.020)	0.8256
Session	All Subs	0.054 (0.0529)	0.308
SDMT	All Subs	0.032 (0.008)	<0.001 ***
Education	All Subs	0.041 (0.027)	0.121
Disease x Reward Level	All Subs	0.029 (0.020)	0.136
Intercept	PD Only	0.038 (0.370)	0.918
Medication	PD Only	0.005 (0.063)	0.938
Reward Level	PD Only	0.019 (0.031)	0.553
Session	PD Only	0.042 (0.064)	0.513
SDMT	PD Only	0.042 (0.009)	<0.001 ***
Medications x Reward Level	PD Only	0.021 (0.024)	0.368
Intercept	HC Only	1.518 (0.824)	0.056
Reward Level	HC Only	0.006 (0.053)	0.907
Session	HC Only	0.091 (0.090)	0.312
SDMT.W	HC Only	0.022 (0.017)	0.190

Supplementary Table 2. Reward association phase model estimates. SDMT = Symbol Digit Modalities Test. All Subs refers to the model including Parkinson's patients and control subjects. PD Only refers to the model that includes only Parkinson's patients and HC Only refers to the control only model Estimates are presented alongside the standard error of the estimate (SE). *** p<0.001.

Predictor	Model	Estimate	P-Value
Intercept	PD Only	0.033 (0.026)	0.224
Reward Vector 1	PD Only	0.004 (0.001)	0.002 **
Reward Vector 2	PD Only	0.001 (0.014)	0.553
Medication	PD Only	0.008 (0.003)	0.006 **
Session	PD Only	-0.006 (0.003)	0.021 *
SDMT	PD Only	-0.002 (0.001)	<0.001 ***
Reward Vector 1 x Medication	PD Only	-0.000 (0.001)	0.840
Reward Vector 2 x Medication	PD Only	0.001 (0.001)	0.373
Intercept	All Subs	0.010 (0.033)	0.751
Reward Vector 1	All Subs	0.002 (0.001)	0.041 *
Reward Vector 2	All Subs	0.001 (0.001)	0.163
Disease	All Subs	0.001 (0.006)	0.863
Session	All Subs	-0.012 (0.002)	<0.001 ***
SDMT	All Subs	-0.002 (0.001)	<0.001 ***
Education	All Subs	0.002 (0.002)	0.193
Sex	All Subs	-0.017 (0.011)	0.137
Reward Vector 1 x Disease	All Subs	0.002 (0.001)	0.019 *
Reward Vector 2 X Disease	All Subs	-0.001 (0.001)	0.585
Intercept	HC Only	0.014 (0.045)	0.772
Reward Vector 1	HC Only	-0.000 (0.001)	0.838
Reward Vector 2	HC Only	0.002 (0.001)	0.163
Session	HC Only	-0.016 (0.002)	<0.001 ***
SDMT	HC Only	-0.002(0.001)	0.089

Supplementary Table 3. Attention test phase model estimates. SDMT = Symbol Digit Modalities Test. All Subs refers to the model including Parkinson's patients and control subjects, PD Only refers to the model that includes only Parkinson's patients and HC only refers to the control only model. Estimates are presented alongside the standard error of the estimate (SE). * p<0.05, ** p<0.01, *** p<0.001.

Distractor Levels Compared	Source Model	Estimate	P-Value
Low vs High	PD Only	0.004 (0.003)	0.170
Low vs None	PD Only	0.010 (0.002)	<0.001 ***
High vs None	PD Only	0.006 (0.002)	0.007 **
Low vs High	All Subs	0.003 (0.002)	0.115
Low vs None	All Subs	0.004 (0.002)	0.015 *
High vs None	All Subs	0.001 (0.002)	0.423
Low vs High	HC Only	-0.002 (0.003)	0.411
Low vs None	HC Only	0.001 (0.003)	0.590
High vs None	HC Only	0.004 (0.002)	0.121

