June 2014

Functional role of the striatum in stimulus-response learning: Evidence from functional MRI and patients with Parkinson's disease

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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FUNCTIONAL ROLE OF THE STRIATUM IN STIMULUS-RESPONSE LEARNING: EVIDENCE FROM FUNCTIONAL MRI AND PATIENTS WITH PARKINSON'S DISEASE

(Thesis format: Integrated Article)

by

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Graduate Program in Physiology and Pharmacology

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

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Abstract

Cognitive impairment is recognized in Parkinson’s disease (PD). Understanding striatum-mediated cognitive functions will help elucidate some of these abnormalities. Learning is often impaired by dopaminergic medication. However, dorsal striatum (DS) has been implicated in learning; an unexpected result given that dopaminergic therapy, the gold standard treatment for PD, remediates DS functioning. In two separate experiments, stimulus-response association learning and decision-making were examined in healthy individuals using functional magnetic resonance imaging (fMRI), and in PD patients using behavioural methods. In Experiment 1, healthy individuals completed a stimulus-response learning task, and brain regions associated with learning versus decision-making were investigated using fMRI. In Experiment 2, patients with PD completed a similar task on and off their dopaminergic medication. Results from both experiments suggest that DS mediates decision-making and not learning. This greater understanding of striatum-mediated cognition will ultimately prompt clinicians to devise medication strategies that consider both motor and cognitive symptoms of PD.

Keywords

Parkinson’s disease, fMRI, dorsal striatum, ventral striatum, caudate nucleus, stimulus-response learning.
Co-Authorship Statement

I completed all aspects of Experiment 1 myself, receiving assistance in fMRI analysis from Dr. Adam Hampshire. For Experiment 2, I received assistance in data collection from Andrew Vo and Allison Partridge, as well as data processing and analysis assistance from Ken Seergobin and Dr. Penny MacDonald. I prepared the manuscripts for both experiments that were edited by Dr. Penny MacDonald. Experiment 1 was completed at Robarts Research Institute, University of Western Ontario, and Experiment 2 was completed at the Brain and Mind Institute, University of Western Ontario, as well as Health Sciences North in Sudbury, Ontario.
Acknowledgments

I would like to express my gratitude to the following people that contributed to a memorable experience as a Master’s student in the Penny Lab.

- Dr. Penny MacDonald for her exceptional guidance and mentorship, and for establishing a collaborative and dynamic lab filled with brilliant minds to help me further my research.
- Dr. Adrian Owen for his support and guidance on all aspects of my research and beyond.
- To the rest of my committee, Dr. Marco Prado, Dr. Adam Hampshire and Dr. Jessica Grahn for support and advice in completing my research.
- Andrew Vo for his sarcastic remarks and advice regarding all aspects of my research and life. Also, for waking up very early in the morning because I refused to book patients later in the day.
- Ken Seergobin for his “behind-the-scenes” assistance in the research process, including contributions to design, for programming experiments, and teaching data management.
- Allison Partridge and Brian Robertson for participant recruitment and data collection assistance. The two of you assisted in maintaining my sanity over the last two years.
- Aja Lee for her unwavering support, love, and encouragement. And of course, for always letting me respond to work emails and texts during dates.
- My family for their help and encouragement.

This work was supported by start-up funds and an Opportunity Grant from the Academic Medical Organization of Southwestern Ontario awarded to Dr. Penny MacDonald, and Canada Excellence Research Chair (CERC) award to Dr. Adrian Owen.
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<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>BG</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-oxygenation-level dependent responses</td>
</tr>
<tr>
<td>DS</td>
<td>Dorsal striatum</td>
</tr>
<tr>
<td>DAT</td>
<td>Dopamine transporter</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FB</td>
<td>Feedback</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GLM</td>
<td>General linear model</td>
</tr>
<tr>
<td>t-dopa</td>
<td>t-3,4-dihydroxyphenylalanine</td>
</tr>
<tr>
<td>MSN</td>
<td>Medium spiny neuron</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>MOCA</td>
<td>Montreal cognitive assessment</td>
</tr>
<tr>
<td>NAcc</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error measure</td>
</tr>
<tr>
<td>SN</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td>SR</td>
<td>Stimulus-response</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s disease rating scale</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>VS</td>
<td>Ventral striatum</td>
</tr>
<tr>
<td>VTA</td>
<td>Ventral tegmental area</td>
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</tbody>
</table>
Chapter 1

1 Literature Review

1.1 Basal Ganglia

The basal ganglia (BG) are a collection of sub-cortical nuclei responsible for the generation of motor movements, and increasingly, in cognitive functions (Grahn et al., 2009; Monchi et al., 2001). The BG are comprised of four interconnected structures: the striatum, globus pallidus, substantia nigra (SN), and subthalamic nucleus (Kandel et al., 2013). The striatum can be subdivided anatomically into the caudate nucleus, and putamen, and functionally into dorsal striatum (DS), and ventral striatum (VS; Kandel et al., 2013; MacDonald and Monchi 2011; Wickens et al., 2007a; see Figure 1.1).

![Figure 1.1 The functional and anatomical divisions of the striatum](image)

The striatum can be subdivided functionally and anatomically. **A.** The striatum can be subdivided functionally into the dorsal and ventral striatum. The dorsal striatum is composed of the bulk of the caudate nucleus and putamen, shown in blue, whereas the ventral striatum is composed of ventral aspects of the caudate nucleus, putamen as well as the nucleus accumbens. **B.** The anatomical subdivisions of the striatum: caudate nucleus (shown in red), putamen (shown in green), and nucleus accumbens (shown in orange). Figure adapted from Haber and Knutson, 2010.
The striatum is the main input nuclei, receiving glutamatergic afferents from all cortical areas except for primary visual and primary auditory cortices, as well as dopaminergic afferents from SN and ventral tegmental area (VTA; Kandel et al., 2013). Striatal efferents project to either the internal globus pallidus (i.e., direct pathway) or to the external globus pallidus; which, in turn, projects to the subthalamic nucleus and then the internal globus pallidus (i.e., indirect pathway). Subsequently, both pathways project to the thalamus; which, in turn, project to the cortex (Kandel et al., 2013). An illustration of the basic cortico-basal ganglia-thalamocortical circuit is presented in Figure 1.2. One of the functions of dopamine in the striatum is to regulate the balance between the indirect, and the direct pathways (Kandel et al., 2013). When the concentration of dopamine is altered greatly, as in Parkinson’s disease (PD), a variety of motor and cognitive symptoms develop.

![Schematic diagram of the basal ganglia and its afferents and efferents](image)

**Figure 1.2: Schematic diagram of the basal ganglia and its afferents and efferents**

Lines that terminate in arrowheads are excitatory connections; lines that terminate in circles are inhibitory connections; purple lines are dopaminergic connections; grey solid lines represent the direct pathway and grey dotted lines represent the indirect pathway. VTA – Ventral tegmental area; SN – Substantia nigra.
1.2 Parkinson’s disease

PD is a neurodegenerative disorder affecting 1% of the population over 60 years of age and 3% of the population over 80 in industrialized countries (Tanner and Goldman, 1996). It is mainly characterized by the motor symptoms of bradykinesia, or slow movement, rigidity, and tremor. The cardinal motor symptoms of this disorder are caused by the degeneration of dopamine-producing neurons in the SN. When enough degeneration occurs in the SN, delivery of dopamine to its nearly exclusive efferent, the DS, declines causing the balance between the direct and indirect pathways of the cortico-basal ganglia-thalamocortical motor circuit to increase signaling through the indirect pathway, and decrease signaling through the direct pathway (Kandel et al., 2013). These changes result in increased activity in the internal segment of the globus pallidus, inhibiting the thalamus, and ultimately, regions of the motor cortex. When between 50-80% of the SN dopaminergic neurons degenerate, the hypokinetic features seen in PD begin to emerge.

At all stages of the disease, dopamine replacement is an effective treatment for improving motor symptoms. Dopamine replacement therapy can be prescribed in a variety of forms, namely dopamine precursors such as L-3,4-dihydroxyphenylalanine (L-dopa), or dopamine agonists. Dopamine precursors are often prescribed in conjunction with a dopamine decarboxylase inhibitor to prevent the conversion of L-dopa to active dopamine in the peripheral circulation, thereby increasing the availability of L-dopa within the brain. Dopamine precursors elevate dopamine levels in the brain, alleviating the motor symptoms associated with PD. Dopamine agonists are chemical substrates with a similar structure to dopamine, and can bind to and activate dopamine receptors.

Cognitive dysfunction is now an undisputed, non-motor symptom of PD that leads to significant impairment in quality of life (Barone et al., 2009; Schrag et al., 2000). Increasingly, it is evident that the striatum itself mediates several cognitive functions. In PD, some cognitive deficits relate to dopamine depletion in DS, and are remediated, at least partially, by dopaminergic therapy. Other cognitive deficits arise as a consequence of dopaminergic therapy. Increasingly, it is understood that impairment can occur due to overdose of brain
regions that receive dopamine from VTA (See Cools, 2006; MacDonald and Monchi, 2011 for reviews). These regions include VS, prefrontal, and limbic cortices. Unlike SN, the VTA is relatively spared throughout the course of PD, and as a result, regions innervated by VTA retain near-normal levels of dopamine (Cools, 2006). Therefore, it has been proposed that dopamine replacement therapy overdoses VTA-innervated regions, impairing functioning.

The most common method in testing the effect of dopaminergic therapy on cognition is through the use of the exogenous dopamine withdrawal procedure. Patients are instructed to abstain from taking dopamine precursors for a minimum of 12 to a maximum of 18 hours, and dopamine agonists for a minimum of 16 to a maximum of 20 hours before testing begins, constituting the OFF state. Performance in this state is then compared to the ON state where the patient takes the medication as prescribed. Another method for investigating this effect involves comparing performance of medicated PD patients with patients who have never been medicated, or de novo PD patients. The advantage of the former method is that it removes the confound of disease severity. By comparing performance in ON and OFF states in a single patient, within-subject differences can be examined without the likelihood of comparing patients who have different disease durations.

1.3 Dopamine Overdose Hypothesis

The dopamine overdose hypothesis attempts to explain the cognitive impairments seen in PD as a function of varying concentrations of endogenous dopamine in different brain regions. Those that are dopamine depleted at baseline are improved; whereas, brain regions that are dopamine replete are impaired by dopaminergic therapy. DS is a brain region that is improved by dopamine replacement therapy; whereas, those that are impaired are mediated by a VTA-innervated region.

Gotham and colleagues (1988) were among the first to propose the overdose hypothesis. They investigated cognitive function in patients with PD both on and off dopaminergic medication using a series of tasks including the Paced Auditory Serial Addition Task, Wisconsin Card Sorting Task, Visual-visual Conditional Associative Learning Test, Word Fluency Tasks, and Subject-ordered Pointing Task. A short description of each task is presented below.
1) The Paced Auditory Serial Addition Task is a measure of general attention, and working memory. Participants hear a series of numbers and are instructed to add the most recent number to the number that followed it in the series. For example, in the series one, two, three, the participant would be required to add the number two with one, resulting in three and then add the next number, three, to the previous numbers, resulting in six.

2) The Wisconsin Card Sorting Task is a measure of set-shifting, or the ability to flexibly update changing rules. Briefly, participants are told to match sample cards containing objects of various shapes, colours, and numbers to a probe card. They are not told on what dimension (i.e., colour, shape, or number) to match sample cards to the probe card, however, and need to determine this using a trial-and-error approach. The category matching rules change throughout the task.

3) The Visual-visual Conditional Associative Learning Test involves learning associations between arbitrary visual stimuli. Before the test, one of six cards with geometric designs is randomly paired to one of six colours. Participants are shown cards with geometric designs and are instructed to choose the colour that the card belongs to, and are given feedback. Through trial and error, participants learn to associate a particular colour to each geometrical design.

4) In the Word Fluency Tasks, participants are instructed to generate words based on a category cue, in a defined period of time (i.e. animals or boys names).

5) Finally, the Subject-ordered Pointing Task involves initiating a series of responses whilst monitoring their execution. Briefly, a series of stimuli are arranged on a sheet of paper. On several successive sheets of paper, the stimuli are presented in a different order. The participant is instructed to point to one stimulus per page, aiming to point to each different stimulus without pointing to the same one twice. Stimuli include representational drawings, abstract images, and words that evoke a low amount of imagery.

All participants completed all of these measures and were tested both on and off dopamine replacement therapy. The delay between the two testing sessions was approximately one week.
PD patients were randomly divided into two groups with order of testing counterbalanced across patients such that one group began the first testing session on dopaminergic medication, and the other first performed testing off medication. Each testing session involved a different version of the tasks listed above, and the order of the tasks was further counterbalanced with half of the participants beginning with one version, and the other half with the other version.

