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Pharmacogenetics of Non-Motor Symptoms in Parkinson's Disease

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Graduate Program in Physiology and Pharmacology
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Abstract

Memory deficits are recognized in Parkinson's disease (PD). The nature of these memory deficits is unclear because few studies have both isolated memory encoding and retrieval processes while testing patients on and off their dopamine replacement medication. Previous work suggests encoding depends upon regions innervated by the ventral tegmental area, which is relatively spared in PD, while retrieval depends upon dorsal striatum, which is dopamine deficient even early in PD. We investigated the impact of a dopamine transporter (DAT1), a dopamine reuptake protein, polymorphism (a 40-base-pair variable repeat affecting expression) on encoding and retrieval in healthy, elderly controls as well as in patients on and off medication. We only found encoding deficits in PD patients who carry a DAT1 polymorphism when on, relative to off, medication, suggesting interactive effects of medication and genotype. We found improvements in memory retrieval in patients who were on, relative to off, medication, but this effect may be independent of DAT1 genotype. This work demonstrates the need for further investigation of interactive effects of medication and genetic profile in PD.

Keywords

Parkinson's disease, polymorphism, dopamine transporter, dorsal striatum, ventral striatum, memory encoding, memory retrieval.

Co-Authorship Statement

I completed all aspects of the following experiment, but received assistance with data collection from Ken Seergobin, Alex MacDonald, Abdullah Al Jaja, Marissa Burns, and Connor Lewicki. Additionally, all genotyping work was completed in the lab of Dr. Richard Kim. Ken Seergobin and Dr. Penny MacDonald also assisted with data processing and analysis. I prepared the manuscript myself, which was edited by Dr. Penny MacDonald. This experiment was completed at Sudbury Regional Hospital and the Brain and Mind Institute, located at the University of Western Ontario.

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List of Abbreviations

9R	9-repeat allele
10R	10-repeat allele
AComm	Anterior communicating artery
AFLT	Aggie Figures Learning Test
ANART IQ	National Adult Reading Test IQ estimation
ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
cAMP	Cyclic adenosine monophosphate
DAT1	Dopamine transporter
DS	Dorsal striatum
dIPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
L-dopa	l-3,4-dihydroxyphenylalanine
LED	Levodopa equivalent dose
MOCA	Montreal Cognitive Assessment
MSN	Medium spiny neuron
OFC	Orbital frontal cortex
PD	Parkinson's disease
PET	Positron emission tomography
PFC	Prefrontal cortex

PKA	Protein kinase A
RAH	Recurrent artery of Heubner
RAVLT	Rey Auditory Visual Learning Test
SAS	Starkstein Apathy Test
SEM	Standard error of the mean
SN	Substantia nigra
UPDRS	Unified Parkinson's Disease Rating Scale
VNTR	Variable nucleotide tandem repeat
VS	Ventral striatum
VTA	Ventral tegmental area

1.0 Literature Review

1.1 Motor Symptoms in Parkinson's Disease

Parkinson's disease (PD) is a common neurodegenerative disorder that affects 173 of every 100,000 55-64 year olds worldwide, with increasing prevalence later in life (Pringsheim et al., 2014). PD is characterized by the motor symptoms of slowness of movement (i.e., bradykinesia), increased muscular tone (i.e., rigidity), and resting tremor. These symptoms occur due to degeneration of dopamine-producing neurons in the substantia nigra (SN), a midbrain region belonging to the basal ganglia. When ~70% of these neurons degenerate, the SN's primary efferent region, the dorsal aspect of the striatum (DS), becomes sufficiently dopamine depleted, causing motor symptoms to arise (Kish et al., 1988). The striatum is the input region of the basal ganglia, as detailed below.

1.2 Basal Ganglia

The basal ganglia are a collection of subcortical nuclei implicated in motor control and, increasingly, in cognitive function (Cools, 2006; Grahn et al., 2008; MacDonald and Monchi, 2011). These nuclei consist of the striatum, SN, globus pallidus, and subthalamic nucleus (Kandel et al., 2013). The striatum, the input structure to the basal ganglia, can be anatomically divided into the caudate nucleus and putamen (Kandel et al., 2013). It receives glutamatergic afferents from the thalamus and all cortical regions, save the primary visual and auditory cortices (Alexander et al., 1986). The SN supplies dopamine almost exclusively to the bulk of the caudate nucleus and putamen, which together form the DS. The VTA supplies dopamine to the most ventral aspects of the caudate and putamen, as well as to the nucleus accumbens, which together constitute the VS. The ventral tegmental area (VTA) also provides dopaminergic innervation to frontal cortical

regions, and limbic cortices, including hippocampus and amygdala (Cools, 2006; MacDonald & Monchi, 2011).

Though at a gross level of inspection the caudate and putamen appear to be separate structures, at a microscopic level these regions cannot be discriminated (David, et al., 2005; Iversen and Dunnett, 1990). Further, although sub-regions of both caudate and putamen differ in the cortical inputs they receive, even these are somewhat overlapping (Choi, et al., 2012; Draganski, et al., 2008; Lehericy, et al., 2004; Postuma & Dagher, 2006) as is their dopamine supply. In line with this, despite claims that the caudate and putamen are functionally separate (Balleine, et al., 2009; Ashby et al., 2007; Jessup and O'Doherty, 2011), these distinctions do not hold up upon closer inspection of the literature. The operations implicating these brain regions are in fact quite corresponding (Grahn et al., 2008; Burgaleta, et al., 2014; DeGutis and D'Esposito, 2007; Jiang, et al., 2015; Jueptner, et al., 1997; Kimura, 1992; Lam, et al., 2016; Monchi, et al., 2001; Samejima, et al., 2005; Foerde, et al., 2013; Lehericy, et al., 2005). Consequently, at this time, there is insufficient evidence that caudate and putamen are distinct operationally, rationalizing our strategy of referring to caudate and putamen as DS. In contrast, distinctions between VS and DS are justified by distinct histological features that adapt them to different functions and based on entirely non-overlapping reciprocal cortical afferents as well as different dopamine supplies (Kincaid, et al., 1998; Leh, et al., 2007; Voorn, et al., 2004; Wickens, et al., 2007). Finally, VS and DS functions are quite dissimilar (MacDonald and Monchi, 2011).

Medium spiny neurons (MSNs) are the main cell type in the striatum. MSNs are gamma-aminobutyric acid-ergic and can be divided into two separate types. The direct pathway contains

MSNs that predominately express D1 dopamine receptors and project directly to the internal globus pallidus/SN pars reticulata. The indirect pathway contains MSNs that predominately express D2 dopamine receptors and project to the external globus pallidus, which is in turn connected to the internal globus pallidus/SN pars reticulata either directly or through the subthalamic nucleus (Kandel et al., 2013). Both pathways project from the internal globus pallidus to regions of the thalamus. The thalamus then projects back to the cortex (Kandel et al., 2013; Figure 1), with different cortical regions receiving efferents from the striatal regions to which they initially projected, forming reciprocal connections (Alexander et al., 1986; Postuma and Dagher, 2006). D1 receptor-expressing MSNs of the direct pathway are coupled to a G-protein coupled second messenger system through $G\alpha_{(s/olf)}$, which activates adenylyl cyclase, resulting in increased cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) activity (Beaulieu et al., 2011). Therefore, the presence of dopamine leads to increased activity in direct pathway MSNs, which causes disinhibition of the thalamus through the internal globus pallidus (Kandel et al., 2013). D2 receptor-expressing MSNs of the indirect pathway are coupled to $G\alpha_{(i/o)}$ and lead to decreased PKA activity (Beaulieu et al., 2011). The presence of dopamine leads to disinhibition of the subthalamic nucleus. The subthalamic nucleus then releases more glutamate onto the internal globus pallidus, leading to inhibition of corresponding thalamic neurons. In addition, the external globus pallidus also sends projections directly to the internal globus pallidus. Dopaminergic activity in the striatum modulates synaptic activity and helps maintain a balance between direct and indirect pathway activity (Kandel et al., 2013). In this way, the net effect of dopamine is increased cortical activity through activation of direct pathway and depression of the indirect pathway. Alterations to dopaminergic activity in the striatum, as seen in Parkinson's disease (PD), leads to a variety of motor and non-motor symptoms.