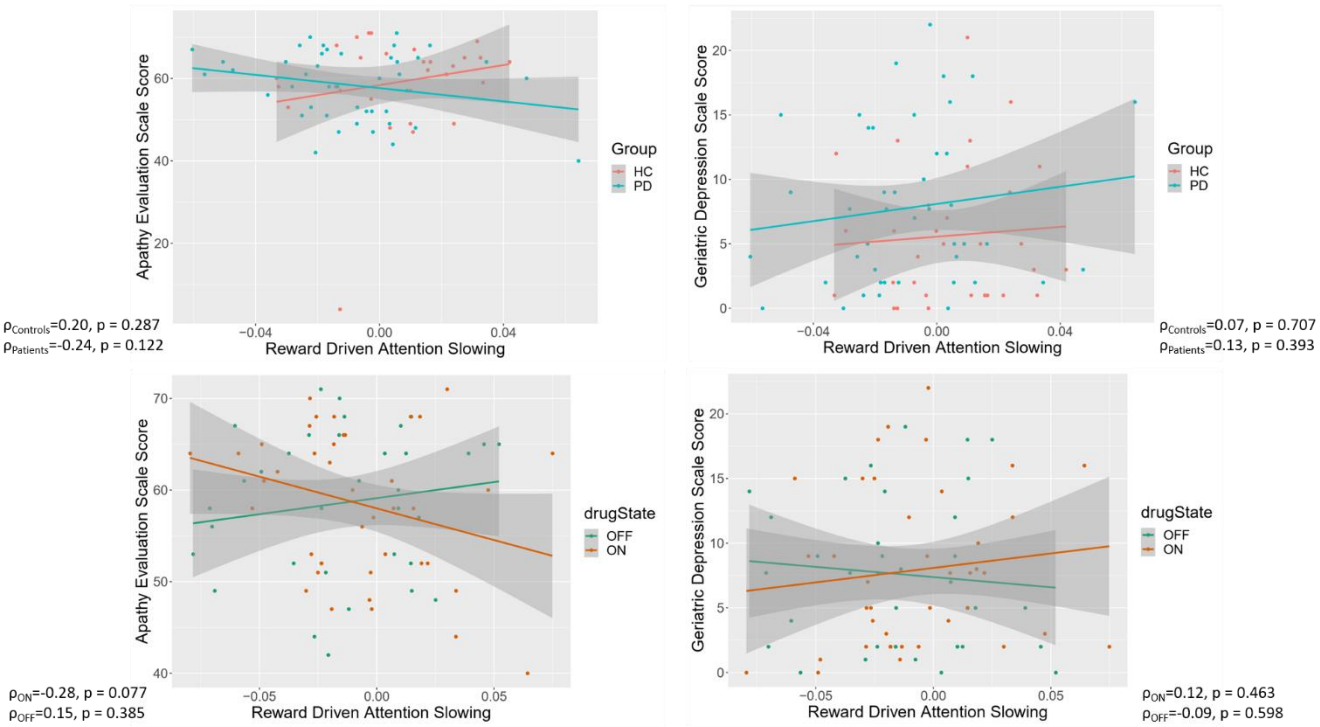
Supplementary Table 4. Weighted sum comparisons for reward level. Results from comparing the weighted sums of Reward Level estimates in attention test phase models. Comparisons for the All Subs model used the Reward Level X Disease estimate. Estimates are presented alongside the standard error of the estimate (SE). * p<0.05, ** p<0.01, *** p<0.001.

Disease Status	Medication Status	Reward Level	Reaction Time (s)	Differences (X-None) (ms)
Control	NA	None	0.871 (0.230)	NA
Control	NA	Low	0.875 (0.233)	3.6
Control	NA	High	0.881 (0.235)	10.2
Parkinson's	OFF	None	0.894 (0.237)	NA
Parkinson's	OFF	Low	0.907 (0.237)	13.3
Parkinson's	OFF	High	0.895 (0.235)	1.3
Parkinson's	ON	None	0.905 (0.236)	NA
Parkinson's	ON	Low	0.916 (0.237)	11.0
Parkinson's	ON	High	0.908 (0.236)	3.7
Parkinson's	collapsed	None	0.900 (0.237)	NA
Parkinson's	collapsed	Low	0.912 (0.237)	12.0
Parkinson's	collapsed	High	0.902 (0.236)	2.6

Supplementary Table 5. Raw reaction times for attention test phase. In the case of Controls and when Parkinson's are collapsed across drug conditions, the reaction times are averaged across both sessions.