When tested in the OFF state, PD patients made more errors in the Wisconsin Card Sorting Task, and generated fewer words per category on the Word Fluency Tasks compared to their ON state. When tested on their medication, they performed more poorly on the Visual-visual Conditional Associative Learning Task, as well as the Subject-ordered Pointing Task. At its most basic level, the Wisconsin Card Sorting Task, and the Word Fluency Tasks are measures of decision-making, or response selection. Conversely, the Visual-visual Conditional Associative Learning Test and the Subject-ordered Pointing Task involve learning and working memory. Studies of decision-making and response selection have implicated DS, a result that is entirely in line with the results of Gotham and his colleagues. In addition, VS and the prefrontal cortex, two regions that are innervated by VTA, have been shown to mediate association learning and working memory, respectively.

1.4 Functional Magnetic Resonance Imaging

In addition to manipulating the medication status of PD patients, another method for investigating the functions of DS and VS is through the use of functional magnetic resonance imaging (fMRI) with healthy participants. FMRI is a non-invasive technique that allows for the visualization of brain activity by mapping changes in blood flow. FMRI uses an electromagnet to visualize differences in oxygenated and deoxygenated blood, referred to as blood-oxygenation-level dependent responses (BOLD) in the brain. This BOLD response in different brain regions can be correlated with various functions relative to rest or other control functions. The theory behind fMRI is that areas of the brain that recruit more oxygenated blood are more active than areas that do not. While in the fMRI scanner, subjects complete tasks, or just simply rest, and active brain areas can be visualized during these processes. Using healthy participants, fMRI-generated BOLD responses can suggest brain regions that are preferentially correlated with certain functions. Once the cognitive functions have been mapped in healthy individuals using fMRI, testing functions of interest in patient populations that have
demonstrated impairment in the target brain regions can better assess whether these regions are critical for the function under investigation.

1.5 Dorsal Striatum

1.5.1 Anatomy

The striatum can be subdivided functionally into dorsal and ventral aspects. Anatomically, slight cytoarchitectural differences, as well as divergent dopaminergic and glutamatergic afferents, and non-anastomosing blood supplies separate DS and VS. On a macroscopic level, there is no wholly agreed upon point of division. Different anatomical landmarks, such as the internal capsule (MacDonald et al., 2011), or fMRI slices along the z-axis have been used (Postuma and Dagher, 2006). DS is comprised of the bulk of the caudate nucleus and putamen and is vascularized by the lateral lenticulostriate arteries, off of the middle cerebral artery (Feekes and Cassell, 2006). The main neuronal type in the striatum is the medium spiny neuron (MSN). Through a wide range of firing frequencies, dopamine stimulation from SN is rapid and maximal in DS (Wickens et al., 2007b; Zhang et al., 2009). This is a result of a high concentration of dopaminergic afferents to these MSNs. Dopamine Transporter (DAT), a membrane-spanning protein responsible for the synaptic clearance of dopamine, is in high abundance in DS, resulting in rapid clearance, and therefore, short stimulation periods (Wickens et al., 2007b). The anatomical makeup of DS, with high concentrations of dopaminergic afferents and DAT, results in almost binary responding, with maximal stimulation at a range of dopamine firing frequencies, followed by rapid clearance of synaptic dopamine. Through reciprocal glutamatergic afferents, DS is connected to the primary, supplementary, and pre-motor cortex, as well as to the dorsolateral prefrontal cortex, parietal association cortex, and somatosensory cortex (Leh et al., 2008). As a result of the rapid binary responding of DS, coupled with reciprocal connections to effector areas such as the motor cortex, and dorsolateral prefrontal cortex, it is well-adapted to perform functions such as deciding among alternatives and response selection.
1.5.2 Function

Cognitive functions ascribed to DS have been delineated using a variety of methods including non-human animal models, fMRI, and human pathological conditions such as strategic DS lesions secondary to strokes, or physiological impairment due to dopamine deficiency in PD. Much of the research surrounding DS-mediated cognition can be categorized into one of two bodies of literature, the first implicating DS in executive functions with respect to selection of responses and actions, and the second in learning motor sequences or associations between stimuli and motor responses. For example, one of the most common executive functions investigated in PD is attentional set-shifting (Cools et al., 1984; Downes et al., 1989; Owen et al., 1992; Van Spaendonck et al., 1996), specifically with respect to visual discrimination learning. Briefly, subjects are presented with stimuli that contain two stimulus dimensions (i.e. colour and shape) and through feedback-guided trial and error, participants must determine which stimulus dimension is the to-be-attended one, and which particular exemplar within a category is the target. Over a series of trials, the correct stimulus dimension will change, and the participant must learn the new rule. The change can either be intra-dimensional (i.e. correct choice switched from the colour blue to the colour red), or extra-dimensional (i.e. correct choice switched from colour to shape). Many investigations have concluded that PD patients show impairments in extra-dimensional set-shifting when in the OFF state relative to PD patients in the ON state (Cools et al., 1984; Downes et al., 1989; Owen et al., 1992; Roberts et al., 1998). Impairments in the OFF state suggest that set-shifting is DS-mediated, and is remedied with dopamine replacement therapy.

DS has also been implicated in learning associations between stimuli and responses (See Ashby et al., 2007; Yin and Knowlton, 2006 for reviews), including early goal-directed or feedback-guided learning (Balleine et al., 2009; Boettiger and D'Esposito, 2005; Brovelli et al., 2011; Brown and Stern, 2013; Foerde et al., 2013; Garrison et al., 2013; Hart et al., 2013). Despite considerable evidence suggesting that DS mediates learning, in some cases, learning is preserved in non-human animals (Attalah et al., 2007; McDonald and Hong, 2004; Ragozzino, 2007), and in patients (Ell et al., 2006; Exner et al., 2002; Shin et al., 2005) with DS lesions, casting doubt on this notion. Furthermore, learning is often worsened by dopaminergic therapy in PD (See MacDonald and Monchi, 2001 for a review).
In an elegant experiment, Atallah and colleagues (2007) investigated the role of DS in learning versus selecting responses relying on learned associations. In a Y-maze task using odour cues, Atallah and colleagues observed impairment in rats’ ability to consistently select a rewarded versus unrewarded arm for animals receiving infusions of inhibitory gamma-amino butyric acid (GABA) agonist into DS compared to a saline solution during the learning phase of the experiment. At first blush, this seemed to suggest that animals receiving inhibitory infusions to DS were learning associations between odour cues and rewards more poorly. When both groups were later tested once the infusions were stopped, however, both experimental and control groups performed the selection task similarly. This demonstrated that associations were learned equally well for both experimental and control (i.e. saline-infused) groups during Session 1 and suggested that inhibition of DS impaired the animal’s ability to use learned associations to perform selections reliably. To complement this interesting finding, in another study, they found that GABA infusions to DS, at test phase, resulted in impaired selection performance compared to saline infusions to DS, although both groups had previously shown identical learning of these odour-reward associations during the training phase. Taken together, these studies challenge the direct involvement of DS in learning and instead suggest a more specific role in performing selections based on previously-learned associations.

This discrepancy in the literature regarding DS’ role in learning is potentially explained by increasing evidence that DS mediates decision-making, coupled with a methodological feature of many fMRI learning studies. Investigations of learning frequently do not separate enacting decisions from learning per se (Jessup and O'Doherty, 2011; McDonald and White, 1993). For example, typical paradigms proceed as follows: a) a stimulus is presented and participants decide among a set of responses, b) feedback about accuracy of response is provided, through which stimulus-response associations are learned. In fMRI studies, a) selecting and enacting a response, and b) learning from feedback are treated as a single event, neural activity is merged, and all significantly-activated brain regions are ascribed a role in learning (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Jessup and O'Doherty, 2011; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008). As mentioned before, learning is often impaired in patients with PD when they are tested on dopaminergic medication. In a stimulus-response learning experiment performed in my lab, patients learned stimulus-response associations via feedback during one session, and subsequently performed the learned
associations during the following day in the absence of feedback. PD patients learned the associations more poorly when on dopaminergic medication, compared to off dopaminergic medication (Vo and Hiebert et al., 2014 submitted). These results cast doubt upon the role of DS in learning.

1.6 Ventral Striatum

1.6.1 Anatomy

VS is vascularized by the recurrent artery of Heubner, a branch of the anterior cerebral artery (Feekes and Cassell, 2006), and is composed of the nucleus accumbens (NAcc), and ventral portions of the caudate nucleus and putamen. As in DS, VS is populated by MSNs. However, MSNs in VS are smaller, and the dopaminergic input to VS is less dense compared to DS. Consequently, a dopamine pulse from VTA will stimulate VS more slowly, and with more variable intensity (Wickens et al., 2007b). In an experiment by Zhang and colleagues (2009), neurons in rats were stimulated by nicotine, and firing frequency was monitored in both the dorsolateral striatum, and NAcc, homologous to DS and VS respectively in humans. In NAcc, dopamine responses to nicotine were graded and incremental, depending on the frequency and intensity of the stimulation. This is in stark contrast to the maximal stimulation of DS in response to even the lowest frequency and intensity. In addition, VS stimulus durations are longer due to lower DAT concentration (Wickens et al., 2007b). These characteristics of VS suggest that it is adapted to a different function than DS, and perhaps that these attributes suit it to associating events or stimuli over time, for example in associative learning. The presence of specific glutamatergic connections aids in confirming this function. VS is connected, reciprocally, to the orbitofrontal, anterior cingulate, anterior temporal, as well as several limbic areas including the hippocampus, amygdala and hypothalamus (Kincaid et al., 1998). These areas are heavily involved in encoding and associating salient environmental aspects.

1.6.2 Function

Initially, VS was considered a region specialized for reward learning and processing (Camara et al., 2010; Cools et al., 2002; Delgado et al., 2000; Delgado, 2007; Knutson and Cooper, 2005; O’Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010). However, some recent
studies implicate VS in learning situations that are devoid of reward, punishment, or any feedback at all, challenging this specialization (Feigin et al., 2003; Ghiladri et al., 2007; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2004; Shohamy et al., 2006; Tremblay et al., 2010).

A result often reported is that VS and DS are both ascribed a role in feedback-based learning. For example, Delgado et al. (2005) examined learning to associate cards with concepts of ‘high’ versus ‘low’ via feedback using fMRI. As is typical, they considered response selection (i.e., high vs. low decisions), and feedback portions of each trial as a single event. Compared to baseline, they found significant peaks in dorsal caudate nucleus, and VS; concluding that both mediate learning. Furthermore, in a recent meta-analysis of 35 fMRI studies of reinforcement learning through feedback – the majority of which confounded neural activity for response selection and feedback phases – found both VS and DS to be equally strongly associated with performing feedback-based learning. We argue that combining decision-making, and feedback events causes ambiguity. A plausible alternative explanation, consequently, is that preferential DS activation could relate to the response selection operation, whereas VS activity reflected learning through feedback. Exploring this possibility was the central aim of the studies presented here.

1.7 Hypotheses

We hypothesized that VS is implicated in learning stimulus-response associations via deterministic feedback (i.e. feedback that always reflects the accuracy of a response) and that DS mediates response selection. To probe VS and DS functions separately, we employed two methods, carried out in two separate experiments. In our fMRI paradigm, we modeled the stimulus-response, or decision-making phase, separately from the feedback, or learning phase, to reveal brain areas that are specifically active in each. In our study with PD patients, we contrasted performance in a similar stimulus-response task both on and off their dopaminergic medication. To review, functions mediated by DS have been shown consistently to be impaired off dopamine replacement therapy, and improved with medication. However, functions mediated by VTA-innervated regions, such as VS, are impaired on medication due to dopamine overdose, and are normal off medication. Contrasting PD patients on and off dopamine replacement therapy, therefore, allows for a double dissociation of function.
1.8 Objectives

The objectives of this study were to:

1. Delineate the functions of DS and VS in stimulus-response learning

2. Determine how dopaminergic therapy affects stimulus-response learning versus performing decisions based on that learning

The overarching objective of the two separate investigations that follow is to clarify the functions of DS and VS, to provide a better understanding of cognition in PD, and to predict the effect of dopaminergic therapy on these functions.
1.9 References


Chapter 2

2 Striatum in stimulus-response learning via feedback and decision-making

Cognitive deficits are recognized in PD. Understanding cognitive functions mediated by the striatum can clarify some of these impairments, and inform treatment strategies. DS, an impaired region in Parkinson’s disease, has long been implicated in stimulus-response learning. However, most investigations fail to separate acquisition of associations between stimuli, responses, or outcomes (i.e., learning), and expression of learning through response selection, and decision enactment, confounding these separate processes. Using neuroimaging, we provide evidence to support the view that DS does not mediate stimulus-response learning from feedback, but rather underlies decision-making once associations between stimuli and responses are learned.