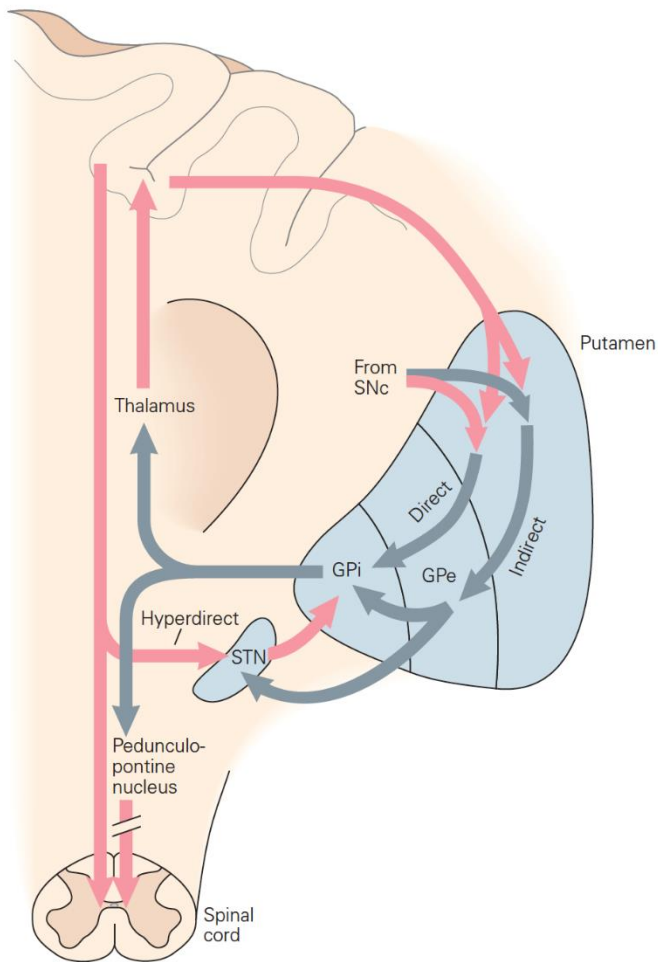


Figure 1.1: Basal Ganglia-Thalamocortical Loops. Cortical input to the basal ganglia is received by the striatum (here only showing putamen). This information may then travel down the direct (monosynaptic) or indirect (polysynaptic) pathways before reaching the internal globus pallidus (GPi). GPi projects onto the thalamus to reroute processed information back to the cortical regions that provided the initial input to the striatum. Excitatory synapses are shown in red. Inhibitory synapses are shown in grey. Figure reproduced from Kandel et al., 2013.

1.3 Pathophysiology of Motor Symptoms in PD

The motor symptoms of PD result from decreased direct pathway signaling and increased indirect pathway signaling in the cortico-basal ganglia-thalamocortical motor circuit (Kandel et al., 2013), both related to dopamine depletion. This imbalance results in increased activity of the internal

globus pallidus which causes inhibition of the thalamus and its target regions of the motor cortex. This in turn produces the cardinal motor symptoms of PD.

As would be expected based on the pathophysiological basis for movement abnormalities, dopamine replacement therapy is an effective treatment for motor symptoms at all stages of PD. Dopamine precursors such as l-3,4-dihydroxyphenylalanine (L-dopa) are most commonly used. L-dopa is often formulated to include a dopamine decarboxylase inhibitor that prevents the conversion of L-dopa to dopamine in the peripheral circulation, resulting in fewer side effects and higher concentrations of dopamine in the brain. Dopamine agonists, which are drugs that are similar in structure to dopamine, may also be used. These drugs are not converted to dopamine, but rather interact with dopamine receptors in their current state, mimicking the effect of dopamine.

1.4 Cognitive Symptoms in PD

The non-motor symptoms of PD lead to decreased quality of life (Barone et al., 2009; Schrag et al., 2000) and significant disability (Aarsland et al., 2003, 2009; Verbaan et al., 2007). Over time, it has become apparent that cognitive symptoms are prominent in PD, especially at later stages of disease (Muslimovic et al., 2007; Owen et al., 1992). 20-50% of patients eventually manifest dementia (Bosboom et al., 2004; Caballol et al., 2007; Owen, 2004) and a greater percentage demonstrate milder cognitive deficits (Aarsland et al., 2003, 2009; Litvan et al., 2011). In non-demented PD patients with milder cognitive impairment, learning functions in particular seem intact whereas cognitive flexibility (i.e., the ability to alter response strategies to match changing environments or to shift attention among stimuli) is impaired (Cools, 2006; MacDonald and

Monchi., 2011). At later stages, cognitive deficits become more pronounced and varied, with a complete list far from defined.

1.4.1 Pathophysiology of Cognitive Symptoms in PD

Unlike the relatively straightforward pathophysiology of motor symptoms, the etiology of cognitive impairments in PD appears more complex. Whereas some cognitive abnormalities result from cortical degeneration, which occurs particularly at later stages in PD (Pereira et al., 2012), other pathological changes almost certainly contribute to abnormal cognition in PD. For example, there is evidence that some cognitive deficits are attributable to degeneration of neurotransmitter systems, in addition to dopamine, such as acetylcholine and serotonin (Calabresi et al., 2006; Scatton et al., 1983). Studies have repeatedly failed to demonstrate correlation between severity of cognitive impairment and cortical dispersion of abnormal deposits of alpha-synuclein that form Lewy bodies (Jellinger, 2008; Parkkinen et al., 2005, 2008). Using convergent methodologies, a growing number of studies now clearly support a role for the striatum in cognition and dopaminergic abnormalities in striatum are suggested as central mechanisms for cognitive abnormalities in PD, especially in PD patients with milder cognitive impairment and at earlier stages of disease (Aarsland et al., 2009; Cools, 2006; Cools et al., 2001, 2003; Frank et al., 2004; Grahn et al., 2008; Hayes et al., 1998; Hood et al., 2007; MacDonald and Monchi, 2011; Owen et al., 1992; Shook et al., 2005).