Predictor	Model	Estimate (SE)	P-Value
Intercept	All Subs	0.010 (0.033)	0.767
Disease	All Subs	0.001 (0.006)	0.923
Distractor Presence	All Subs	0.003 (0.001)	<0.001 ***
Session	All Subs	-0.012 (0.002)	<0.001 ***
SDMT	All Subs	-0.002 (0.001)	<0.001 ***
Education	All Subs	0.002 (0.002)	0.195
Sex	All Subs	-0.017 (0.011)	0.136
Disease x Distractor Presence	All Subs	0.001 (0.001)	0.053
Intercept	PD Only	0.031 (0.026)	0.241
Medication	PD Only	0.007 (0.003)	0.007 **
Distractor Presence	PD Only	0.004 (0.001)	<0.001 ***
Session	PD Only	-0.006 (0.003)	0.0.02 *
SDMT	PD Only	-0.002 (0.001)	<0.001 ***
Medication x Distractor Presence	PD Only	0.001 (0.001)	0.421

Supplementary Table 6. Distractor only model estimates. SDMT = Symbol Digit Modalities Test. All Subs refers to the model including Parkinson's patients and control subjects. PD Only refers to the model that includes only Parkinson's patients. Estimates are presented alongside the standard error of the estimate (SE). * $p < 0.05$, ** $p < 0.001$, *** $p<0.001$.



Supplementary Figure 1. Individual differences in reward driven attention allocation are not related to depression or apathy measures. Pearson correlations between reward driven attention slowing (Reaction time in the high reward – low reward conditions) and Apathy Evaluation Scale scores (left) and Geriatric Depression Scale scores (right). Shown for Patients (ON and OFF) and older controls.

Chapter 3: General Discussion

Summary

The principal goal of this thesis was to examine mechanisms underlying early cognitive deficits in Parkinson's disease patients. More specifically, we were interested in the role of reward and dopamine in the selective allocation of cognitive resources, specifically attention and working memory. Cognition in Parkinson's is often studied from the perspective of capacities or abilities, in the sense that patients are compared to controls or to other patients with different doses of dopaminergic medication in the hopes of identifying "deficits" in one cognitive domain or another. Though these experiments have helped to characterize the extent of the cognitive impairment seen in early Parkinson's disease, the full extent of the mechanisms underlying such deficits has not been fully explored. Instead of looking at executive dysfunction in Parkinson's as a *lack* of various cognitive abilities, another relatively unexplored approach is to consider it from the perspective of optimal resource *allocation*. In other words, perhaps patients do not have reduced cognitive resources but rather are not optimal or efficient at allocating the resources that they have available to them. Though there are several mechanisms of such resource allocation that could be considered, we focused here on reward-driven selectivity. Reward signals have been shown to guide the allocation of both attention (Anderson et al., 2011; Anderson, 2013) and working memory (Gong & Li, 2014; Infanti et al., 2015; Klink et al., 2017), two domains of cognition that have received substantial attention in Parkinson's (Dirnberger & Jahanshahi, 2013; Kudlicka et al., 2011; Robbins & Cools, 2014). This mechanism was particularly appealing in our case because Parkinson's patients are known to suffer from a series of reward processing deficits (Bódi et al., 2009; Frank et al., 2004; Muhammed et al., 2016). Furthermore, there is evidence to suggest that reward-driven cognitive selectivity involves striatal dopamine

(Anderson et al., 2016, 2017), which is compromised in Parkinson's disease. With this in mind we aimed to expand our understanding of Parkinson's disease cognition by testing the role of reward and dopamine on selective attention in patients.

Overall, our data suggest that Parkinson's patients are impaired at using reward information in the environment to guide the allocation of attention resources. What this might suggest is that reward processing deficits in Parkinson's limit the ability of reward-associations to draw patients' attention. Additionally, we found that general selective attention deficits in patients are not altered by dopamine replenishment. This was surprising to us, as earlier correlational studies suggest a role of striatal dopamine (Anderson et al., 2016, 2017). However, there is growing evidence for the role of other neuromodulatory systems in Parkinsonian cognition, especially attention impairments (Bohnen et al., 2006; Kim et al., 2017, 2018). In this light, one interpretation of our data is that healthy dopamine signaling is not necessary for reward-dependent allocation of attention resources and that this process relies on the functioning of a different neurotransmitter. A full discussion of our results and possible interpretations can be found in the preceding chapter.