In the experiment, 11 males and 5 females (mean age 22) learned to associate abstract images to specific button-press responses through deterministic feedback in Session 1. In Session 2, they were asked to provide responses learned in Session 1. Feedback was omitted in Session 2, precluding further feedback-based learning in this session. Using fMRI, DS activation in healthy, young participants was observed at the time of response selection, and not during feedback, when learning presumably occurs. Moreover, DS activity increased across the duration of Session 1, peaking after most associations had been well learned, and was equivalent across Sessions 1 and 2, even though feedback-guided learning was precluded in Session 2. Preferential VS activity occurred during feedback, and was maximal early in learning.

Taken together, the results suggest that the VS underlies learning associations between stimuli and responses via feedback, whereas the DS mediates enacting decisions.

A version of this chapter is under review at NeuroImage: Hiebert, N. M., Vo, A., Hampshire, A., Owen, A. M., Seergobin, K. N., MacDonald, P. A. Striatum in stimulus-response learning via feedback and decision-making.
2.1 Introduction

PD is a common movement disorder, though cognitive impairments are now recognized. Movement symptoms associated with PD appear when degeneration of dopamine-producing cells of the SN is sufficient to seriously interrupt dopamine supply to DS (Kish et al., 1988). In contrast, dopamine-producing cells in the VTA are relatively spared, and dopamine supply to its efferent, VS, along with limbic and prefrontal cortices, is better preserved (Haber and Fudge, 1997). The striatum is the input region for a collection of subcortical nuclei, known as the basal ganglia that are generally implicated in movement regulation, and increasingly, in cognitive functions. VS includes the NAcc and ventral portions of the caudate nucleus and putamen, and is considered separately from DS—comprising the bulk of the caudate, and putamen—because they have distinct dopaminergic inputs (Voorn et al., 2004; Wickens et al., 2007), vascular supplies (Feekes and Cassell, 2006), and functions (Cools, 2006; MacDonald and Monchi, 2011). As the pathophysiology predicts, dopamine replacement medications, such as ι-dopa or dopamine receptor agonists, considerably improve DS-mediated symptoms, both motor and cognitive. However, in PD, these medications impair cognitive functions performed by VTA-innervated regions, such as VS, seemingly a result of dopamine overdose of these relatively dopamine-replete regions (Cools, 2006). Accordingly, understanding cognitive functions mediated by these striatal sub-regions is an important aim. Along with motor symptoms, this knowledge could guide medication titration to address cognitive symptoms that are ranked highly as a cause of reduced quality of life in PD (Barone et al., 2009; Schrag et al., 2000).

As stated previously, DS has long been implicated in learning associations between stimuli and responses (See Ashby et al., 2007; Yin and Knowlton, 2006, for reviews). However, in some cases, learning is preserved in patients, and non-human animals with DS lesions (Atallah et al., 2007; Ell et al., 2006; Exner et al., 2002; McDonald and Hong, 2004; Ragozzino, 2007; Shin et al., 2005), casting doubt on this notion. Furthermore, learning is often worsened by dopaminergic therapy in PD, not expected if DS mediates learning stimulus-response associations. The result that DS mediates learning could be a misinterpretation due to a methodological feature, where enacting decisions is coupled with learning (Jessup and O'Doherty, 2011; McDonald and White, 1993). In fMRI studies, brain activation resulting from making a decision and receiving feedback is grouped together, and all activated brain areas are
ascribed a role in learning (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Jessup and O’Doherty, 2011; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008).

VS has been implicated in reward learning and processing (Camara et al., 2010; Cools et al., 2002; Delgado et al., 2000; Delgado, 2007; Knutson and Cooper, 2005; O’Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010). However, some recent studies suggest that VS may also be involved in learning situations that are devoid of reward, challenging this specialization (Feigin et al., 2003; Ghiladri et al., 2007; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2004; Shohamy et al., 2006; Tremblay et al., 2010).

Our aim was to directly test the contention that DS underlies early learning of associations between stimuli and responses. In the experiment, participants learned to associate abstract images and specific button-press responses through feedback. Using fMRI, we investigated whether DS was differentially activated at the time of response selection versus during feedback-based learning.

2.2 Method

2.2.1 Participants

Sixteen healthy, young adults participated in this experiment (11 males and 5 females). Participants had a mean (SEM) age and education level of 22 (0.56) and 16.20 (0.31) years, respectively. Two participants were excluded from the analyses. One participant failed to reach a pre-set learning criterion as described further below, and imaging data from the other participant did not sync correctly with the behavioural task. Participants abusing alcohol, prescription or street drugs, or taking cognitive-enhancing medications including Methylphenidate (Ritalin) were excluded from participating. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study. All participants provided informed written consent to the approved protocol before beginning the experiment, according to the Declaration of Helsinki (1991).
2.2.2 Experimental Design

All participants performed a task during which they learned to associate 12 abstract images with one of three button-press responses in Session 1. Images were computer-generated with GroBoto (Braid Art Labs, Colorado Springs, USA). On each trial, an abstract image appeared in the centre of a projection screen until the participant responded with a button-press. Feedback (i.e., ‘Correct’ or ‘Incorrect’) was provided after every response, and in this way, participants learned to associate each of the abstract images with the appropriate button-press response through trial and error in Session 1. Trials were organized into blocks. After each block, participants were provided with a percentage score, summarizing their learning performance. A minimum learning criterion of 74% on two successive blocks was required to complete Session 1. The performance criterion was selected for two reasons: 1) piloting data indicated that most participants could achieve 74% in a reasonable number of blocks, and 2) our aim was to investigate early learning. Before proceeding to Session 1, participants received 20 practice trials with different images from those employed during the main experimental sessions. In Session 2, recall of the correct button-press response for each of the abstract images presented during Session 1 was tested. No feedback was provided, to preclude new feedback-based learning during this session.

Sessions 1 and 2 of were performed in the fMRI scanner. Twelve abstract images were used in the experiment (Fig. 2.1). There were 24 trials per block in Session 1, with each abstract image occurring twice in random order. Four images were assigned to each the second, third, and fourth button on the button box, and participants pressed these buttons with their index, middle, and ring fingers, respectively. A button-press response was required to advance from the feedback phase to the next trial. In this way, motor responses were included in both decision-making and feedback phases.
Trials in Session 1 proceeded as follows: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented until a button-press response (mean range: 564-4200 ms); (iv) a blank screen appeared for 1400-1800 ms; (v) feedback (i.e., “Correct” or “Incorrect”) appeared for 1000-1500 ms, the screen went blank until the participant pressed the first button with his/her thumb to advance to the next trial (mean range: 1800-6000 ms); (vi) a blank screen appeared for 400-800 ms.

Two distractor tasks (data not shown) were employed between Sessions 1 and 2 to prevent rehearsal of stimulus-response associations. In Session 2, participants performed three blocks of 24 trials, in which the same 12 images studied during Session 1 were presented in random order, twice per block. Participants provided the button-press response that they had learned for each image in Session 1. No feedback regarding accuracy was provided, precluding new learning. Parameters for each trial in Session 2 were otherwise identical to those in Session 1. Figure 2.2A and B present example trials in Sessions 1 and 2.
The experiment was completed in the fMRI scanner with healthy participants. **A. Session 1:** Participants learned to associate 12 abstract images with a button-press response through feedback. Trials in Session 1 proceeded as follows: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented until a button-press response (mean range: 564-4200 ms); (iv) a blank screen appeared for 1400-1800 ms; (v) feedback (i.e., “Correct” or “Incorrect”) appeared for 1000-1500 ms, the screen went blank until the participant pressed the first button with his/her thumb to advance to the next trial (mean range: 1800-6000 ms); (vi) a blank screen appeared for 400-800 ms. The time between the response, and the onset of the feedback, and the inter-trial intervals were randomly jittered between 1400-1800 ms to maximize differences in BOLD responses between the stimulus-response and feedback events. **B. Session 2:** During the test phase, stimulus-specific button-press responses for stimuli learned in Session 1 were performed in the absence of feedback. The parameters for each trial in Session 2 were otherwise identical to those in Session 1.

### 2.2.3 Behavioural Data Analysis

Efficiency of encoding stimulus-response associations across Session 1 was estimated by the rate of change of correct responses across the session. The slope of change was measured by summing the scores obtained at the end of each block over the total number of blocks required...
to reach the pre-set learning criterion (i.e., standard slope of the linear regression function, Microsoft Excel, 2011), as follows:

\[
b = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sum (x - \bar{x})^2}
\]

where \( b \) is the slope, and \( x \) and \( y \) are the sample means of the number of blocks and block scores, respectively. Slopes were calculated in the same manner separately for the first and second halves of Session 1 to investigate differential rates in learning across the session. The percentage of accurate responses in the final block of Session 1 (i.e., the highest accuracy score achieved) measured learning efficacy. In Session 2, decision-making based on previously-learned associations was measured with an adjusted-savings score, calculated as follows: average accuracy in Session 2/accuracy in the last block of Session 1.

2.2.4 FMRI Data Acquisition

FMRI data were collected in a 3 Tesla Siemens Magnetom Trio with Total Imaging Matrix MRI at Robarts Research Institute at the University of Western Ontario. We obtained a scout image for positioning the participant, and T1 for anatomical localization. Number of runs of T2*-weighted functional acquisitions varied depending on the participant’s rate of learning, but ranged from a minimum of one to a maximum of three runs. Each run consisted of three blocks of 24 trials. Distractor tasks were administered after Session 1. All participants performed Session 2 as the final run. All runs lasted on average eight minutes with one whole brain image consisting of 43, 2.5 mm-thick slices taken every 2.5 s. The field of view was oriented along the anterior and posterior commissure with a matrix of 88 × 88 pixels, an isotropic voxel size of 2.5 × 2.5 × 2.5 mm³. The echo time was 30 ms, and the flip angle was 90°.

2.2.5 FMRI Data Analysis

Statistical Parametric Mapping version 5 (SPM5; Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used in conjunction with Matrix Laboratory (MATLAB; MathWorks, Inc., Natick, Massachusetts, United States) to complete fMRI analysis. The first ten functional volumes (i.e., 25 sec) were discarded, during which participants became familiar with the testing situation. Images were slice-time corrected,
reoriented for participant motion, spatially normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8 mm full-width half-maximum Gaussian kernel, and high-pass filtered (0.0056 Hz).

Individual participants’ data were modeled using fixed effects analyses in SPM5. Predictor functions were formed by convolving onsets and durations of psychological events of interest, namely stimulus-response and feedback events, with the canonical hemodynamic response function. The stimulus-response event was defined as the time from onset of the abstract image until the participant made a button-press response. The feedback event was defined as the time from onset of feedback, (i.e., “Correct” or “Incorrect”) for 1000-1500 ms, until the button-press to advance to the next trial. In this way, a motor response was included in both stimulus-response, and feedback events. General linear models (GLM) were created for both stimulus-response, and feedback for Session 1. The first GLM investigated regional BOLD activity associated with the stimulus-response event relative to rest for all trials in a block. Number of regressors corresponded to number of blocks to reach the pre-set learning criterion in Session 1. An analogous model was created for feedback events, which convolved onsets and durations of feedback in Session 1. Finally, a GLM investigated stimulus-response events relative to rest in Session 2 for all trials in a block, with three regressors corresponding to the three blocks performed by all participants.

To investigate brain areas with activity that paralleled learning, models examining activity early and late for both stimulus-response and feedback events in Session 1 were created. Because number of blocks to reach the pre-set learning criterion varied across participants, individualized contrasts were implemented. Session 1 was divided in half, and blocks in the first half were considered early, and blocks in the second half were considered late. Contrast images were collected and examined together at the group level in a $t$-test in SPM5 for both stimulus-response and feedback events separately. A secondary analysis separated correct and incorrect feedback events, modeling them separately.