Reviewing cognitive functions ascribed to the striatum initially reveals a diverse and almost confusing array. Increasingly, it is understood that this apparent miscellany owes to regional functional specificity within the striatum. Dorsal and ventral portions of striatum are characterized

by subtle cytoarchitectural differences as well as non-overlapping cortical and dopaminergic afferents (Wickens et al., 2007; Zhang et al., 2009; Cowan and Wilson, 1994; Kincaid et al., 1998). By partitioning cognitive functions attributed to DS and VS, two more cohesive sets of cognitive operations are emerging. The DS is linked to executive functions such as flexibly switching response strategies and shifting attention whereas the VS seems particularly implicated in learning (Atallah et al., 2007; Benke et al., 2003; Cameron et al., 2010; Cools, 2006; Cools and D'Esposito, 2011; Cools et al., 2003, 2011; Ell et al., 2006; Grahn et al., 2008; Hiebert et al., 2014; Leber et al., 2008; MacDonald and Monchi, 2011; MacDonald et al., 2011; Robertson et al., 2015; Shohamy et al., 2006; Yehene et al., 2008).

In addition to being implicated in different cognitive functions, sources of dopamine for DS and VS are distinct and degenerate at different times and to varying degrees in PD (Kish et al., 1988). Unlike the SN, which is significantly degenerated at the time of diagnosis, the dopamine-producing cells of the VTA are relatively spared in early PD (Kish et al., 1988). The result is that the SN-innervated DS is severely dopamine-depleted and its functions are impaired. In contrast, the brain regions supplied by the VTA, namely the VS, prefrontal cortex (PFC), and limbic cortices, including hippocampus, are relatively dopamine replete and their cognitive functions are preserved (Cools, 2006; MacDonald & Monchi, 2011). In this way, awareness that DS and VS mediate separate cognitive processes and that SN and VTA degenerate differentially, has yielded a framework for understanding cognitive dysfunction in PD, particularly prior to late disease stages.

In contrast to motor symptoms that are uniformly improved by dopaminergic therapy in PD, cognitive functions are dissimilarly affected by dopamine replacement therapy. Some cognitive

functions are ameliorated or redressed, whereas others are worsened by dopaminergic medication. There is now an ample literature suggesting that cognitive functions that depend upon DS, or cortical regions reciprocally connected to DS, are improved by dopaminergic therapy (Cools, 2006; Cools and D'Esposito, 2011; Cools et al., 2001, 2003; Frank, 2005; Frank et al., 2004; Hood et al., 2007; Lewis et al., 2005; MacDonald and Monchi, 2011; MacDonald et al., 2011; Moustafa et al., 2008a, 2008b; Shook et al., 2005; Slaboz et al., 2006; Tremblay et al., 2010). The detrimental effects of dopaminergic therapy on cognition have been attributed to an overdose of dopamine in regions of the brain (e.g., VS, orbitofrontal cortex (OFC), limbic regions, including hippocampus) that receive dopamine from VTA (Cools, 2006; Cools and D'Esposito, 2011; MacDonald and Monchi, 2011). Because the VTA is relatively spared in PD (Kish et al., 1988), regions supplied by VTA have normal or near-normal levels of dopamine at baseline. Many researchers have proposed that dopamine replacement therapy overdoses VTA-innervated brain regions, which results in impaired function (Cools and D'Esposito, 2011; Cools et al., 2001, 2002, 2006; Dias et al., 1996; Feigin et al., 2003; Ghilardi et al., 2007; Gotham et al., 1988; Graef et al., 2010; Seo et al., 2010; Shohamy et al., 2006; Spaniol et al., 2009; Swainson et al., 2000; Tremblay et al., 2010).

Commonly, the effects of dopamine replacement therapy are tested using an 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. This is referred to as the OFF state. Performance in the OFF state is compared to performance in the ON state, which is characterized by testing patients who are taking their regularly prescribed dopaminergic medications. Comparing performance in ON and OFF states in a single patient allows within-subject differences to be

examined. The effects of dopaminergic therapy performance are also understood by comparing functions of PD patients to those of healthy controls. Although control participants are not provided any dopamine replacement medications, they are also tested twice to understand how potential practice, test-retest, and fatigue effects may contribute to performance.

1.4.2 Dopamine Overdose Hypothesis

A number of studies now confirm that at least some of the cognitive impairments that occur in PD arise as a side effect of dopaminergic therapy. These results have been related to the dopamine overdose hypothesis. Cognitive abilities mediated by relative dopamine-replete regions (i.e., VTA-innervated regions) are impaired by dopaminergic therapy, whereas abilities mediated by brain regions that are dopamine-deplete at baseline (e.g., DS) are improved by dopaminergic therapy (Figure 1.2).

The dopamine overdose hypothesis was first formulated by Gotham and colleagues (1988). They tested PD patients both on and off medication in a series of tasks—with a one-week delay between testing sessions. The ordering of on and off sessions was counterbalanced, and different versions of each task was used in both sessions. PD patients in the OFF state made more errors in tasks that probed decision-making and response selection processes compared to when they were tested in the ON state. In contrast, PD patients in the ON state performed more poorly on tasks that involved learning and working memory processes compared to when they were tested in the OFF state. As such, Gotham and colleagues (1988) were the first to show these differential effects of dopaminergic therapy in PD, and they explained their findings by the fact that learning and working memory processes depend upon VTA-innervated brain regions which are dopamine

replete in PD. As discussed below, subsequent studies have clearly demonstrated that decision-making and response selection implicates (Ali et al., 2010; Atallah et al., 2007; Daniel et al., 2010; Grinband et al., 2006; Helie et al., 2010; Liu et al., 2010; Monchi et al., 2001; Rogers et al., 2000; Seger et al., 2010; van Schouwenburg et al., 2010) or, in fact, depends (Benke et al., 2003; Cools et al., 2006; Ell et al., 2006; Yehene et al., 2008; Rieger et al., 2003; Thoma et al., 2008; Vakil et al., 2004) on DS, and that VTA-innervated regions, such as VS, limbic cortex (e.g., hippocampus), and PFC are implicated in learning (Atallah et al., 2007; Feigin et al., 2003; Ghiladri et al., 2007; Lisman and Grace, 2005; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2006; Tremblay et al., 2010) and working memory (Barbey et al., 2013; Lara and Wallace, 2015; Salazar et al., 2012; Wang et al., 2013), respectively.