One point of discussion that was not considered in Chapter 2, concerns the effect of rewards compared to *losses* in allocating attention resources in Parkinson's patients. There are several reasons to believe that these two valences may act differently in a selective attention environment. A seminal study by Frank et al. (2004) demonstrated that dopamine level led to divergent outcomes with regards to learning from rewards versus losses. Patients ON medication were more accurate than Patients OFF when learning from rewards but the opposite was true when learning from losses (Frank et al., 2004). This effect was replicated using unmedicated patients who then came in again after having taken dopaminergic medications for 12 weeks

(Bódi et al., 2009). Another study found that patients ON medication were impaired compared to patients OFF in learning from unexpected punishment in a reversal learning paradigm (Cools et al., 2006). Additionally, preliminary neuroimaging work has shown that dopaminergic replenishment attenuates striatal responses to punishment learning but not reward learning in Parkinson's patients (Argyelan et al., 2018). Put together, these findings suggest that dopaminergic dysregulation due to Parkinson's disease differentially affects how the brain interacts with positive versus negative reinforcement signals in the environment. From this perspective it is reasonable to hypothesize that dopamine replenishment may lead to differences in how loss/punishment associations guide the allocation of attention resources. Furthermore, biases in attentional orienting due to punishment are poorly described relative to those driven by reward (Anderson, 2016). Previous work has shown that stimuli paired with monetary loss (Wang et al., 2013; Wentura et al., 2014), aversive noises (Koster et al., 2004; Smith et al., 2006), or painful shocks (L. J. Schmidt et al., 2015a, 2015b) all draw additional attention resources, though the biological underpinning of these findings remains unexplored. With the above in mind, understanding attentional orientation mechanisms in Parkinson's disease will require studies that investigate the allocation effects of positive valence signals such as reward-associations, but also negatively valenced signals that include associations to punishments and losses.

Looking Beyond Attentional Selectivity

It is important to point out that attention is only one domain in a series of interlinked cognitive issues faced by patients and it is not entirely clear if our results point to a *general* inability to use reward mechanisms to signal the prioritization of cognitive resources in

Parkinson's disease or rather a specific issue in the orientation of attention. If it is true that patients are unable to use reward to guide allocation across multiple cognitive processes in which it is established that healthy individuals do use reward signals, a case could be made that reward-driven cognitive selectivity may have a more general role in early executive dysfunction in Parkinson's. To that end there is a need for experiments outside of the attention domain which investigate how reward guides the allocation of other cognitive resources.

For several reasons, working memory represents an area of executive dysfunction in Parkinson's that is a clear next step for reward selectivity research. One approach to studying the allocation of working memory has been to design experiments where the utility or value of items destined for memory is explicitly instructed to participants and where the task goals are tied to this explicit utility (Christopher H Chatham & Badre, 2015). Interestingly, evidence suggests the striatum is involved in tracking the value of items stored in working memory (Chatham et al., 2014; Chatham & Badre, 2013). However, few studies have investigated whether reward exerts an influence on working memory resource allocation in a more automatic way, i.e. helping to 'capture' resources in the way that attention and declarative memory have been shown to be sensitive to reward. Using a change detection paradigm, Gong and Li (2014) showed that subjects had greater ability to detect changes in the orientations of coloured stimuli held in working memory when those stimuli were in colours that were associated with reward in a previous task (Gong & Li, 2014). This result was conceptually replicated using a different paradigm but with a small sample (Klink et al., 2017). Similarly, subjects had poorer recall of stimuli orientations, when distractors that were previously reward associated were positioned amongst the stimuli that had to be encoded into working memory (Infanti et al., 2015). Taken together these results provide initial evidence for the involvement of reward driven cognitive

resource allocation mechanisms during the working memory process. However, these experiments have only touched on the *encoding* of items into working memory, even though the working memory process is often considered an amalgamation of several distinct cognitive steps (Gazzaley & Nobre, 2012). There is room for expanding the current work to other aspects of the working memory process such as *maintenance*, which is known to be impaired in Parkinson's disease (Liozidou et al., 2012; Rottschy et al., 2013; Sawamoto et al., 2008; Ventre-Dominey et al., 2014).