### 2.2.5.1 Region of Interest Analysis

To test our predictions regarding the involvement of striatum in stimulus-response learning and decision-making, regions of interest (ROIs) were created using the MarsBar toolbox for SPM5
We selected separate ROIs for VS and DS. For VS, coordinates \((x = \pm 10,\ y = 8,\ z = -4)\) were taken from Cools et al. (2002), centering on the NAcc, and including portions of the posterior ventral caudate and putamen. Another ROI for VS was created to incorporate anterior portions of the VS. Coordinates for the anterior VS ROI \((x = \pm 12,\ y = 18,\ z = -6)\) were taken from MacDonald et al. (2011). Brovelli et al. (2011) employed a stimulus-response learning paradigm with healthy participants using fMRI. Peaks of activity that were related to learning were reported in the bilateral head of the dorsal caudate nucleus, as well as in anterior and middle portions of the left dorsal putamen, and anterior right putamen. The activation that centered on the left dorsal caudate head, and not the surrounding cortex, served as the centre of our dorsal caudate ROI \((x = 18,\ y = 24,\ z = 6)\). The average coordinates in MNI space of the left and right dorsal anterior putamen activations served as the centre of our dorsal putamen ROI \((x = \pm 29,\ y = 9,\ z = 6)\). Spheres with a radius of 5 mm were centred on the ROIs discussed above. Peaks within the striatum were reported at a significance level of \(p < 0.05\), corrected for multiple comparisons, using Bonferroni correction for the eight ROIs in the analysis. Figure 2.3 depicts each ROI in MNI space. Striatal areas were defined using the Harvard-Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). All \(x,\ y,\ z\) values are reported in MNI space.
Regions of interest (ROIs) used in the fMRI analysis. **A.** Spherical ROI for dorsal caudate (±18, 24, 6) with a radius of 5mm. **B.** Spherical ROI for dorsal putamen (±29, 9, 6) with a radius of 5mm. Coordinates for the dorsal caudate and dorsal putamen ROI were taken from Brovelli et al. (2011). **C.** Spherical ROI for posterior VS (±10, 8, -4) with a radius of 5mm. Coordinates were taken from Cools et al. (2002). **D.** Spherical ROI for anterior VS (±12, 18, -6) with a radius of 5mm. Coordinates were taken from MacDonald et al. (2011). * When average BOLD signal was examined using beta values, beta values from the left and right dorsal caudate, and dorsal putamen were combined to obtain an average signal change for DS. An average signal change for VS was similarly obtained by combining the left and right posterior VS, and anterior VS beta values.

Beta values were used to determine the level of activation present in VS and DS in each of the contrasts of interest described above. Further, average beta values for DS and VS are presented graphically in Figure 2.5. For the figures, average beta values for DS in each contrast of interest were obtained by averaging beta values of the bilateral dorsal caudate and putamen ROIs. Average beta values for VS were similarly calculated by combining beta values for the bilateral anterior and posterior VS ROIs.
2.2.5.2 Correlation Analysis

Correlation analyses were carried out to identify brain regions that were associated with individual differences in a) efficiency of learning stimulus-response associations in Session 1 and b) accuracy of stimulus-response decisions in Sessions 1 and 2. Efficiency of learning was modeled by ranking participants with respect to their stimulus-response learning slopes. Contrasts for stimulus-response events were rank ordered across participants from slowest to fastest learners. Each participant’s learning slope was entered as a covariate respecting this rank order. A similar approach was implemented to investigate brain regions that correlated with accuracy of stimulus-response decisions for Sessions 1 and 2. The covariate in these analyses was the scores obtained in the final block of Session 1 and the average score obtained in Session 2, ordered from lowest to highest. Striatal regions with activity positively correlating with learning slope or accuracy were thus determined. ROIs were defined based on peak activations in striatum for these correlations. Average neural activity for each participant in the ROI was extracted and plotted against a) learning slope, b) Session 1 final block score, and c) Session 2 average score. Brain regions that correlated with learning slope, or more accurate decision-making in Session 1 might simply index factors such as differences in stimuli familiarity, or in fatigue across participants, relating to number of learning blocks performed to reach criterion. To eliminate these confounds, we also correlated average activity extracted from the ROIs for the first three blocks of Session 1 with learning slope and accuracy achieved in the final block of Session 1.

There were fourteen contrasts of interest involving Sessions 1 and 2: (i) stimulus-response events versus rest in Session 1; (ii) feedback events versus rest in Session 1; (iii) stimulus-response versus feedback events in Session 1; (iv) early stimulus-response events versus rest in Session 1; (v) late stimulus-response events versus rest in Session 1; (vi) early feedback events versus rest in Session 1; (vii) late feedback events versus rest in Session 1; (viii) early stimulus-response versus feedback events in Session 1; (ix) late stimulus-response versus feedback events in Session 1; (x) correct versus incorrect feedback in Session 1; (xi) stimulus-response events versus rest in Session 2; (xii) correlation of stimulus-response-related activation in striatum and learning slope; (xiii) correlation of stimulus-response-related activation in striatum
and accuracy in final block of Session 1; and (xiv) correlation of stimulus-response-related activation in striatum and accuracy in Session 2.

2.3 Results

2.3.1 Behavioural Results

Behavioural data for Sessions 1 and 2 are presented in Table 2.1. Efficiency of learning stimulus-response associations was estimated by the slope of accuracy scores achieved for each block over the total number of blocks required to reach the pre-set learning criterion using the standard slope of the linear regression function in Microsoft Excel (2011). Learning slopes were significantly greater than zero ($t = 10.32$, $p < 0.001$); evidence that participants successfully learned stimulus-response associations through feedback across Session 1. Participants on average required five blocks to complete Session 1. We expected that greater learning would occur early relative to late in the session. To test this assumption, Session 1 was divided into early and late, to investigate changes in the rate of learning. Indeed, the slope of learning was significantly steeper early relative to late in the session ($t = 4.00$, $p = 0.002$; Fig. 2.4).

![Figure 2.4: Average learning slope early and late in Session 1 of Experiment 1](image)

Average learning slopes were calculated for early and late halves of Session 1. Error bars represent standard error of the mean. Participants’ scores obtained after each block in Session 1 were first divided into early and late halves, and slopes were calculated for each phase using the standard slope of the linear regression function in Microsoft Excel (2011). Asterisks indicate a statistically significant difference between the early and late slopes (***$p < 0.01$).
The percentage of correct responses in the final block in Session 1 was not statistically different from accuracy in the initial block of Session 2 ($t = 1.79, p = 0.097$, with numerically greater accuracy in Session 1 than Session 2), confirming that no new learning occurred in Session 2 where feedback was omitted. In Session 2, an adjusted-savings score was obtained to measure retention of associations learned in Session 1 (Table 2.1). On average, in Session 2, participants had a mean (SEM) percentage accuracy of 91.8% (0.01).

### Table 2.1: Behavioural results of Experiment 1

<table>
<thead>
<tr>
<th></th>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning slope</td>
<td>0.143</td>
<td></td>
</tr>
<tr>
<td>Final block score (%)</td>
<td>92.86</td>
<td>89.00</td>
</tr>
<tr>
<td>First block score (%)</td>
<td></td>
<td>99.25</td>
</tr>
<tr>
<td>Adjusted-savings (%)</td>
<td>0.014</td>
<td>5.70</td>
</tr>
<tr>
<td>adjusted-savings (%)</td>
<td></td>
<td>1.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.81</td>
</tr>
</tbody>
</table>

All values reported are means (SEM). Learning slope was measured by the standard slope of the linear regression function in Microsoft Excel (2011) using the scores obtained at the end of each block over the total number of blocks required to reach the pre-set learning criterion. Adjusted-savings (%) in Session 2 was calculated by the following equation: (average score in Session 2/ score in the last block of Session 1).

### 2.3.2 FMRI Results

Significant activations in ROIs are reported at a significance level of $p < 0.05$, corrected for multiple comparisons (Table 2.2). Analyses of beta values for contrasts of interest are presented in Figure 2.5. All coordinates ($x, y, z$) reported are in MNI space.
Figure 2.5: Mean beta values for VS and DS for contrasts of interest in Experiment 1

Mean beta values for VS were determined by combining beta values in the left and right posterior VS and anterior VS. Mean beta values for DS were similarly determined by combining beta values in the left and right dorsal caudate and putamen. Mean beta values for DS and VS are presented for each contrast of interest. Error bars represent standard error of the mean. SR – Stimulus-response event; FB – Feedback event. A. Mean beta values for SR events minus rest and FB events minus rest in Session 1. B. Mean beta values for FB events minus rest early and late in Session 1. C. Mean beta values for SR events minus rest early and late in Session 1. D. Mean beta values for FB minus SR events in Session 1. E. Mean beta values for FB minus SR early and late in Session 1. F. Mean beta values for correct minus incorrect FB events. G. Mean beta values for SR events minus rest in Session 2. Asterisks indicate a statistically significant difference in each condition from zero (*$p < 0.05$, •$p < 0.1$).

2.3.2.1 Session 1

2.3.2.1.1 Enacting stimulus-response decisions and receiving feedback: Overall

Activation in the left dorsal caudate during stimulus-response decision events relative to rest trended toward significance ($t = 2.57, p = 0.089$). During this period, stimuli are presented, and a specific response is selected and enacted. For the stimulus-response minus feedback events contrast, no significant striatal activation occurred.
Significant activation occurred in the right posterior VS ($t = 3.48, p < 0.05$) in the feedback event relative to rest. During the feedback phase, the response outcome was revealed and participants learned whether or not a stimulus was associated with a specific response. DS activity was not detected during the feedback phase, even using a liberal criterion of $p < 0.05$, uncorrected for multiple comparisons. Significant activation occurred in the left and right posterior VS ($t = 3.02, p < 0.05$, and $t = 3.35, p < 0.05$, respectively) in the feedback minus stimulus-response events contrast.

### 2.3.2.1.2 Enacting stimulus-response decisions and receiving feedback: Early

From our behavioural analyses, learning to associate stimuli to specific button-press responses was maximal early, and slowed late in Session 1. We predicted that brain regions implicated in learning would be most active early in Session 1. When stimulus-response events were examined during the early part of Session 1 alone, no striatum activity was associated significantly with stimulus-response events relative to rest or relative to feedback events, even when we used a liberal threshold of $p < 0.05$, uncorrected for multiple comparisons.

For feedback events relative to rest early in Session 1, significant activation occurred in the right posterior VS ($t = 3.19, p < 0.05$), and trended toward significance in the right anterior VS ($t = 2.53, p = 0.07$). Significant activation occurred in the left posterior VS ($t = 3.36, p < 0.05$), right anterior VS ($t = 3.81, p < 0.05$), and right posterior VS ($t = 4.03, p < 0.05$) for the contrast of feedback minus stimulus-response events early in Session 1.

### 2.3.2.1.3 Enacting stimulus-response decisions and receiving feedback: Late

Considering trials late in Session 1 only, significant activation in the right dorsal putamen ($t = 3.19, p < 0.05$) occurred for the stimulus-response minus rest contrast as well as the stimulus-response minus feedback events contrast ($t = 2.95, p < 0.05$).

For the reverse contrast (i.e., feedback minus stimulus-response events) significant activation occurred in the left anterior VS ($t = 2.12, p < 0.05$), left and right posterior VS ($t = 3.37, p < 0.05$ and $t = 3.81, p < 0.05$, respectively), and trended towards significance in the right anterior VS ($t = 1.66, p = 0.055$).
2.3.2.1.4 Correct versus incorrect feedback

Brain regions that mediate learning should be sensitive to the outcomes associated with actions (i.e., feedback). Significant bilateral posterior VS activation arose (Left posterior VS: $t = 3.86, p < 0.05$; Right posterior VS: $t = 4.33, p < 0.05$), and right anterior VS ($t = 2.72, p < 0.05$) for correct minus incorrect feedback. For incorrect minus correct feedback, there were no significant striatal activations. Therefore, overall, there were no significant peaks in DS for correct minus incorrect or for incorrect minus correct feedback.

2.3.2.2 Session 2

2.3.2.2.1 Enacting stimulus-response decisions in the absence of feedback

Brain regions that mediate feedback-based learning should not be significantly active once stimulus-response decisions are well learned and when no feedback is provided. Significant bilateral dorsal caudate activation arose in the stimulus-response events minus rest contrast (left dorsal caudate: $t = 3.18, p < 0.05$; right dorsal caudate: $t = 3.18, p < 0.05$) in Session 2.
Table 2.2: Significant ROI activations in the contrasts of interest in Experiment 1