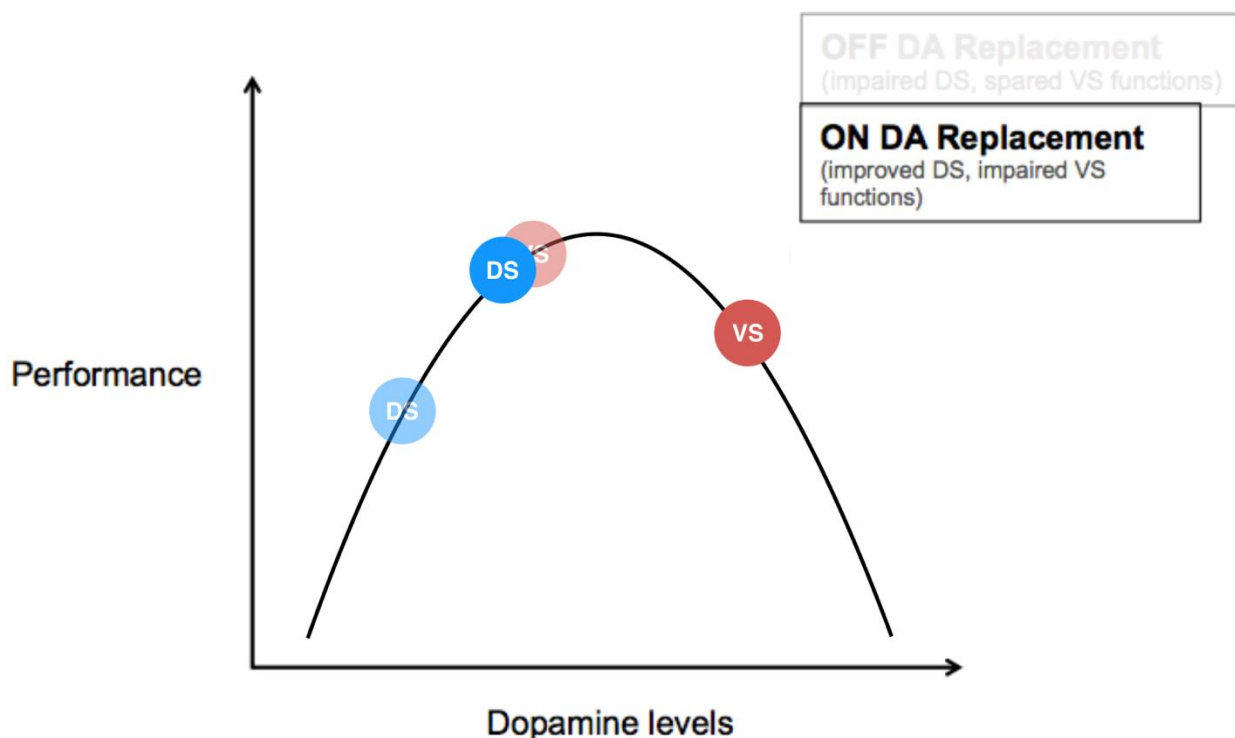


Figure 1.2. Inverted-U function of dopamine levels and performance. The darker DS and VTA symbols represent the effects of dopamine replacement therapy in PD. The lighter symbols represent the effects of PD in the absence of dopamine replacement therapy. DS, dorsal striatum; VS, ventral striatum; VTA, ventral tegmental area.

1.5 Memory Impairments in PD

Early reports of explicit memory impairment in PD established these deficits as part of PD progression itself, and not merely as a comorbidity of Alzheimer's dementia (Helkala et al., 1988; Sagar et al., 1988; Sahakian et al., 1988). Despite some contradictory findings (Taylor et al., 1990; Weiermann et al., 2010), memory deficits are now a recognized symptom of PD (Aarsland et al., 2009, 2011; Verbaan et al., 2007) and have been shown to worsen with disease progression (Muslimovic et al., 2007).

1.6 Memory

Explicit memory refers to conscious, intentional remembering and can relate to general knowledge or information about specific episodes, events, or personal experiences (Vandenbos, 2015). Explicit memory can be further subdivided. Semantic memory refers to long-term memory for factual information. Episodic memory refers to long-term memory for discrete events, with recall of the time and place these memories were formed. Autobiographical memory refers to memories from an individual's life and is composed of both semantic and episodic memories. In contrast to explicit memory, implicit memory refers to unconscious, unintentional remembering (Vandenbos, 2015). For example, implicit memory is invoked in the acquisition and later retrieval of procedural skills—like those necessary to ride a bicycle. A skilled cyclist does not need to be able to verbally describe how to ride a bike to be proficient; this skill is acquired in an unconscious manner over repetitive attempts and can be accessed without conscious awareness. Implicit memory is also implicated in repetition priming effects and learning and conditioning without awareness (Schacter, 1987). For the purposes of the present study, we will be focusing specifically upon explicit memory.

1.6.1 Memory encoding

Successful remembering depends on effectively encoding and retrieving information. Memory encoding is the process by which new information is transformed and stored in a long-term form. This process occurs at synaptic and systems levels (Dudai, 2012).

At the synaptic level, it is theorized that encoding is initiated by a “teaching signal” that leads to activation of intracellular signaling cascades resulting in posttranslational modifications, modulation of gene expression, and protein synthesis that alter synaptic strength (Cohen and Frank, 2009; Dudai, 2012). These teaching signals have been identified as phasic responses in populations of midbrain dopaminergic cells that burst-fire in response to positive feedback and have depressed firing frequencies in response to negative feedback (Cohen and Frank, 2009; Schultz et al., 1997; Frank, 2005; Frank and Fossella, 2011). These bursts and dips modify synaptic plasticity in downstream brain regions (Wickens et al., 2003; Frank, 2005; Reynolds et al., 2001). Phasic dopamine bursts result in long-term potentiation through D1 receptors of the direct pathway (Kerr and Wickens, 2001; Kravitz et al., 2012; Reynolds et al., 2001; Shen et al., 2008). Long-term potentiation is a process by which periods of synaptic activity produce long-term increases in synaptic strength, facilitating future firing of these neurons (Baudry et al., 2015; Beaulieu and Gainetdinov, 2011; Lisman et al., 2012; Malenka and Bear, 2004). Disinhibition of D2 receptors, through the dissociation of dopamine from D2 receptors, as occurs during dopamine dips, increases long-term potentiation in this cell population (Kravitz et al., 2012; Shen et al., 2008).

The effects of dopamine on the direct and indirect pathways have been modelled by Cohen and Frank (2009) in regards to Go (i.e., approach) and NoGo (i.e., avoidance) reinforcement learning. Dopamine is viewed as playing a modulatory role in the basal ganglia. Agonism or facilitation of D1 receptors is seen as enhancing the signal-to-noise ratio by relatively increasing the activity of highly active cells that are responding in a pulsatile fashion and diminishing basal activity of cells that are not. Agonism of D2 receptors, on the other hand, is always inhibitory. Bursts of dopamine, as seen during the reception of positive feedback, facilitate Go activity through the direct pathway and inhibits NoGo activity through the indirect pathway. On the other hand, dopamine dips, which occur during the reception of negative feedback, decrease signal-to-noise in the direct pathway and disinhibit cells in the indirect pathway, facilitating NoGo learning. Although Cohen and Frank (2009) were discussing reinforcement learning specifically, the same actions of dopamine on direct and indirect pathways are also exemplified motor control in PD. Because of decreased dopaminergic tone, due to the loss of dopaminergic innervation from SN, PD patients experience a biasing toward enhanced indirect pathway signaling, which leads to bradykinesia (Surmeier et al., 2007). Given the above, the effects of dopamine on direct and indirect pathway signaling in the basal ganglia may serve an explanatory role in the effects that medication and PD have on memory encoding and retrieval.

At the systems level, there is abundant literature revealing that loss of integrity of the hippocampus leads to dramatic failures in encoding new information explicitly. Early studies in patients with medial temporal lobectomies revealed an inability to encode new explicit information—a phenomenon known as anterograde amnesia (Milner, 1968, 1972; Scoville and Milner, 1957). Using neuroimaging, explicit memory encoding has been shown to preferentially engage VTA-

innervated medial temporal structures, such as the hippocampus (Schrager et al., 2008; Spaniol et al., 2009). It has also been suggested that hippocampus and VTA form a functional loop that regulates the encoding of information into long-term memory (Lisman and Grace, 2005). Lisman and Grace (2005) propose that the hippocampus acts as a gate to this loop, such that if it detects novel information, a signal is sent downstream, through the subiculum and VS, to the VTA, where it contributes to the firing of dopaminergic cells in response to novelty. Subsequently, dopamine is released to the hippocampus from the VTA and long-term potentiation is facilitated, leading to encoding. Indeed, hippocampal activity has been detected during the presentation of novel stimuli using single-unit recordings (Fyhn et al., 2002), positron emission tomography (PET; Tulving et al., 1996), fMRI (Strange and Dolan, 2001; Yamaguchi et al., 2004) and c-Fos quantification (Jenkins et al., 2004), which is a marker of cellular activity and gene transcription. Following the proposed pathway from the hippocampus through the subiculum and VS to the VTA, it has been found that VS cells fire in response to both subicular innervation (Wood and Rebec, 2004) and novel stimuli (Ihalainen et al., 1999). Increased VS innervation then disinhibits the ventral pallidum, which leads to increased firing of dopaminergic neurons in the VTA (Floresco et al., 2003).