Another reason to extend our current research question to encompass working memory stems from its overlap with attention. There has been substantial thought put into the idea that classic conceptions of working memory are fundamentally interrelated with selective attention processes (Bahmani et al., 2019; Clark & Noudoost, 2014; Gazzaley & Nobre, 2012; Störmer et al., 2012). For example, studies point to the idea that selective attention is the mechanism which dictates what information in the environment enters working memory (Gazzaley, 2011; Rutman et al., 2009; Vogel et al., 2005; Zanto & Gazzaley, 2009). Importantly, in an fMRI experiment Mayer et al. (2007) showed that BOLD signals in the prefrontal cortex and insula heavily overlapped during visual search and working memory encoding in a combined selective-attention/working-memory task suggesting common neural resources for selective attention and early working memory processing (Mayer et al., 2007). This was later causally demonstrated when TMS-driven inhibition of the prefrontal cortex (inferior frontal junction) disrupted performance in a combined selective-attention/working memory task (Zanto et al., 2011).

In addition to the role of selective attention during working memory encoding, there has also been some discussion of how selective attention may act *within* working memory during the maintenance of working memory representations (Gazzaley & Nobre, 2012; Störmer et al.,

2012). It has previously been suggested that the maintenance of items in working memory occurs due to internal shifts of attention between encoded representations (Awh et al., 2006; Awh & Jonides, 2001; Gazzaley & Nobre, 2012; RepovŠ & Baddeley, 2006; Smyth & Scholey, 1994). This is evidenced by work showing that working memory performance is influenced by facilitating or disrupting attention towards working memory representations during maintenance (Awh et al., 1998; Griffin & Nobre, 2003). Studies looking at event-related potentials have shown that cueing locations held in working memory led to greater neural responses than cueing locations not being maintained (Awh et al., 2000; Jha, 2002). Additionally, neuroimaging studies have shown large overlap in brain activity when comparing the shifting of attention between mental representations and between external visual stimuli (Nobre et al., 2004; Tamber-Rosenau et al., 2011). Furthermore, directing attention to locations or items stored in working memory modulates neural representations of those encoded items and the extent of this modulation predicts working memory performance (Lepsien et al., 2005, 2011; Lepsien & Nobre, 2007).

Lastly, as pointed out by Gazzaley and Nobre (2012), the presence of predictive cues similarly aids the orientation of attention as well as working memory performance (Gazzaley & Nobre, 2012). In the attention literature, there is a long history of work showing enhancement to the deployment of attention when some aspect of the target (e.g. its location) is cued (some well-known examples: Ball & Sekuler, 1980; Dosher & Lu, 2000; Egeth et al., 1984; Eriksen & Hoffman, 1973; Posner et al., 1980)) and this is thought to depend on top-down signals from frontal and parietal regions (Bressler et al., 2008; Corbetta & Shulman, 2002). An analogous mechanism appears in the working memory literature as well. Studies using spatial cues in advance of a stimulus array that needs to be remembered show improvement in working memory performance for cued-items (Botta et al., 2010; Murray et al., 2011; Schmidt et al., 2002). Again,

there is evidence for top down contributions from the pre-frontal and parietal cortices (Bollinger et al., 2010; McNab & Klingberg, 2008). Together, the overlap between selective attention and working memory processes makes working memory a suitable candidate for the next steps in our reward-driven selectivity investigation.

The final motivation to explore reward-driven working memory resource allocation in Parkinson's disease is that the role of selective attention in working memory impairments is not clear. Working memory deficits have been studied at length in Parkinson's disease patients (Dirnberger & Jahanshahi, 2013; Kudlicka et al., 2011; Robbins & Cools, 2014). Impairments have been described with regards to working memory capacity (Grogan et al., 2018; Lee et al., 2010; Liozidou et al., 2012; Merkl et al., 2017), encoding items into working memory (Fallon et al., 2017; Uitvlugt et al., 2016; Wiesman et al., 2016; Zokaei et al., 2014), maintaining stimulus representations in working memory (Liozidou et al., 2012; Rottschy et al., 2013; Sawamoto et al., 2008; Ventre-Dominey et al., 2014), updating items held within working memory (Laura Alonso-Recio et al., 2014; Beato et al., 2008; Moustafa et al., 2013; Simioni et al., 2017; Torta et al., 2009), and manipulating items in working memory (Bublak et al., 2002; Lewis et al., 2003, 2005). Some studies have explicitly tested the role of dopamine using medication manipulations with mixed results that seem to depend on which aspect of working memory is targeted by the task. Dopamine replenishment in Parkinson's patients does not alter N-back performance (Beato et al., 2008; Torta et al., 2009) nor working memory capacity (Grogan et al., 2018). Using a delayed response task, Lewis et al. (2005) showed working memory performance improvement in patients ON medication compared to OFF, while Moustafa et al. (2008) showed slight improvement for patients ON in a continuous performance task (Lewis et al., 2005; Moustafa et al., 2008). With regards to distraction, patients ON are more impaired when distractors are