<table>
<thead>
<tr>
<th>Anatomical Area</th>
<th>t</th>
<th>p</th>
<th>Anatomical Area</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR events minus rest in Session 1</td>
<td></td>
<td></td>
<td>FB events minus rest in Session 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left dorsal caudate</td>
<td>2.57</td>
<td>0.089*</td>
<td>Right posterior VS</td>
<td>3.48</td>
<td>0.016</td>
</tr>
<tr>
<td>SR events minus rest late in Session 1</td>
<td></td>
<td></td>
<td>FB events minus rest early in Session 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right dorsal putamen</td>
<td>3.19</td>
<td>0.015</td>
<td>Right anterior VS</td>
<td>2.53</td>
<td>0.070*</td>
</tr>
<tr>
<td>FB minus SR events in Session 1</td>
<td></td>
<td></td>
<td>Right posterior VS</td>
<td>3.03</td>
<td>0.021</td>
</tr>
<tr>
<td>Left posterior VS</td>
<td>3.02</td>
<td>0.022</td>
<td>FB events minus rest late in Session 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right posterior VS</td>
<td>3.35</td>
<td>0.0099</td>
<td>Right posterior VS</td>
<td>2.54</td>
<td>0.068*</td>
</tr>
<tr>
<td>SR minus FB events late in Session 1</td>
<td></td>
<td></td>
<td>FB minus SR events early in Session 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right dorsal putamen</td>
<td>2.95</td>
<td>0.026</td>
<td>Left posterior VS</td>
<td>3.36</td>
<td>0.0097</td>
</tr>
<tr>
<td>FB correct versus incorrect trials in Session 1</td>
<td></td>
<td></td>
<td>Right anterior VS</td>
<td>3.81</td>
<td>0.0031</td>
</tr>
<tr>
<td>Correct minus Incorrect</td>
<td></td>
<td></td>
<td>Right posterior VS</td>
<td>4.03</td>
<td>0.0018</td>
</tr>
<tr>
<td>Left anterior VS</td>
<td>2.59</td>
<td>0.061*</td>
<td>FB minus SR events late in Session 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left posterior VS</td>
<td>3.86</td>
<td>0.0027</td>
<td>Left anterior VS</td>
<td>2.12</td>
<td>0.022</td>
</tr>
<tr>
<td>Right anterior VS</td>
<td>2.72</td>
<td>0.045</td>
<td>Left posterior VS</td>
<td>3.37</td>
<td>0.0012</td>
</tr>
<tr>
<td>Right posterior VS</td>
<td>4.33</td>
<td>0.0008</td>
<td>Right anterior VS</td>
<td>1.66</td>
<td>0.055*</td>
</tr>
<tr>
<td>SR events minus rest in Session 2</td>
<td></td>
<td></td>
<td>Right posterior VS</td>
<td>3.81</td>
<td>0.0004</td>
</tr>
<tr>
<td>Left dorsal caudate</td>
<td>3.18</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right dorsal caudate</td>
<td>3.18</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coordinates of each ROI are as follows: Dorsal Caudate (x = ± 18, y = 24, z = 6), Dorsal Putamen (x = ± 29, y = 9, z = 6), Posterior VS (x = ± 10, y = 8, z = -4) and Anterior VS (x = ± 12, y = 18, z = -6). Striatal regions that trended toward significance are reported with an asterisk (*).
2.3.2.3 Regional brain activity and performance correlations

Results from the correlation analyses are presented in Table 2.3. Activity in brain regions that underlie learning stimulus-response associations should correlate with rate or efficiency of learning. There was a significant positive correlation between average VS activation across all of Session 1, and slope of learning ([18, 14, -11], $t = 4.47$, $r = 0.79$, $p < 0.001$; Fig. 2.6A). VS activation was stronger in participants who completed Session 1 in fewer blocks of learning trials. The correlation between average VS activation across only the first three blocks in Session 1 and learning slope also held, ([18, 14, -11], $t = 4.47$, $r = 0.79$, $p < 0.001$; Fig. 2.6A), reducing the likelihood that our correlation owed to differences across participants in number of blocks completed, familiarity with stimuli, or fatigue. Average DS activity across Session 1 was marginally significantly correlated with learning rate ($t = 1.86$, $p = 0.043$).

Average level of DS activity across all blocks, and the first three blocks of Session 1 did correlate significantly with higher overall accuracy achieved in the final block of Session 1 ([12, 8, 10], $t = 3.59$, $r = 0.72$, $p < 0.002$ & [-27, 2, 13], $t = 3.40$, $r = 0.75$, $p < 0.003$ respectively; Fig. 2.6C and D). Greater DS activation occurred in participants who ultimately achieved highest accuracy in stimulus-response decisions. Levels of DS activity also correlated significantly with stimulus-response decision accuracy in Session 2 ([21, 8, 4], $t = 3.70$, $r = 0.73$, $p < 0.002$; Fig. 2.6E), where no feedback was provided, and hence, feedback-based learning was precluded. Taken together, these results suggest that DS mediates decision enactment rather than learning per se. Mean VS activity across all, and the first three blocks of Session 1 also correlated with higher final performance scores ([21, 17, -8], $t = 4.13$, $r = 0.77$, $p < 0.001$ & [15, 11, -5]; $t = 3.41$, $r = 0.71$, $p < 0.003$ respectively).
Figure 2.6: Correlations of activations in striatum and learning slope and accuracy performance in Experiment 1

Beta values for each participant are presented. Error bars represent standard error of the mean. **A.** Correlation between mean signal change in the VS (18, 14, -11) and slope of learning in Session 1. **B.** Correlation between mean signal change in the VS (-18, 29, -2) for the first three blocks and slope of learning in Session 1. **C.** Correlation between mean signal change in the DS (12, 8, 10) and final percentage correct achieved in the final block in Session 1. **D.** Correlation between mean signal change in the DS (3, 8, 10) for the first three blocks and final percentage correct achieved in Session 1. **E.** Correlation between mean signal change in the DS (-24, 8, 4) and percentage correct in Session 2.
Table 2.3: Coordinates (x, y, z) and cluster sizes of significant activations in the correlation analysis in MNI space in Experiment 1

<table>
<thead>
<tr>
<th>Anatomical Area</th>
<th>Cluster Size</th>
<th>t statistic</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation correlated with slope of learning in Session 1 for SR events</td>
<td>Right ventral putamen</td>
<td>38</td>
<td>4.47</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Activation in the first three blocks of Session 1 correlated with slope of learning in Session 1 for SR events</td>
<td>Right ventral putamen</td>
<td>9</td>
<td>3.38</td>
<td>-18</td>
<td>29</td>
</tr>
<tr>
<td>Activation correlated with final block score in Session 1 for SR events</td>
<td>Right dorsal caudate</td>
<td>-**</td>
<td>3.59</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Right ventral putamen</td>
<td>59</td>
<td>4.13</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Activation in the last three blocks of Session 1 correlated with final block score in Session 1 for SR events</td>
<td>Right dorsal caudate</td>
<td>28</td>
<td>3.94</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Activation correlated with average block score in Session 2 for SR events</td>
<td>Left dorsal putamen</td>
<td>9</td>
<td>3.70</td>
<td>-24</td>
<td>8</td>
</tr>
</tbody>
</table>

Coordinates are in standard MNI space as given by SPM5. Striatal regions with a $p_{uncorrected} < 0.005$ are reported. Cluster size is measured in voxels. Significant activations where cluster size was unable to be determined due to another larger cluster adjacently located are reported with a double asterisk (**).

2.4 Discussion

Using a relatively standard paradigm (Boetigger and D’Esposito, 2005) we tested a prevalent view that DS mediates aspects of feedback-based stimulus-response learning (see Ashby et al., 2007; Garrison et al., 2013; Hart et al., 2013; Yin and Knowlton, 2006, for reviews). In the experiment, participants learned to associate abstract images and specific button-press responses through feedback. Using fMRI, the pattern of DS activity was inconsistent with what
would be expected of a brain region mediating learning. DS was preferentially activated at the time of response selection rather than during learning via feedback, and did not appear to track the progression of learning.

### 2.4.1 DS in feedback based learning or decision-making?

We modeled stimulus-response and feedback events independently to examine brain regions associated with performing decisions versus early learning of stimulus–response associations based on feedback, respectively. This design differs from typical learning studies that combine decision-making (i.e., stimulus-response events), and learning from outcomes (i.e., feedback events) into a single event, and implicate all regions differentially activated for these merged processes in learning (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008, but see Aron et al., 2004; Daniel and Pollmann, 2010; Haruno and Kawato, 2006; Helie et al., 2010; Rodriguez, 2009; Waldschmidt and Ashby, 2011 for investigations that separated SR and FB events).

Significant DS activation arose in the stimulus-response or decision-making event of our trials, and not in the feedback or learning phase. DS activation was preferentially increased in the stimulus-response event compared to either rest periods or feedback events. To eliminate the possibility that DS activity arose for stimulus-response events simply because a motor response occurred during this phase, a specific button-press response was also required in the feedback event of our experiment.

There was no significant DS activation in the early part of Session 1 when learning was maximal according to our behavioural data. In contrast, significant DS activation arose only late in Session 1, after stimulus-response associations were well learned. This pattern is opposite to what is expected for brain regions that mediate learning. Brain regions underlying learning are also expected to be sensitive to feedback valence. There were no significant peaks in DS for contrasts of correct versus incorrect feedback. Further, if DS mediates feedback-based learning, it should be more active in Session 1 than in Session 2, where feedback is omitted and feedback-guided learning is precluded. However, there were no differences in DS activity contrasting Sessions 1 and 2. Finally, DS activation was not correlated with efficiency of learning but rather with stimulus-response decision accuracy achieved at the end of Session 1 and in Session 2, suggesting a more important role in decision-making informed by prior
learning. Collectively, these results refute the contention that DS mediates early stimulus-response learning based on feedback, and instead suggest a more primary role in decision-making.

We used multiple strategies for uncovering brain regions that support learning versus decision-making. The patterns of DS activation repeatedly and consistently were those expected for a brain region associated with decision-making, and not feedback-based learning. Our results are, therefore, at odds with the well-entrenched notion that DS mediates learning associations between stimuli and responses via feedback (Ashby et al., 2007; Foerde et al., 2013; Garrison et al., 2013; Yin and Knowlton, 2006). So how can our findings be reconciled with an extensive, long-standing literature supporting this claim? Again, many fMRI investigations of learning confound decision-making and learning by combining neural activity associated with both response-selection and feedback events (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Jessup and O'Doherty, 2011; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008). The conclusion that DS activation in these studies reflects a role in learning could be a misinterpretation. For example, Delgado et al. (2005) examined learning to associate cards with concepts of ‘high’ versus ‘low’ via feedback. They considered response selection (i.e., high vs. low decisions) and feedback phases of each trial as a single event. Compared to baseline, they found significant peaks in DS and VS, concluding that both mediate learning. Combining decision-making and feedback events caused ambiguity. Consequently, concluding that preferential DS activation was related to the response selection operation, whereas VS activity reflected learning through feedback is an alternative explanation for these data that is equally plausible, and entirely in line with our findings.

Our finding that DS activation was maximal late in the learning session when behavioural change and learning are actually reduced has been reported by others (Boettiger and D'Esposito, 2005; Seger et al., 2010; Toni and Passingham, 1999). Ignoring the disconnect with behavioural indices of learning, and focusing on the fact that experience appears to modulate DS activity, this result is offered as support for its role in learning nonetheless (Boettiger and D'Esposito, 2005; Seger et al., 2010; Toni and Passingham, 1999). The frequent finding that DS activity remains significantly increased above baseline after sequences (Reiss et al., 2005),
categorization rules (Helie et al., 2010; Seger et al., 2010), or stimulus-reward (Daw and Doya, 2006; Seger et al., 2010), and response-reward (Delgado et al., 2005; Ohira et al., 2010) associations have been acquired should challenge the notion that DS underlies learning, yet has not instigated such a revision. The alternative interpretation that DS mediates response selection, which predictably improves once stimulus-response associations are learned, accounts for both the pattern of brain-behaviour relations and the observation that DS activity changes with exposure to learning events. Using single-cell recording in a go/no-go reversal learning paradigm in rats, Takahashi et al. (2007) found increased DS activity for rewarded odour cues only after behavioural learning criteria were achieved. These findings, like ours, support the view that DS mediates decision-making, not learning per se. Indeed, there is a growing literature that implicates DS in performing decisions (Atallah et al., 2007; Grahn et al., 2008; Jessup and O'Doherty, 2011; McDonald and Hong, 2004; Postle and D'Esposito, 1999; Smittenaar et al., 2012), and consequently the results presented here unite two literatures that have advocated disparate functions for DS.

2.4.2 DS in habit formation or decision-making?

Regions of DS have also been theorized to support later forms of learning that do not depend upon feedback, such as habit formation (Ashby et al., 2010; Balleine et al., 2009; Ruge and Wolfenstetter, 2013; Tricomi et al., 2009). Habit formation refers to strengthening of stimulus-response associations that become independent of outcomes, and even resistant to feedback (Adams, 1982; Tricomi et al., 2009). The notion is that early stages involve goal-directed learning, which implicates VS and dorsomedial striatum/caudate. This early learning is transferred to dorsolateral striatum/putamen, which is instrumental in strengthening associations (i.e., later habit formation; Tricomi et al., 2009).

Although we have shown that early, goal-directed, feedback-based learning is not associated with DS activation, even in our dorsomedial/caudate ROI, we cannot entirely rule out the possibility that DS activation observed late in Session 1 and only at the time of response enactment reflected a role in habit formation. To reduce this possibility, we focused on early phases of learning, having set our learning criterion at 74% accuracy on two consecutive blocks to avoid over-learning.
Others have failed to support the notion that habit formation depends upon DS (de Wit et al., 2011). Further, a recent meta-analysis of 35 fMRI studies of reinforcement learning through feedback—the majority of which confounded neural activity for response selection/decision and feedback phases—found both VS and DS to be equally strongly associated with performing feedback-based learning. This meta-analysis casts doubt on the theory that VS first mediates feedback-based learning and DS underlies later habit formation (Garrison et al., 2013) given that both of these regions seemed to be active at the same stages of learning. Finally, more recent versions of these theories of striatal involvement in learning and action control surprisingly predict information transfer from DS to VS (Hart et al., 2013).