In addition to the novelty-dependent loop suggested by Lisman and Grace (2005), medial temporal cortices have strong connections to the OFC and medial frontal areas (Petrides, 2007). These areas both receive dopaminergic innervation from the VTA, and appear to be implicated in novelty detection and processing, as well as in the valuation of stimuli and reward processing (Tzschentke and Schmidt, 2000; Haber and Knutson, 2010). The OFC is connected bi-directionally via the uncinated fasciculus to entorhinal and perirhinal cortices, as well as hippocampus and

parahippocampus (Barbas, 1993; Barbas and Blatt, 1995; Catenoix et al., 2005; Cavada et al., 2000). Monkeys with OFC lesions do not habituate to novel stimuli (Butter, 1964), and a population of neurons in OFC (referred to as area 11) are selectively activated by novel, but not familiar, stimuli in the absence of reward (Rolls et al., 2005). In humans, PET studies have evidenced OFC activation when viewing novel faces, and this activity was positively correlated with subsequent memory performance (Frey and Petrides, 2003). Interestingly, in another human PET study, participants viewed two side-by-side abstract images. Some images had graffiti-like designs superimposed on them. Participants were not required to make any decisions in regards to these images; they simply pressed a button to proceed to the next set of images. Presentation of images with graffiti-like designs activated OFC, indicating that viewing deviant visual stimuli activated OFC (Petrides et al., 2002).

1.6.2 Memory Retrieval

Explicit memory retrieval refers to the act of accessing previously encoded information. This can be accomplished by freely recalling information as when a participant is asked to first encode a list of words or images and later generate the list of items without cues or prompts (i.e., free recall). Serial recall is tested when a participant is asked to present the retrieved information in the order in which it was encoded. Recall can also be cued (i.e., cued recall) when prompts or cues are provided to help the participant retrieve the requested information. Finally, explicit memory retrieval processes are also engaged when an individual is asked to recognize previously-presented information from among newly-presented stimuli, as in a recognition memory test (Spaniol et al., 2009).

Synaptic and systems level accounts of memory retrieval are far less elaborated, and this area has received much less research attention than memory encoding (Spaniol et al., 2009). In fact, at the synaptic level, a consistent and sufficiently well-supported account for memory retrieval has not yet been advanced. At the systems level, retrieval seems to implicate more distributed and varied brain regions as detailed below.

A role for medial temporal structures has been demonstrated in free recall. For example, deficient long-delay free recall has been found to correlate with smaller parahippocampal volume in PD patients (Pirogovsky-Turk et al., 2015). Additionally, free recall performance has been shown to correlate with integrity of the fornix, a white matter tract composed mostly of connections associated with the hippocampal formation (Metzler-Baddeley et al., 2010, 2012). A posteromedial network of brain regions, containing hippocampus, retrosplenial cortex and frontal regions, have been shown to be engaged throughout free recall processes (Kragel and Polyn, 2013). Other brain regions have also been consistently implicated in memory retrieval. Humans with dorsolateral PFC (dlPFC) lesions evidenced recall deficits in a list learning paradigm of unrelated items with five study-immediate recall phases (Gershberg and Shimamura, 1995). These patients had reduced levels of self-initiated organization of list items and also reported less use of organizational strategies. This finding is in line with other studies showing patients with frontal lobe lesions evidence deficits in subjective organization in free recall paradigms (Eslinger and Grattan, 1994; Stuss et al., 1994). Additionally, recent findings suggest that a dorsal frontoparietal network of brain regions, including dlPFC, is transiently engaged early during free recall (Kragel and Polyn, 2013).

Despite these findings in free recall reviewed above, most studies of memory retrieval have focused on recognition memory (Spaniol et al., 2009), Spaniol and colleagues conducted a quantitative meta-analysis of encoding and recognition memory related to neuroimaging. retrieval—the latter measured during memory recognition tests. Further evidence for the role of striatum, medial temporal cortices and frontal regions in memory encoding and retrieval are seen in this meta-analysis (Spaniol et al., 2009). For the purposes of their encoding meta-analysis, they included studies in which participants were imaged using fMRI while they were explicitly encoding objects or words. To determine brain regions implicated in memory encoding, regional brain activity was compared during encoding of subsequently-recognized items and encoding of items that were later forgotten. Twenty-six studies were included in this part of the meta-analysis. For the memory retrieval analysis, they included studies in which participants were imaged while they were performing a recognition memory test. In a recognition memory test, participants are asked to indicate whether they believe a displayed item is “old” and was previously presented to them during the encoding or study period or whether they believe the displayed item is “new” and did not appear at study. The contrast of interest in the retrieval portion of their meta-analysis was regional brain activity correlating with correct “old” item presentations, referred to as “hits”, compared to activity during correct “new” item presentations, referred to as “correct rejections”. Thirty studies were included in this part of the meta-analysis.

For encoding, not surprisingly, they found preferential activation in many VTA-innervated regions, including medial temporal structures such as the hippocampus, parahippocampal gyrus, and amygdala, as well as VTA-innervated frontal regions. For the retrieval meta-analysis, many VTA-innervated regions were also activated during recognition memory testing, including

parahippocampal gyrus, VS, and frontal regions. In addition, however, there were large clusters of activation found in DS and several in dlPFC, a primary cortical partner of DS (Alexander et al., 1986; Postuma and Dagher, 2006). Further, the encoding and retrieval contrasts were then contrasted with one another to determine which brain regions were preferentially engaged during encoding and retrieval. Many medial temporal and frontal structures were engaged for both encoding and retrieval. Hippocampus and amygdala were found to be preferentially engaged during encoding, whereas DS and frontal regions, which are reciprocally connected to DS, such as dlPFC, frontal eye fields, and motor cortices were preferentially engaged during retrieval. In sum, this meta-analysis provided evidence for VTA-innervated regions playing a role in memory encoding and DS, and dorsal frontal regions functionally connected to DS, are engaged during retrieval processes.

1.7 Memory Encoding and Retrieval in PD

Successful memory depends upon both an encoding phase, where new information is transferred from working memory to long-term memory, as well as a retrieval phase, during which long-term memory is successfully retrieved from long-term memory stores. Impaired remembering can arise due to impairments in either encoding or retrieval. In PD, few studies have investigated memory encoding and retrieval separately. In those that did, most investigated memory impairment in PD patients who were on their usual dopaminergic medication only. As we have detailed above, dopaminergic therapy can have complex effects on cognition. Without an off medication comparison, it cannot be known whether deficits owe to PD pathophysiology or medication overdose effects. Further, normal performance in PD patients tested only in the ON state could reflect either intact encoding and retrieval, or baseline memory impairment that is improved by

medication. In this way, interpretation of these results is mired. Reviewing these memory studies in PD patients in the ON state only has further revealed highly inconsistent findings. Some studies found deficits only in encoding (Chiaravalloti et al., 2014; Ellfolk et al., 2013; Knoke et al., 1998; Pirogovsky-Turk et al., 2015), others only in retrieval (Ellfolk et al., 2012; Higginson et al., 2005), whereas some found impairments in both domains (Ibarretxe-Bilbai et al., 2011; Vingerhoets et al., 2005).