present during encoding (Uitvlugt et al., 2016), however, there have been mixed results with regards to distraction during working memory maintenance with one study finding that dopamine replenishment aided performance (Fallon et al., 2017) and another in which it impaired performance (Cools et al., 2010). Despite, these more recent studies that incorporate elements of selective attention into their design (i.e. distraction), the role of reward in the process and how it interacts with dopamine is undefined.

Testing the Selective Allocation of Working Memory in Parkinson's Disease

To test the role of reward in working memory resource allocation in Parkinson's disease, we designed two tasks that explore different aspects of the working memory process. The tasks are similar in that they use different levels of reward/value associations to either facilitate or impair working memory processing. We were interested in probing the role of reward in guiding both the encoding of items into working memory, but also disrupting working memory representations that are trying to be maintained. They differ from the task described in Chapter 2 in that there is no specific training phase to either of them. The tasks discussed here are in development and are not finalized therefore specific trial numbers and screen presentation times will not be mentioned. Their inclusion in this thesis serves to further the discussion and orient the reader towards the future directions of the research discussed in the previous chapter.

Distracted AX-Continuous Performance Task

The first proposed task is an adaptation to the A-X version of the continuous performance task, a standard working-memory task that has been used in humans (Braver & Cohen, 2000; Cohen et al., 1997), Parkinson's patients (Moustafa et al., 2008) and computational studies (Frank et al.,

2001) (see Figure 4). Subjects are presented with a series of sequential letters, shown on the screen one at a time: A, X, B or Y. They are instructed to press one of two keys upon the presentation of each letter according to specific instructions. For a correct answer, they must press the "z' key for the presentation of every letter *unless* the letter is an X that followed an A, in this case the correct key press is the "m" key. Unbeknownst to the subject, the letters form a series of two-letter pairs. The first letter is always an A or a B while the second letter is always an X or Y. This pattern creates four types of pairs: A-X, A-Y, B-X and B-Y. A-X trials are the odd trials out as this is the only pair that will contain an "m" response. The first letter in the pair acts as a context for the response to the second letter as the "m" response is only made to an X that follows an A. This task tests working memory because subjects have to maintain the context letter during a short variable delay in order to make the correct response to the second or *probe* letter. A-X trials represent 70% of the total trial number while each of the other pair accounts for 10% respectively. The reason for this trial distribution is to establish a response tendency to A-X trials which is when challenged by other context-probe trial types. In order to test the role of reward, we have modified this paradigm slightly to include a distracting food image on some trials during the interval between the context letter and the probe letter. In order to ensure equal amount of trials at various distractor-reward-levels across subjects, subjects first rate a series of food-image stimuli using a 1-5 Likert scale. This stimulus set was developed for use in controlled value-based experiments (Satterthwaite & Fellows, 2018). Images are sorted according to the subject's rating and then distributed pseudo-randomly across the four context-probe letter pairs to ensure an even spread of rated stimuli for each trial type. In other words, this results in roughly equal low, mid and high-rated images across the different trial types. There are two types of blocks: 'distraction' blocks where trials include a previously-rated food image

which are intended as a distractor, and control blocks where trials include a neutral stimulus that the subject has not previously been shown instead. We predict that the higher the value of the distractor image, the less accurate and the slower responses to the probe letter will be. This would indicate that previously established reward associations (to different types of food) may disrupt the maintenance of items in working memory by drawing cognitive resources away from the task at hand.