Compelling evidence that supports our preferred interpretation of the current findings and that is at odds with the notion that DS specifically mediates habit formation is provided by Atallah et al. (2007). They investigated the role of DS in learning versus selecting responses relying on learned associations. In a Y-maze task using odour cues, rats receiving GABA infusions to DS were impaired in consistently selecting the rewarded versus unrewarded arm; however, the associations were learned equally well for both GABA-infused, and saline-infused (control) animals. Furthermore, they found that GABA infusions to DS at test phase resulted in impaired decision-making compared to control animals, although both groups had previously shown identical learning of these odour-reward associations during the training phase. Taken together, these studies challenge the direct involvement of DS in learning, and instead suggest a more specific role in performance, as we claim here. The fact that DS inhibition did not impair early feedback-based learning disputes contentions that portions of DS are critical for goal-directed, early, learning through feedback (Brown and Stern, 2013). That DS integrity was essential for adequate stimulus-response performance even early in the training phase is at odds with the notion that portions of DS mediate habit formation.

### 2.4.3 VS in stimulus-response learning

Our results implicate VS in learning stimulus-response associations. VS activation occurred during the feedback event, peaked early, and decreased across Session 1. VS was sensitive to valence of feedback, exhibiting greater activity for correct than incorrect outcomes. VS activity was significant only in Session 1, when stimulus-response associations were learned via feedback, and not in Session 2, where decisions were performed without feedback precluding
further feedback-guided learning. Finally, VS activation was significantly, positively correlated with learning efficiency. Together, these results are highly consistent in suggesting that VS mediates early stimulus-response learning via feedback as has been suggested by others (Abler et al., 2006; Daniel and Pollmann, 2010; O'Doherty et al., 2003, O'Doherty, 2004).
2.5 References


Chapter 3

3 Dopaminergic therapy affects stimulus-response learning in Parkinson’s disease

The aim of this investigation was to evaluate the effect of dopaminergic therapy on cognition in PD. Results from Experiment 1 suggested that VS mediates stimulus-response learning, and that DS underlies response selection and decision-making processes. This understanding lead to predictions that stimulus-response association learning will be worsened by dopaminergic medication, whereas response selection will improve. The overarching aim of this investigation was to better delineate the cognitive profile in PD by investigating striatum-mediated cognitive functioning and to inform treatment.

Forty PD patients were tested on and/or off their usual dopaminergic medication, compared to 34 healthy age-matched controls, on consecutive days. On Day 1, participants learned to associate abstract images with spoken, ‘right’ or ‘left’ responses via deterministic feedback (Session 1). On Day 2, participants recalled these stimulus-specific responses in the absence of feedback (Session 2). We found that PD patients learned stimulus-response associations normally off medication; learning was impaired by dopaminergic medication. Regardless of medication status, patients recalled the stimulus-response associations from Day 1 as well as their age-matched controls. We interpret that learning relies on a region supplied by VTA. These findings have implications for dopaminergic treatment in PD.

A version of this chapter has been submitted to Annals of Clinical and Translational Neurology: Hiebert, N. M., Seergobin, K. N., Vo, A., Ganjavi, H., MacDonald, P.A. Dopaminergic therapy affects learning and impulsivity in Parkinson’s disease.
3.1 Introduction

PD is a neurodegenerative illness with prominent motor symptoms of tremor, bradykinesia, and rigidity. These motor symptoms result from degeneration of the dopamine-producing cells of the substantia nigra, leading to dopamine deficiency and dysfunction in DS. Cognitive dysfunction has long been recognized as a feature of PD (Aarsland et al., 2005; Aarsland et al., 2010; Brown and Marsden, 1984). The causes of cognitive impairments in PD are complex, and the effect of dopaminergic therapy is variable.

The cognitive profile in PD has many determinants. Clarifying the etiology of these symptoms has implications for treatment. Increasingly, it is evident that the striatum itself mediates cognitive functions (Cools, 2006; Monchi et al., 2006; Provost et al., 2010). In PD, some cognitive deficits relate to dopamine depletion in DS, and are remediated, at least partially, by dopaminergic therapy. Other cognitive deficits arise as a consequence of dopaminergic therapy (Cools, 2006; Gotham et al., 1986; Gotham et al., 1988; Swainson et al., 2000). Increasingly, it is understood that this occurs due to overdose of brain regions that receive dopamine from VTA that is relatively spared in PD (Cools et al., 2001; Cools, 2006; Gotham et al., 1986; Gotham et al., 1988; Mehta et al., 2001; Mehta et al., 2004; Swainson et al., 2000). These regions include VS, prefrontal, and limbic cortices (Cools, 2006). Finally, some abnormalities likely relate to changes in other neurotransmitter systems, cortical degeneration and Lewy body deposition, and are therefore, neither improved nor worsened by dopaminergic therapy (Bohnen et al., 2012; Jellinger, 2012; Nishio et al., 2010).

Learning, in many different forms, is often the cognitive function worsened by dopamine replacement therapy. Studies that have contrasted PD patients’ performance on relative to off their prescribed dopaminergic medication have found impairments in learning from negative feedback (Frank et al., 2004), probabilistic associations (Jahanshahi et al., 2010; Torta et al., 2009), motor sequences (Feigin et al., 2003; Ghilardi et al., 2007; Seo et al., 2010; Tremblay et al., 2010), stimulus-reward reversals (Cools et al., 2002; Graef et al., 2010; Seo et al., 2010; Swainson et al., 2000), and stimulus-stimulus facilitation (MacDonald et al., 2011). Unlike Experiment 1, many investigations fail to separate the act of learning from the separate process of decision-making or response selection; processes that tend to be used to probe new learning (Jessup and O’Doherty, 2011; McDonald and White, 1993). In the stimulus-response paradigm
in Experiment 1, an abstract image was presented and participants decided among a set of responses. This was followed by feedback about the accuracy of the response provided. Stimulus-response association learning is estimated by measuring the accuracy of the stimulus-specific responses. Impairment in either learning or response selection could result in poor performance.

The aim of this study was to investigate the effect of dopamine replacement therapy in PD on stimulus-response learning and decision-making based on this learning. In Session 1, PD patients, and healthy age- and education-matched controls learned to associate abstract images with either a ‘left’ or ‘right’ verbal response through deterministic feedback. Session 1 constituted a typical stimulus-response learning study in which the acts of learning and response selection are confounded. To address this confound, Session 2 assesses only response selection. In Session 2, participants perform the ‘left’ and ‘right’ associations learned in Session 1 in the absence of feedback, to preclude new learning.

Half of the PD patients learned stimulus-response associations off medication, whereas the other half performed Session 1 on medication. Similarly, half of the PD patients performed Session 2 off, and the other half on their prescribed dose of dopaminergic therapy. Because performance in Session 2 depended upon the effectiveness of learning in Session 1, and we expected that learning would be influenced by medication status, we ensured that each off and on group in Session 2 was composed of an equal number of participants who completed Session 1 off and on medication.

3.2 Method

3.2.1 Participants

Forty PD patients, and 34 age- and education-matched healthy controls participated in this experiment. All PD patients were previously diagnosed by a licensed neurologist, had no co-existing diagnosis of dementia or another neurological or psychiatric disease, and met the core assessment for surgical interventional therapy, and the UK Brain Bank criteria for the diagnosis of idiopathic PD (Hughes et al., 1992). All PD and no control participants were treated with dopaminergic therapy. Participants abusing alcohol, prescription or street drugs, or taking cognitive-enhancing medications including Donepezil, Galantamine, Rivastigmine, or
Memantine were excluded from participating. No PD patients were diagnosed with an impulse control disorder. Four PD, and four control participants performed less than 50% of the associations correctly either in Session 1 or 2, explained below, and therefore, their data were not included in the analysis.

The motor sub-scale of the Unified Parkinson’s Disease Rating Scale (UPDRS) was scored by a licensed neurologist with sub-specialty training in movement disorders (P. A. M.) to assess the presence, and severity of disease for all patients both on and off dopaminergic medication. Control participants were also screened to rule out undiagnosed neurological illness. Mean group demographics (Table 3.1), as well as cognitive and affective screening scores (Table 3.2) for all patients and controls in each experimental group were recorded. UPDRS motor subscale scores on and off dopaminergic therapy, daily doses of dopamine replacement therapy in terms of t-dopa equivalents, and mean duration of PD were also recorded (Table 3.1). Calculation of daily t-dopa equivalent dose for each patient was based on the theoretical equivalence to t-dopa as follows: t-dopa dose + t-dopa × 1/3 if on entacapone + bromocriptine (mg) × 67 + ropinerole (mg) × 20 + pergolide (mg) × 100 + apomorphine (mg) × 8.

There were no significant demographic differences between PD and control participants (Table 3.1). Screening cognitive measures confirmed that no participants suffered significant cognitive impairment (Table 3.2). PD patients scored significantly higher on both Beck Depression Inventory II and Beck Anxiety Inventory, and significantly lower on the Montreal Cognitive Assessment (MOCA), compared to controls. UPDRS scores were significantly higher in PD patients measured off relative to on dopaminergic medication.

All participants provided informed written consent to the protocol that was approved by ethics before beginning the experiment, according to the Declaration of Helsinki (1991). This study was approved by the Health Sciences Research Ethics Board (HSREB) of the University of Western Ontario and the Ethics Review Board of the Sudbury Regional Hospital.
Table 3.1: Demographic and clinical information in Experiment 2

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (± SEM)</th>
<th>Education (± SEM)</th>
<th>Years of disease (± SEM)</th>
<th>ι-dopa (mg) (± SEM)</th>
<th>DA (n)</th>
<th>UPDRS ON (± SEM)</th>
<th>UPDRS OFF (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>36</td>
<td>64.67 (1.39)</td>
<td>14.64 (0.47)</td>
<td>6.31 (0.82)</td>
<td>632.52 (80.36)</td>
<td>17</td>
<td>14.42 (1.09)</td>
<td>17.48 (1.31)</td>
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<tr>
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<td>64.50 (2.57)</td>
<td>13.75 (0.75)</td>
<td>7.38 (1.66)</td>
<td>586.00 (83.77)</td>
<td>5</td>
<td>14.38 (2.20)</td>
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<td>70.22 (0.85)</td>
<td>15.11 (1.07)</td>
<td>5.56 (1.43)</td>
<td>653.78 (128.13)</td>
<td>3</td>
<td>15.61 (1.78)</td>
<td>19.94 (1.94)</td>
</tr>
<tr>
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<td>62.20 (1.45)</td>
<td>14.40 (1.00)</td>
<td>7.80 (1.93)</td>
<td>529.40 (109.94)</td>
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<td>–</td>
<td>16.55 (2.64)</td>
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<td>15.22 (0.95)</td>
<td>4.44 (1.45)</td>
<td>767.20 (268.30)</td>
<td>4</td>
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<tr>
<td>Control</td>
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<td>14.10 (0.50)</td>
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<td>–</td>
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<td>14.00 (0.96)</td>
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<td>–</td>
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<td>14.43 (1.31)</td>
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<td>–</td>
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<td>61.29 (3.30)</td>
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</tbody>
</table>

Values are presented as group means (SEM). Control participants did not receive dopaminergic therapy during any session of the experiment. Their data are presented to correspond to the ON-OFF order of the patient with Parkinson’s disease to whom they were matched. All control participants presented with normal neurological exams. Education = years of education; Years of disease = years since diagnosis of PD; ι-dopa = daily ι-dopa equivalent dose in mg; DA = number of PD patients taking DA agonists; UPDRS ON = Unified Parkinson’s Disease Rating Scale motor score off medication; UPDRS OFF = Unified Parkinson’s Disease Rating Scale motor score on medication.
### Table 3.2: Cognitive and affective screening measures in Experiment 2