Few studies have been conducted in PD patients off dopaminergic medication. In a study of verbal list learning, drug-naïve PD patients evidenced both encoding and retrieval deficits (Bronnick et al., 2011). Encoding deficits were found in the PD patient group. These deficits were not predicted, given our review of the literature clearly implicating VTA-innervated structures in encoding and the fact that VTA-innervated brain regions are relatively dopamine replete, especially at early stages of disease. As such, these encoding deficits may be resultant from the chosen methodology. This study used a verbal list learning paradigm, with list items belonging to one of four semantic categories. On closer evaluation, a regression analysis showed that the encoding deficit in these drug-naïve patients was attributable to an inability to use semantic clustering as a learning strategy. As such, this deficit might not have reflected deficient memory encoding *per se*, but may have been related to impaired semantic organizational processes. These processes have been shown to implicate DS and dorsal frontal networks (Seger et al., 2010; Helie et al., 2010), especially in ambiguous contexts (Daniel et al., 2010). Frontal lesion patients have previously been shown to evidence deficits in self-directed organization of list items during recall (Eslinger and Grattan, 1994; Gershberg and Shimamura, 1995; Stuss et al., 1994). DS is significantly dopamine depleted, even early in PD, and functions supported by this structure and its cortical partners are expected

and consistently observed. As predicted, PD patients also evidenced deficient free recall, both after short and long delays, compared to controls (Bronnick et al., 2011). This is consistent with brain regions that have preferentially been implicated in explicit retrieval processes (Spaniol et al., 2009).

Few studies to date have examined memory deficits in PD using an ON-OFF paradigm. Review of the literature revealed four previous ON-OFF PD studies of memory. However, two of these studies did not separate memory performance into encoding and retrieval processes (Drag et al., 2009; Edelstyn et al., 2010). Failure to separately assess encoding and retrieval processes as well as to evaluate the distinct effects of PD and dopaminergic therapy in ON-OFF designs have yielded significant inconsistencies in the PD memory literature. Encoding and retrieval depend on different brain regions—as detailed above—and, given our current understanding of the pathophysiology of cognitive dysfunction in PD, these operations are expected to be dissimilarly affected by dopamine replacement. The degree to which a particular memory evaluation stresses encoding relative to retrieval is expected to determine how PD patients perform in the OFF and ON states.

Only two studies have investigated encoding and retrieval separately in PD using an ON-OFF design. Grogan and colleagues (2015) tested memory encoding and retrieval using the Hopkins Verbal Learning Task-Revisited in PDs and healthy controls. This is an episodic memory test that assesses encoding and delayed recall. On Day 1, 12 words from three semantic categories were read aloud to participants, who were instructed to recall as many words as they could after each verbal presentation. There were three study-immediate recall phases. The total number of items recalled during these three immediate recall phases was considered as a measure of encoding. After

a 30-minute delay, participants recalled as many items as they could. On Day 2, participants were asked to recall these items once again without being provided any additional study sessions. PD patients completed these two days of testing in either OFF-OFF, OFF-ON, ON-ON, or ON-OFF medication orders. Overall, controls outperformed PDs on measures of encoding and delayed recall, independent of medication status. On Day 2, PD patients revealed superior delayed recall in the ON relative to the OFF state. Further, the OFF-ON PD group, in particular, clearly outperformed all other medication groups on Day 2. This pattern is entirely predictable based on brain regions suggested to mediate encoding and retrieval processes respectively—as reviewed above (e.g., Spaniol et al., 2009)—combined with the differential effects of dopamine replacement medication on VTA-innervated brain regions and those areas receiving dopamine from SN, particularly DS (Cools et al., 2006; MacDonald & Monchi, 2011). Encoding has been shown to depend on and implicate VTA-innervated brain regions, particularly hippocampus, OFC, and VS (Frey and Petrides, 2003; Lisman and Grace, 2005; MacDonald et al., 2013; Milner, 1968, 1972; Scoville and Milner, 1957; Spaniol et al., 2009). In contrast, retrieval preferentially implicates DS and frontostriatal loops containing DS (Eslinger and Grattan, 1994; Gershberg and Shimamura, 1995; Kragel and Polyn, 2013; MacDonald et al., 2013; Spaniol et al., 2009; Stuss et al., 1994). VTA-innervated brain regions are dopamine replete and function normally in the OFF state for PD patients, particularly early in disease (Kish et al., 1988). Performance actually worsens due to dopamine overdose in the ON state for functions mediated by VTA-innervated brain regions. In contrast, DS is significantly dopamine depleted, with clear impairment in the OFF state for functions mediated by DS or cortical networks implicating DS. These deficits are improved by treatment in the ON state. In this way, the observed results are easily interpreted as owing to more successful encoding for PD patients in the OFF state on Day 1 and better retrieval for PD patients

in the ON state on Day 2. Consistent with this interpretation, on Day 1, absolute recall after a 30-min delay was performed better in the OFF than ON state, the reverse of the pattern on Day 2.

These results are presented in Figure 1.3.