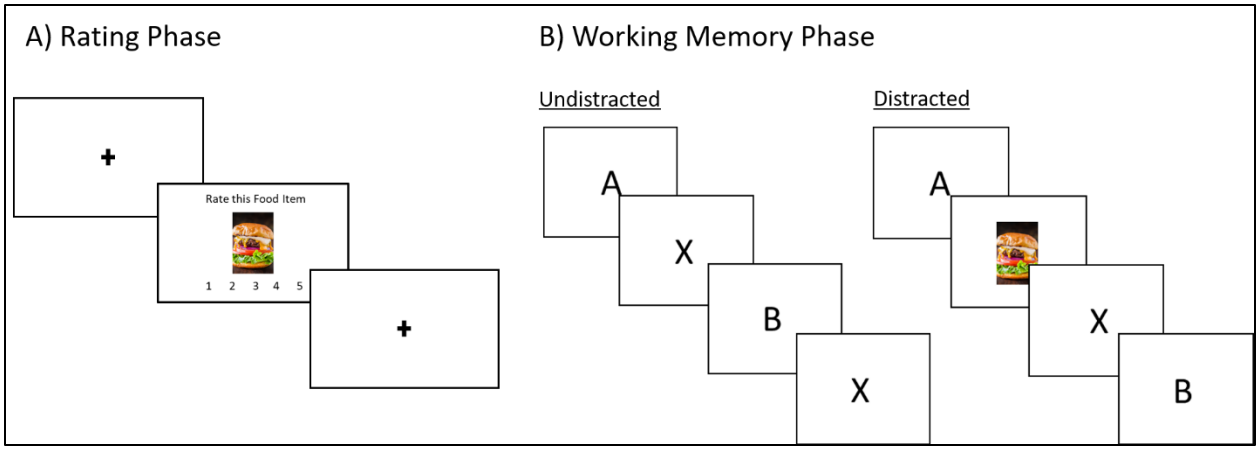


Figure 4. Distracted A-X Continuous Performance Task. A) The rating phase of the task. Subjects first rate a series of food stimuli between 1-5 in terms of how much they like the food. They are encouraged to use the entire scale. B) The working memory phase of the task in which previously-rated distractor images are used to disrupt working memory maintenance. Subjects respond to and maintain an initial context letter (either A or B) for a brief delay and make a specific response to a probe letter (either X or Y). The response, a key press of either "z" or "m" is dependent on the context letter. On some of the trials, a distractor image appears during the delay between the context letter and the probe letter.

Spatial Memory and Reward Task (SMaRT)

Our second task relies on a two-part trial design. Here, reward associations are formed with spatial locations on the screen allowing us to test the role of reward in enhancing working memory encoding mechanisms (Figure 5). On each trial, subjects are presented with six boxes that are evenly spaced along the X-axis of the screen with their Y-coordinate randomized. They have to select three of these boxes on each trial using the cursor. Upon selecting a box, a number appears to indicate that box's value on this trial. In order to create location-reward associations, we assigned different reward values to different zones of the screen that corresponded with the X-coordinates of the boxes (see Figure 5. A for details). The values increase as you go from one side of the screen to the other and the direction of this reward gradient (left to right or right to left) is counterbalanced across subjects. Subjects are not explicitly told this is the case, but it is expected that they will develop some degree of awareness. Eighty percent of the time the number that appears on a box will be the true value of the corresponding zone, and 20% of the time the box's value will be zero. This probabilistic reward association was intended to prevent overt encoding strategies and to help to make the task more ecologically valid, given that reward associations are rarely deterministic in our environments.

Once the subject has made three selections on a given trial there is a brief pause and then they are shown six neutral image-stimuli, one in each of the reward zones. It is important to note that the Y-coordinates of these stimuli are randomized on each trial and *are not* linked to the Y coordinates of the boxes. Subjects are asked to remember the items and their location during a relatively fast encoding window. After a moderate delay of several seconds, subjects are shown a probe image that corresponds to one of the stimuli that they were supposed to remember. Their task is to identify the location on the screen in which that item had been presented. Subjects are

told at the start of the task that, on each trial, for a correct response, they will receive the points that they turned over during the box selection task and that these points will correspond to real money at the end of the experiment. The aim of this task is to slowly build an implicit reward gradient through the selection of the boxes and have this reward gradient bias the encoding of certain items in working memory over others. If the task works as intended, we predict that subjects will be more accurate on probed items that are located in higher zones of the reward gradient.