<table>
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<tr>
<th>Group</th>
<th>ANART IQ</th>
<th>BDI-II Day 1</th>
<th>BDI-II Day 2</th>
<th>BAI Day 1</th>
<th>BAI Day 2</th>
<th>Apathy Day 1</th>
<th>Apathy Day 2</th>
<th>MOCA</th>
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<tr>
<td>PD</td>
<td>124.71</td>
<td>10.72</td>
<td>9.64</td>
<td>12.17</td>
<td>9.28</td>
<td>12.11</td>
<td>11.97</td>
<td>25.58</td>
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<tr>
<td></td>
<td>(0.97)</td>
<td>(1.09)</td>
<td>(1.04)</td>
<td>(1.56)</td>
<td>(1.33)</td>
<td>(0.91)</td>
<td>(0.84)</td>
<td>(0.50)</td>
</tr>
<tr>
<td></td>
<td>(1.19)</td>
<td>(2.40)</td>
<td>(2.78)</td>
<td>(2.10)</td>
<td>(2.38)</td>
<td>(2.40)</td>
<td>(2.13)</td>
<td>(0.68)</td>
</tr>
<tr>
<td>ON - OFF</td>
<td>122.21</td>
<td>9.00</td>
<td>8.67</td>
<td>9.00</td>
<td>7.00</td>
<td>12.44</td>
<td>13.44</td>
<td>25.44</td>
</tr>
<tr>
<td></td>
<td>(2.52)</td>
<td>(1.31)</td>
<td>(1.30)</td>
<td>(1.86)</td>
<td>(1.31)</td>
<td>(0.85)</td>
<td>(0.84)</td>
<td>(0.65)</td>
</tr>
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<td>OFF - OFF</td>
<td>125.76</td>
<td>9.80</td>
<td>8.90</td>
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<td>11.00</td>
<td>12.20</td>
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<td>(2.95)</td>
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<td>124.56</td>
<td>11.44</td>
<td>10.00</td>
<td>16.22</td>
<td>11.56</td>
<td>8.89</td>
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<td></td>
<td>(1.45)</td>
<td>(2.75)</td>
<td>(2.33)</td>
<td>(3.94)</td>
<td>(3.43)</td>
<td>(1.14)</td>
<td>(1.19)</td>
<td>(1.65)</td>
</tr>
<tr>
<td>Control</td>
<td>123.15</td>
<td>4.10</td>
<td>3.16</td>
<td>4.10</td>
<td>2.10</td>
<td>10.40</td>
<td>9.50</td>
<td>27.07</td>
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<td>(0.71)</td>
<td>(0.63)</td>
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<td>(0.90)</td>
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<td>(1.78)</td>
<td>(1.71)</td>
<td>(1.38)</td>
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<td>(2.08)</td>
<td>(1.19)</td>
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<tr>
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<td>121.80</td>
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<td>3.22</td>
<td>5.67</td>
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<td>9.78</td>
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<tr>
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<td>(2.37)</td>
<td>(1.35)</td>
<td>(1.19)</td>
<td>(2.71)</td>
<td>(0.78)</td>
<td>(1.70)</td>
<td>(1.39)</td>
<td>(0.67)</td>
</tr>
<tr>
<td>OFF - OFF</td>
<td>126.14</td>
<td>2.43</td>
<td>1.71</td>
<td>1.57</td>
<td>1.43</td>
<td>9.14</td>
<td>7.57</td>
<td>27.14</td>
</tr>
<tr>
<td></td>
<td>(2.25)</td>
<td>(0.78)</td>
<td>(0.68)</td>
<td>(0.65)</td>
<td>(0.72)</td>
<td>(1.83)</td>
<td>(1.25)</td>
<td>(0.91)</td>
</tr>
<tr>
<td>ON - ON</td>
<td>124.56</td>
<td>4.29</td>
<td>3.00</td>
<td>5.23</td>
<td>3.57</td>
<td>12.14</td>
<td>11.00</td>
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<td>(1.64)</td>
<td>(1.66)</td>
<td>(2.71)</td>
<td>(1.91)</td>
<td>(2.13)</td>
<td>(1.69)</td>
<td>(0.44)</td>
</tr>
</tbody>
</table>

Values are presented as group means (SEM). Screening cognitive and affective measures were completed by PD patients on medication unless PD patients performed both days off dopaminergic medication. Control participants did not receive dopaminergic therapy during any session of the experiment. Their data are presented to correspond to the ON-OFF order of the patient with PD to whom they were matched. All control participants presented with normal neurological exams. **ANART IQ** = National Adult Reading Test IQ Estimation; **BDI-II Day 1** = Beck Depression Inventory II score measured for PD patients and for matched control participants during Day 1; **BDI-II Day 2** = Beck Depression Inventory II score measured for PD patients and for matched control participants during Day 2 of testing; **BAI Day 1** = Beck Anxiety Inventory I score measured for PD patients and for matched control participants during Day 1 of testing; **BAI Day 2** = Beck Anxiety Inventory I score measured for PD patients and for matched control participants during Day 2 of testing; **Apathy Day 1** = Apathy Evaluation Scale score measured for PD patients and for matched control participants during Day 1 of testing; **Apathy Day 2** = Apathy Evaluation Scale score measured for PD patients and for matched control participants during Day 2 of testing; **MOCA** = Montreal Cognitive Assessment measured for PD patients and for matched control participants.
3.2.2 Experimental Design

PD patients were randomly divided into four subgroups (Fig. 3.1), and all participated in two experimental sessions conducted over two consecutive days, as did their age- and education-matched healthy controls. PD patients in Group 1 (OFF-ON) performed Session 1 off and Session 2 on dopaminergic medication, whereas patients in Group 2 (ON-OFF) performed Session 1 on medication and Session 2 off medication. Group 3 (OFF-OFF) performed both sessions off dopaminergic therapy, whereas Group 4 (ON-ON) performed both sessions on dopaminergic medication. We expected that dopaminergic medication might have an effect on learning in Session 1. Performance in Session 2 depended on how well stimulus-response associations were learned in Session 1. To diminish any carry-over effects from Session 1, we i) excluded participants who performed less than 50% of the associations correctly in Session 1 or 2, and ii) included a similar number of participants who learned ON as OFF in Session 1, in both the ON and OFF conditions in Session 2.

![Diagram of experimental design]

**Figure 3.1: Experimental design of Experiment 2**

Half of participants completed the learning phase (Session 1) off medication; the other half learned on medication in Session 1. An equal number in each the OFF and ON groups in Session 2 learned the associations off or on medication in Session 1.
Although control participants did not take dopaminergic medication during any session, their data were analyzed to correspond to the medication order of the PD patients to whom they were matched. Matching was performed prior to data analysis, at the time of experimentation. This controlled for possible order, fatigue, and practice effects. PD patients took their dopaminergic medication as prescribed by their treating neurologist during ON testing sessions, but abstained from taking all dopaminergic medications including: dopamine precursors such as t-dopa, aromatic-L-amino-acid decarboxylase inhibitors such as Carbidopa, and catechol-O-methyltransferase (COMT) inhibitors such as Entacapone (Comtan) for a minimum of 12 to a maximum of 18 hours, and dopamine agonists, such as Pramipexole (Mirapex), Ropinirole (Requip) or Pergolide (Permax), as well as Amantadine (Symmeterel), Rasagiline (Azilect), and Selegiline (Eldepryl or Deprenyl) for 16 to 20 hours before beginning OFF testing sessions.

Both sessions of the experiment were performed using a 14.0’’ widescreen laptop (Lenovo T420) running a resolution of 1600 × 900 on the Windows 7 operating system. The screen was placed at a distance of approximately 50 cm in front of the participant, and angled for optimal viewing.

Participants performed a task where they learned to associate six abstract images with one of two spoken responses, either ‘right’ or ‘left’, via deterministic feedback (Session 1). Images consisted of characters taken from the invented Klingon alphabet (Fig. 3.2). During each trial in Session 1, an image appeared in the centre of the computer screen until the participant responded with a verbal response. Images would appear one at a time, and in random order. Feedback, either the word ‘correct’ or ‘incorrect’, was presented after every response. In this way, participants learned to associate each image with the appropriate verbal response through trial and error. Session 1 consisted of 216 image and verbal response trials, and at the end of the session, participants were given a percentage score, summarizing the number of correct responses provided. Session 1 was completed on the first day of testing, whereas, Session 2 was completed on the following day.
The 6 images were presented in Sessions 1 and 2. Images were taken from the invented *Klingon* language.

Session 2 involved recall of the verbal response learned for each of the six images on the previous day. Each image appeared one at a time, in random order for a total of 72 trials, or 12 trials per image. No feedback was provided in Session 2 to preclude new learning of the stimulus-response associations. Examples of the order of events for trials in each session are presented in Figure 3.3.
Figure 3.3: Example of a single trial in Sessions 1 and 2 of Experiment 2

A. PD patients and age- and education-matched controls learned to associate six abstract images with either a ‘left’ or ‘right’ verbal response in Session 1. The following is an example of a trial: i) a fixation cross appeared in the centre of the computer screen for 700 ms; (ii) a blank screen was presented for 300 ms; (iii) an image was presented in the centre of the computer screen until the participant vocalized a response that was recorded by the microphone; (iv) the image disappeared and the experimenter coded the response using a keyboard; (v) feedback, either the word ‘correct” or ‘incorrect” was presented for 750 ms before the next trial began. B. Participants recalled the responses to the learned images in the absence of feedback in Session 2. Trial parameters were otherwise identical to Session 1.

3.2.3 Data Analysis

Efficiency of learning stimulus-response associations was measured by calculating the slope of learning in Session 1. Session 1 was divided into 12 discrete blocks of 18 trials. At the end of a block, a score summarizing the number of correct trials was logged but not revealed to the participant. Slope was calculated using the standard slope of the linear regression function in Microsoft Excel (2011), given by the following equation:

$$b = \frac{\sum(x-\bar{x})(y-\bar{y})}{\sum(x-\bar{x})^2}$$
where \( b \) is the slope, and \( x \) and \( y \) are the sample means of the number of blocks and block scores, respectively. Larger slope values signified faster learning of the stimulus-response associations. Session 2 was divided into four discrete blocks of 18 trials, and scores summarizing the number of correct trials were logged, as in Session 1. Performance in Session 2 was measured by the number of correct responses to the images based on the associations learned in Session 1.

### 3.3 Results

#### 3.3.1 Session 1: Learning Phase

The average slope of learning to associate six images from the *Klingon* alphabet with one of two spoken responses, either ‘right’ or ‘left’, via deterministic feedback was calculated for PD patients and Controls in each the ON and OFF sessions (Fig. 3.4). We performed a 2 × 2 ANOVA on the slope. To reiterate, slope was calculated using the standard slope of the linear regression function in Microsoft Excel (2011) using the percentage scores for the number of correct responses obtained after each of the 12 blocks in Session 1. Group (PD vs. Control) and Medication Session (OFF vs. ON) were between-subject factors. The Group × Medication Session interaction was significant, \( F_{(1,62)} = 4.78, \text{MSE} = 0.001, p = 0.033 \), though the main effect of Group, \( F_{(1,62)} = 2.03, \text{MSE} = 0.001, p > 0.150 \), and of Medication Session, \( F_{(1,62)} < 1 \), were not.

To further explore the significant Group × Medication Session interaction, separate one-way ANOVAs were performed for PD and control participants, with Medication Session (ON vs. OFF) as the between-subject factor. The main effect of Medication Session was significant for PD patients, \( F_{(1,34)} = 5.88, \text{MSE} = 0.001, p < 0.025 \), reflecting slower learning on relative to off dopaminergic medication, but not for control participants, \( F_{(1,28)} < 1 \).

Comparing PD patients and control participants in terms of learning slope in the matched ON and OFF sessions separately, we found that PD patients learned more slowly than controls ON medication, \( F_{(1,31)} = 6.06, \text{MSE} = 0.001, p < 0.025 \), but there was no group differences in terms of learning rate for PD patients and controls off medication, \( F_{(1,31)} < 1 \).
Figure 3.4: Effect of dopaminergic therapy on association learning in Session 1
of Experiment 2

Slopes of learning in Session 1 for PD patients and healthy control participants. Average slopes of each medication group are presented. Error bars represent standard error of the mean. Slopes were calculated using the standard slope of the linear regression function in Microsoft Excel (2011). The slope of learning for PD patients off dopaminergic medication is significantly higher than PD patients on medication ($t = 2.32, p = 0.033$). Slope of learning was also significantly lower in PD patients on medication compared to controls in the same group ($t = 2.46, p < 0.025$).

3.3.2 Session 2: Test Phase

We performed a 2 × 2 ANOVA on ‘right’ and ‘left’ spoken response accuracy during Session 2. Group (PD vs. Control) and Medication Session (OFF vs. ON) were between-subject factors. There were no significant main effects ($F < 1$ for both Group and Medication Session) or interactions, $F_{(1,69)} = 1.68, MSE = 0.028, p > 0.200$. Average response accuracies for each group are presented in Fig. 3.5. Mean error rates are presented in Table 3.3. A combined
control group was used in Table 3.3, as there were no significant differences between the two medication groups.

![Figure 3.5 Effect of dopaminergic therapy on decision-making in Session 2 of Experiment 2](image)

**Figure 3.5 Effect of dopaminergic therapy on decision-making in Session 2 of Experiment 2**

Average response accuracies in Session 2 were calculated for PD patients and healthy control participants. Error bars represent standard error of the mean. There were no significant main effects ($F < 1$ for both Group and Medication Session) or interactions, $F_{(1,69)} = 1.68$, $MSE = 0.028$, $p > 0.200$. 
Table 3.3: Proportion of errors in Sessions 2 of Experiment 2

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<tr>
<td>PD</td>
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<tr>
<td>OFF</td>
<td>0.178 (0.036)</td>
</tr>
<tr>
<td>ON</td>
<td>0.201 (0.041)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.150 (0.043)</td>
</tr>
</tbody>
</table>

All values reported are means (SEM). Proportion of errors in Session 2 was measured by the number of incorrect responses to the images based on the associations learned in Session 1.