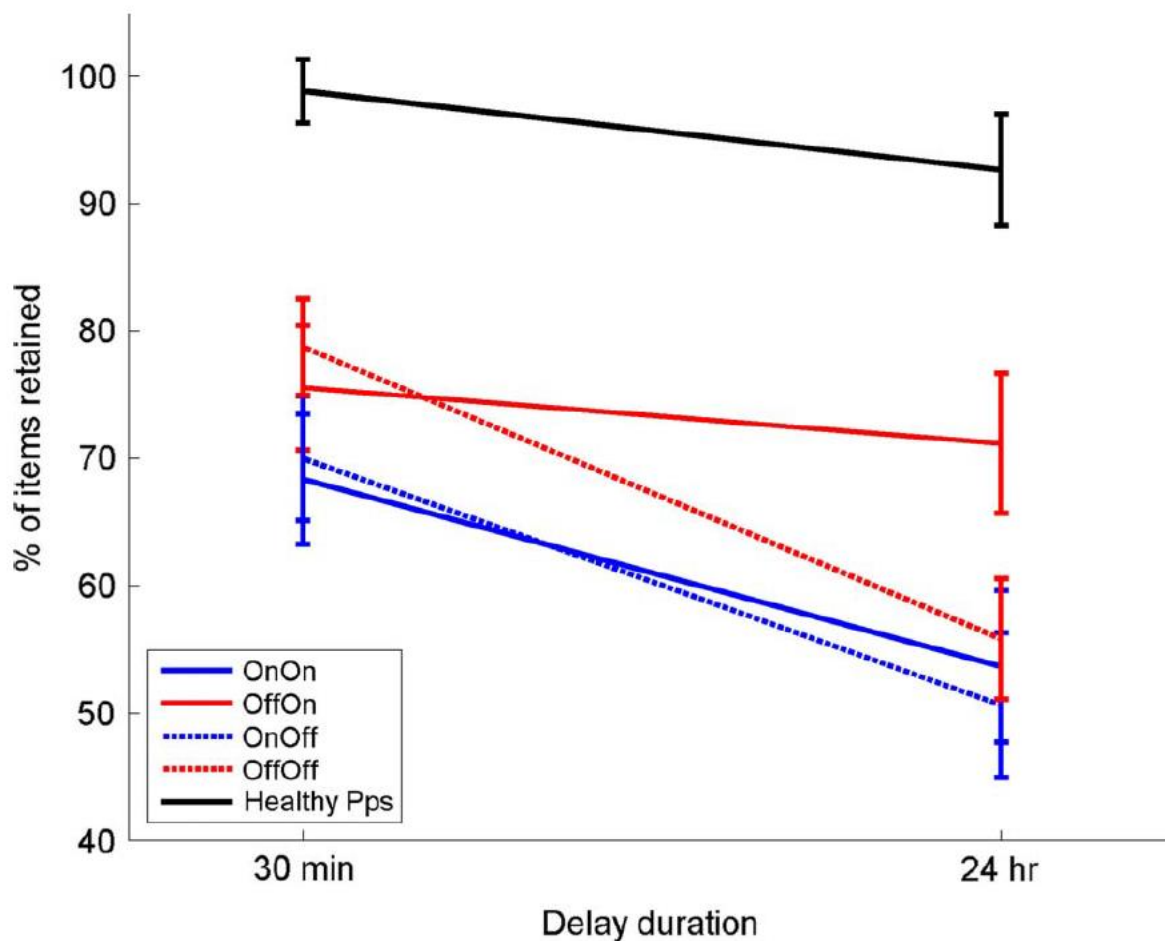


Figure 1.3. Percentage of verbally-presented items successfully recalled after 30-minute and 24-hour delays. PD patients completed these two recall session in either ON-ON, OFF-ON, ON-OFF, or OFF-OFF medication orders. Healthy control data is shown in black. PD patients who were tested in the OFF-ON order outperformed all other PD groups on 24-hour delayed free recall. Reproduced from Grogan and colleagues (2015).

The results of Grogan and colleagues (2015) essentially replicated those of MacDonald and colleagues (2013), who conducted a similar study that isolated encoding and retrieval processes in PD patients. Patients were tested both on and off medication on two consecutive days, using

different stimulus sets on each day, alongside healthy, age- and education-matched controls, with ON-OFF order counterbalanced across participants. Controls were not given any dopamine replacement medication, but were tested on both days with their session yoked to their age-matched control and analyzed in this way. This was to account for potential fatigue, order, or practice effects that owed to performing memory tests on two consecutive days. Two memory tasks were used. The first was the Rey Auditory Verbal Learning Test (RAVLT). This is a test of verbal explicit memory. In each testing session, a list of 15 words, List A, was presented one-at-a-time on a computer screen. Participants were instructed to remember as many of these words as possible. After all 15 words have been displayed, participants are given one minute to write down as many words as they can remember. This study-immediate recall procedure was repeated three times. After the last presentation of List A, a second list of 15 different words, List B, was presented, but only for a single iteration of the study-immediate recall procedure. After this interference list and again after a 30-minute delay, participants were asked to recall as many items as they could from List A without further any intervening study experiences. During the recall test after a 30-minute delay, participants were also asked to provide as many words as they could remember from interference List B. The second memory test was the Aggie Figures Learning Task (AFLT). This task is a non-verbal analogue of the RAVLT. In this task, the same procedures were followed, except that 15 abstract symbols were presented instead of 15 words and there were five study-immediate recall phases rather than three in the RAVLT. All other aspects of the AFLT and the RAVLT were the same. The measure for encoding in this study was the difference in the number of items recalled during the final study-immediate recall phase and the first study-immediate recall phase in both the RAVLT and AFLT. The items successfully recalled in the first study-immediate recall phase were subtracted to control for the effects of working memory and

immediate recall abilities. This subtraction serves to better isolate the memory encoding process (i.e., the extent to which items are transferred from working memory into long-term memory) throughout these study-immediate recall phases. Further, this strategy aims to eliminate effects related to retrieval ability on performance, as retrieval ability is expected to contribute to performance equally for the first and the last study-immediate recall phases. In contrast, memory retrieval was measured by combining the number of items successfully recalled from Lists A and B in the RAVLT and AFLT after the 30-minute delay. Retrieval scores were normalized to the number of items encoded on the final study-immediate recall phase, to account for effects that were related to superior encoding.

When analyzing the memory encoding measure, MacDonald and colleagues found that PD patients performed equivalently to controls while off medication, but encoded more poorly than controls when on medication. Further, PD patients in the OFF state encoded significantly more items than PD patients in the ON state from first to final study-immediate recall phases. This compromised memory encoding (i.e., lower learning rates resultant from not properly encoding symbols into long-term memory) in PD patients while on medication was attributed to a possible overdose of DA in VTA-innervated regions which have been shown extensively to underlie memory encoding (Atallah et al., 2007; Grogan et al., 2015; Hiebert et al., 2014; Lisman and Grace, 2005; MacDonald et al., 2013; Spaniol et al., 2009). In early PD, the VTA is relatively spared (Kish et al., 1988). As such, the administration of exogenous dopamine can lead to overdose of VTA-innervated regions (see Cools et al., 2006; MacDonald and Monchi, 2011 for reviews).

In the recall task, they found that PD patients performed worse than controls while off medication and equivalent to controls when on medication. The within-subject contrast also revealed that PD patients recalled significantly more items when they were tested on relative to off medication. The improved performance of PD patients on medication was attributed to evidence that DS and its cortical partners mediate retrieval and to the fact that DS is significantly dopamine depleted even in early PD. Indeed, dopamine replacement therapy has been shown to reliably improve motor and cognitive performance that relies on DS throughout the disease course (Cools, 2006; MacDonald and Monchi, 2011). As previously detailed, DS and regions reciprocally connected to DS have been implicated in retrieval processes (Gershberg & Shimamura, 1995; Eslinger & Grattan 1994; Spaniol et al., 2009). DS is preferentially activated when recognizing remembered items in an episodic recognition test (Kim, 2010), as well as during explicit remembering of category membership (Seger et al., 2010; Helie et al., 2010; Hiebert et al., 2014).

In summary, the only studies that have looked at encoding and retrieval in PD, accounting for differential effects of dopaminergic therapy on these separate processes, are consistent. Both suggest that encoding is intact in PD at baseline and is worsened by dopaminergic medication, whereas retrieval is impaired in the OFF state and is improved by dopamine supplementation. This is in line with the memory literature that consistently shows that memory encoding is mediated by VTA-innervated brain regions (Atallah et al., 2007; Grogan et al., 2015; Hiebert et al., 2014; Lisman and Grace, 2005; MacDonald et al., 2013; Spaniol et al., 2009). VTA-innervated brain regions are relatively dopamine replete at baseline in PD but are overdosed by dopamine therapy in levels titrated to DS dopamine depletion. In contrast, retrieval (e.g., recall and recognition memory processes) implicate more distributed brain regions, including DS and cortical regions to

which it is reciprocally connected (Gershberg & Shimamura, 1995; Eslinger & Grattan 1994; Kim, 2010; Spaniol et al., 2009). DS is seriously dopamine depleted in PD in the OFF state and this is improved with dopaminergic supplementation. In this way, these results are easily understood in light of the pathophysiology of PD

1.8 Influence of Genotype on Encoding and Retrieval

A number of genes influence baseline DA levels as well as responsivity to DA receptor stimulation. These are presumed to affect cognitive processes as well as to interact with PD pathophysiology. Further, it is expected that these genes interact with exogenous dopamine. Polymorphisms in the gene coding for dopamine transporter (DAT1) are of particular interest in PD.