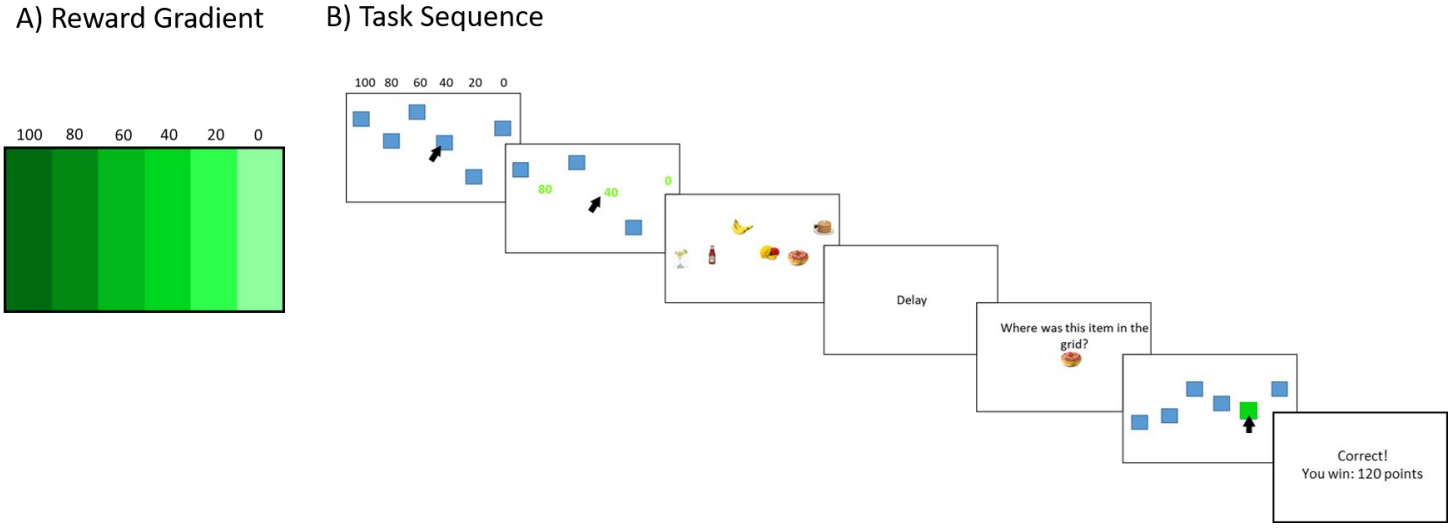


Figure 5. Spatial Memory and Reward Task. A) The invisible reward gradient that controls spatial values. Subjects are unaware of this gradient at the start of the task, and the direction of the gradient is counterbalanced across subjects. B) Trial sequence for the working memory task. Across the entire task, reward associations are made to spatial zones according to the reward gradient. The goal of the task is to determine if these associations enhance encoding of certain items into working memory over others. In the first phase of the trial, subjects are told to pick the three (among six) boxes that will yield the most points. Reward is assigned to each box according to the reward gradient but is also probabilistic; a given box only yields its location-assigned reward 80% of the time. It is expected that participants gradually learn that some zones of the screen are more rewarding than others. In the second phase of the trial, subjects are shown six neutral images, each of which is located in a different reward zone, and are told to remember them. In the final, test phase, of the trial, memory for the location of a single item is probed by showing subjects one of the images and asking them to identify, using the mouse, which of six locations it had been presented in. Correct answers result in awarded points equal to the points uncovered from the boxes in the initial phase of the trial.

Conclusion

Overall the research presented in this thesis was an attempt to take a neurobiologically-guided approach to better understand cognitive impairments in Parkinson's disease. The overall focus was to examine the process of cognitive resource allocation. It is well established that cognitive resources are limited. Recent evidence suggests that across different cognitive processes, reward might play a role in helping to guide, or to prioritize the allocation of cognitive resources. Given the known reward processing deficits in Parkinson's disease, we hypothesized that Parkinson's patients might lose the ability to effectively use reward information to guide the allocation of cognitive resources. We found that, in the domain of attention, Parkinson's patients' attention resources are not guided by reward, but, surprisingly, that this deficit is not sensitive to dopamine state. Because of overlap between attention and working memory, we also developed two tasks that aim to test if reward similarly guides the allocation of working memory resources at different stages of processing. Our approach to understanding executive deficits in Parkinson's disease is rooted in the idea that exploring specific, biologically grounded cognitive mechanisms will allow us to better relate impairments to the known underlying pathology in the disease. By understanding how different keys aspects of cognition in Parkinson's disease – reward processing and executive function – interact with one another and intersect with the pathophysiology of the disease, we will be able to move towards treatments that alleviate the prominent cognitive symptoms faced by patients.

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