3.4 Discussion

We showed that stimulus-response association learning in PD patients is normal off medication, but impaired by dopaminergic medication. Regardless of medication status, PD patients’ recall of stimulus-response associations that they had previously learned in Session 1 was equal to that of age-matched controls. Our four-group design countered any carry-over effects that related to medication status during the learning phase. That is, we ensured that the ON and OFF groups in Session 2 were composed of an equal number of PD patients who had acquired stimulus-response associations on, and off dopaminergic therapy in Session 1.

Performing the previously learned stimulus-response associations in Session 2 was not affected by dopaminergic therapy; a result reported by others (Vo and Hiebert et al., 2014 submitted). The difficulty of Session 1 may have been greater than Session 2, resulting in the effects seen. However, given that performance in Sessions 1 and 2 are comparable, the confound of increased difficulty in Session 1 can be ruled out. A possible limitation that may have resulted in the lack of effects seen in Session 2 could be the four-group design. Including equal numbers of PD patients that learned the associations on and off dopaminergic therapy in each Session 2 group increases the variability within the group, making it more difficult to detect between group differences. Increasing the number of participants in each group may aid in discerning medication effects on response selection.
3.4.1 Learning in PD

We found that stimulus-response association learning is spared in PD, but is impaired by dopaminergic therapy. Other studies have also revealed normal probabilistic, associative, or motor sequence learning in PD patients at baseline, with impairments arising due to dopaminergic medication (Feigin et al., 2003; MacDonald et al., 2011; Seo et al., 2010; Shohamy et al., 2006). Cognitive functions that are worsened by dopaminergic therapy have been widely ascribed to brain regions that are innervated by the VTA, which is relatively spared in PD (Cools, 2006; MacDonald and Monchi, 2011). Dopamine replacement is titrated to the DS-mediated motor symptoms, effectively overdosing VTA-innervated brain regions that are relatively dopamine replete (Cools, 2006; Gotham, 1988). These include VS, limbic, and prefrontal cortex. Indeed, using neuroimaging and behavioural methods, VS has been implicated in learning in healthy participants and in PD patients (Feigin et al., 2003; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2006; Tremblay et al., 2010; Hiebert et al., 2014 under review).
3.5 References


Chapter 4

4 General Discussion

In two separate experiments, we investigated cognitive functions that are mediated by DS using healthy participants in fMRI, and patients with PD on and off dopaminergic medication. In Experiment 1, we demonstrated that (i) DS does not mediate early feedback-based stimulus-response learning, but is implicated in performing response decisions, and (ii) VS underlies stimulus-response learning. Our findings challenge a prevailing claim that DS mediates stimulus-response learning via feedback (see Ashby et al., 2007; Garrison et al., 2013; Hart et al., 2013; Yin and Knowlton, 2006, for reviews), and recast it as a brain region mediating decision-making, integrating with a growing literature supporting this view (Atallah et al., 2007; Grahn et al., 2008; Jessup and O'Doherty, 2011; McDonald and Hong, 2004; Postle and D'Esposito, 1999; Smittenaar et al., 2012).

In Experiment 2, learning stimulus-response associations was normal at baseline in PD, and impaired by dopaminergic therapy. In contrast, PD patients, regardless of medication status, performed stimulus-specific responses equivalently to one another. This pattern of results could reflect reliance of learning on VTA-innervated brain regions. These are relatively spared compared to DS; which is significantly dopamine depleted in PD. This dissimilar effect of medication is related to differences in endogenous dopamine in these brain regions. These findings have implications for dopaminergic treatment in PD.

4.1 The role of DS in stimulus-response learning

The two separate experiments outlined above suggest that DS does not mediate stimulus-response learning, but rather underlies performing stimulus-specific responses. In Experiment 1, DS was active only during the stimulus-response phase of the experiment, and not during the feedback, or learning, phase. This finding is at odds with the prevailing claim that DS mediates learning. Again, in many neuroimaging studies, DS’ role in learning could be misinterpreted because decision-making (i.e., stimulus-response events), and learning from outcomes (i.e., feedback events) are combined into a single event, and all regions that are differentially activated for these merged processes are ascribed a role in learning (Delgado et al., 2005;
Dobryakova and Tricomi, 2013; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008). In Experiment 2, learning was worsened by dopaminergic medication in PD, an unexpected result if DS mediates learning. At baseline DS is depleted of dopamine and its functions, both motor and cognitive, are deficient. DS functions have consistently been shown to be remediated by dopaminergic therapy (see Cools, 2006; MacDonald and Monchi, 2011 for reviews). Indeed, consistent with the larger literature, learning is the cognitive function most often worsened by dopaminergic therapy in PD (Cools et al., 2002; Feigin et al., 2003; Frank et al., 2004; Ghilardi et al., 2007; Graef et al., 2010; Jahanshahi et al., 2010; MacDonald et al., 2011; Seo et al., 2010; Swainson et al., 2000; Tortal et al., 2009; Tremblay et al., 2010).

Taken together, results from Experiments 1 and 2 cast doubt on DS’ role in learning stimulus-response associations. Instead, results from Experiment 1 in particular suggest a role for DS in performing responses. This result adds to a growing literature similarly implicating DS in decision-making and response selection (Atallah et al., 2007; Grahn et al., 2008; Jessup and O'Doherty, 2011; McDonald and Hong, 2004; Postle and D'Esposito, 1999; Smittenaar et al., 2012).

4.2 The role of VS in stimulus-response learning

Results from Experiment 2 suggest that a VTA-innervated such as VS, prefrontal cortex or limbic areas mediate learning stimulus-response associations. VTA-innervated regions are relatively dopamine replete throughout all stages of PD, and dopamine replacement therapy overdoses these regions, impairing their functioning (Cools 2006; MacDonald and Monchi, 2011). Combining our results in Experiment 2 with those obtained in Experiment 1, VS is suggested as a brain region that plays a role in learning. VS was active during the feedback phases only, and seemed to track learning, decreasing when stimulus-response associations were well-learned.

VS is often reported as a region specialized for reward learning (Camara et al., 2010; Cools et al., 2002; Delgado et al., 2000; Delgado, 2007; Knutson and Cooper, 2005; O’Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010) particularly when contingencies are probabilistic (Abler et al., 2006; Delgado, 2007; Haruno and Kawato; 2006). Recently,
however, this specialization has been challenged with studies implicating VS in a broader range of learning situations, including situations where punishment is offered, and other situations in which there is no feedback at all (Feigin et al., 2003; Ghiladri et al., 2007; Seo et al., 2010; MacDonald et al., 2011; Reiss et al., 2005; Shohamy et al., 2004; Shohamy et al., 2006; Tremblay et al., 2010). Results from Experiments 1 and 2 support the recent broadening of VS-mediated learning by implicating VS in learning from deterministic feedback (i.e., when feedback always reflects the accuracy of a response) in the absence of reward.

4.3 Implications for cognition in Parkinson’s disease

Cognitive dysfunction is an undisputed symptom of PD that leads to significant impairment in quality of life (Barone et al., 2009; Schrag et al., 2000). The etiology of cognitive impairments in PD is complex, but it is now clear that at least a subset of these symptoms arise from dysfunction of the striatum itself (Ray and Strafella, 2012). In PD, DS-mediated functions are compromised at baseline, and improved by dopamine replacement therapy. Conversely, VS functions are relatively spared off medication, and worsened by dopaminergic therapy, most notably at early stages of the disease (MacDonald and Monchi, 2011). Understanding VS- and DS-mediated cognitive functions, therefore, informs at least some cognitive symptoms in PD, and has implications for treatment. Currently, dopaminergic therapy is titrated to relieve DS-mediated motor symptoms, without taking into account the potential overdose of VTA-innervated regions. Ultimately, this greater understanding will prompt clinicians to formulate medication strategies that consider both motor and cognitive symptoms, as well as individual patient needs.
4.4 References


frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia, 38*, 596-612.


5 Appendices

5.1 Ethics approval notice from the University of Western Ontario

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Penny MacDonald
Review Number: 18517
Review Level: Full Board
Approved Local Adult Participants: 400
Approved Local Minor Participants: 0
Proposal Title: Distinguishing the role of ventral and dorsal striatum in cognition
Department & Institution: Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, London Health Sciences Centre
Sponsor: Canadian Excellence Research Chair

Ethics Approval Date: April 17, 2012
Ethics Expiry Date: January 31, 2016

Documents Reviewed & Approved & Documents Received for Information:

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<th>Document Name</th>
<th>Comments</th>
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<tr>
<td>Western University Protocol</td>
<td>(including instruments noted in section 8.1)</td>
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<tr>
<td>Letter of Information &amp; Consent</td>
<td>NRRI Studies</td>
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<td>Advertisement</td>
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This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines: and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

[Signature: Janice Sutherland]
[Signature: Grace Kelly]
[Signature: Shantel Walcott]

This is an official document. Please retain the original in your files.

The University of Western Ontario
Office of Research Ethics
5.2 Ethics approval notice from the Sudbury Regional Hospital

To: Dr. Penny MacDonald

Study Title: The role of the basal ganglia in cognition

Sponsor: London Health Sciences Clinical Neurological Sciences Start-up Funds

REB Review Type: Full Board

Date of Meeting: March 4, 2013

Notification of Approval for an Amendment

Documents Approved
Revised HRSRH Study Submission Form (February 13, 2013)
Revised Purpose of Research (February 13, 2013)
Revised Procedures (February 13, 2013)
Description of Protocol Amendment and Rationale (February 2013)
Revised Consent Form (February 13, 2013)

Documents Acknowledged
UWO HSREB Full Board Submission Form: Distinguishing the roles of ventral and dorsal striatum in cognition
UWO HSREB Approval Letter (April 17, 2012)
UWO HSREB Approval Letter (December 13, 2012)
UWO HSREB Full Board Submission Form: Pharmacogenetics and drug response
UWO HSREB Approval Letter (October 25, 2012)
Funding Notice (February 14, 2013)

Project Number: 746

The Research Ethics Board of Health Sciences North has reviewed the amendment request for the above research protocol. The quorum for approval did not involve any member associated with this project.

The above Project Identification Number has been assigned to your project. Please use this number on all future correspondence.

Sincerely,

Dr. Martin Shine, Chair, Health Sciences North Research Ethics Board

The Health Sciences North Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of TCPs 2 - 7th Edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, the International Conference on Harmonization of Good Clinical Practice, Part D, Division II of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations. The HSBN REB is registered with the U.S. Department of Health & Human Services under the HHS registration number #IRB0003335D.
6 Curriculum Vitae

Name: Nole Marcus Hiebert

Post-secondary Education and Degrees

2012 – Present  **Master of Science**, Physiology and Pharmacology, University of Western Ontario – May 2014
Supervisors: Dr. Penny MacDonald and Dr. Adrian Owen

2008 – 2012  **Bachelor of Medical Science**, Honors Specialization in Physiology with distinction, University of Western Ontario – June 2012

Honors, Scholarships and Awards during university:

2008  Western Scholarship of Excellence
2008 – 2012  Dean’s Honor List, University of Western Ontario
2012  Nominated for the Graduate Teaching Assistant Award, University of Western Ontario

Research Experience:

2012 – Present  **Master’s Student**, Department of Physiology and Pharmacology, University of Western Ontario

- Master’s project: investigating the roles of the dorsal and ventral striatum in stimulus-response learning and decision-making using fMRI in healthy participants and patients with Parkinson’s disease on and off dopaminergic medication.
- Conduct additional behavioural and fMRI experiments involving: stimulus-response learning, implicit and explicit learning, working memory, as well as stroop tasks.
- Drafted a research proposal investigating the effect of genetic polymorphisms on cognition in patients with Parkinson’s disease.
- Drafted a research proposal investigating the effect of methylphenidate on cognition in patients with Parkinson’s disease.
- Wrote and revised research ethics approved by Health Sciences Research Ethics Board (HSREB) of the University of Western Ontario and the Ethics Review Board of the Sudbury Regional Hospital.

2011 – 2012  **Undergraduate Student**, Department of Physiology and Pharmacology, University of Western Ontario
- Undergraduate thesis project: examining the effect of Bisphenol A on the expression of specific glucocorticoid-regulated genes in human syncytiotrophoblast cells
- Researched and proposed a project examining the effect of reactive oxygen species on preadipocyte proliferation in rats

Publications, Presentations and Abstracts

Presentations and Abstracts


Submitted Publications


Teaching Experience during University
Teaching Assistant, University of Western Ontario
Course Title: Physiology 4710: Physiology of the Senses
- Assisted the professor in ensuring the accuracy of lecture material.
- Reviewed and revised online quiz, and exam questions.
- Held online and in-class tutorials, and one-on-one tutoring sessions for students.
- Proctored midterm and final exams.