1.8.1 DAT1

DAT1 is a Na^+/Cl^- -dependent plasma membrane transporter protein that reabsorbs synaptic dopamine into presynaptic terminals (Jaber et al., 1997). DAT1 is abundant in the striatum, midbrain, and hippocampus, but scarce and located at a distance from synaptic sites in PFC (Lewis et al., 2001; Sesack et al., 1998; Schott et al., 2006). SLC6A3, the gene coding for DAT1, is located on chromosome 5p15.3 (Kawarai et al., 1997). A 40-base pair variable nucleotide tandem repeat (VNTR) element is located in the 3' untranslated region and is repeated 3-13 times, with 9- and 10-repeat forms being most prevalent, with ~29% and ~69% prevalence in Caucasian populations, respectively (Kang et al., 1999; Sano et al., 1993). Because this VNTR is located in an untranslated region of the SLC6A3 gene, it does not alter protein structure, but may influence DAT1 expression through other mechanisms (Faraone et al., 2014). Recent meta-analyses have concluded that expression of DAT1 9-repeat allele (9R) is ostensibly higher than the 10-repeat allele (10R; Costa

et al., 2011; Faraone et al., 2014) though several earlier studies had concluded the opposite (Jacobsen et al., 2000; van de Giessen et al., 2009; van Dyck et al., 2005). Therefore, in line with recent meta-analyses, 9R homozygotes are expected to have lower concentrations of synaptic and extra-synaptic dopamine compared to 10R carriers at baseline. This is explained by the fact that increased DAT1 expression leads to greater dopamine reuptake.

1.8.2 DAT1 Genotype and Cognition

In 9R carriers, increased expression of DAT1, and consequently lower concentrations of synaptic and extra-synaptic dopamine at baseline, are expected to enhance the ratio between phasic, pulsatile, dopamine bursts related to events such as reward, positive feedback, or behavior, and tonic, basal dopamine release that occurs at rest. This enhanced signal-to-noise ratio is expected to result in more efficient signaling and potentially improved performance; however, given that this superior performance is expected on the basis of lower tonic, basal dopamine, 9R carriers are predicted to be more susceptible to overdose effects of exogenous dopamine.

In line with the hypothesis that 9R carriers have more efficient dopamine signaling and potentially improved performance, 9R carriers have been shown to have enhanced bilateral activity in striatum upon the reception of positive feedback (Forbes et al., 2009; Hariri et al., 2006). Dreher and colleagues (2009) also found that 9R carriers had greater reactivity in the midbrain and lateral PFC upon the reception of reward and, further, showed enhanced reactivity in DS and VS during reward anticipation. Two studies of reward-related activity in VS did not find effects of DAT1 until they accounted for additional dopaminergic polymorphisms (Nikolova et al., 2011; Yacubian et al., 2007). Nikolova and colleagues (2011) created a cumulative dopamine score for participants using

polymorphisms in DAT1, the D2 receptor, catechol-*O*-methyltransferase (COMT), and D4 receptor genes. When accounting for all these genotypes simultaneously, they found that dopamine scores accounted for 11% of the variability in VS reactivity in response to the reception of positive feedback, though they included the 10R allele in the high-dopamine set of polymorphisms. Yacubian and colleagues (2007) found increased VS reactivity in response to reward anticipation only when 9R carriers were also carriers of a COMT allele that leads to increased dopaminergic concentrations in PFC. Interestingly, 10R/10R homozygotes who carried all wild-type COMT alleles evidenced increased VS reactivity, similar to 9R carriers with increased PFC dopamine concentrations. These results indicated that only a high dopamine-low dopamine pairing of DAT1 and COMT alleles led to increased VS reactivity due to reward anticipation. Further, in a PET study of habitual smokers, increased smoking-related VS reactivity—hypothesized to be due to larger phasic dopamine bursts in 9R carriers, who have lower tonic synaptic dopamine concentrations—was seen in 9R carriers relative to 10R/10R homozygotes (Brody et al., 2006). 9R carriers, as compared to 10R/10R homozygotes, have also been shown to evidence a larger frontoparietal, novelty-dependent electroencephalographic response during the presentation of auditory cues signaling a task switch during a test of cognitive flexibility (Garcia-Garcia et al., 2010). These results suggest that 9R carriers are more sensitive to phasic increases in dopamine in the striatum.

This sensitivity in 9R carriers was also observed in a study of the effects of DAT1 genotype on memory encoding and retrieval. Schott and colleagues (2006) examined the effects of DAT1 genotype on memory encoding and retrieval in healthy participants in a study-recall task. Participants studied a list of 20 words in an MRI scanner, one-at-a-time until all words had been

presented. After a 90-second distractor task, they were asked to recall as many of the words as they could. This study-recall procedure repeated three times. Although DAT1 genotype did not affect subsequent remembering of list words, interesting differences in brain activations were seen. During successful encoding, determined by subsequent performance in the recall phase, expected midbrain, fronto-parietal-occipital, and limbic activations were observed. Interestingly, 9R carriers showed stronger activations in VS, inferior PFC, and anterior cingulate at the time of encoding for successfully remembered items. Further, during subsequent recall, 9R carriers showed stronger activation of midbrain/SN. DAT1 genotype was also shown to affect the functional coupling between hippocampus and PFC during successful encoding. Collapsing across genotype, they found the expected increase in functional connection between hippocampus and dorsal PFC and OFC. 9R carriers showed increased functional coupling between the hippocampus and both the OFC and VS, however. Taken together, although no differences were seen at the behavioural level between DAT1 genotypic groups, 9R carriers were more sensitive to activity-induced dopaminergic modulation both within the striatum and in regions to which it is anatomically and functionally connected.

The sensitivity of 9R carriers to exogenous dopamine was examined in a study probing the interactive effects of dopaminergic medication and DAT1 genotype on learning about others' prosociality. Eisenegger and colleagues (2013) tested healthy controls on either 300 mg of L-dopa or a placebo while participating in a task that required them to learn about the behavior of an automated second player in a monetary exchange task. The participants started out with 10 arbitrary units of money. On each trial they were instructed to transfer any amount of their money to a second player. Transfers had an 80% probability of reaching the second player. Transfers that

successfully arrived to the second player were tripled in value. If the transfer did reach the second player, they could choose to either make a repayment to the first player that equalized the payout, or they could choose to keep the entire amount. For the 20% of transfers that did not make it to the second player, the second player received nothing and could not make a repayment. This stochastic delivery of transfers ensured that participants could not determine with certainty the trials on which the second player opted not to repay versus trials on which the transfer did not occur and repayment was precluded. In the experiment, there were two types of second players: a prosocial player, who made repayments the majority of the time, and an antisocial player, who made infrequent repayments. There were no medication or genotypic effects when participants were paired with an antisocial player. In regards to prosocial second players, however, 9R carrier participants on L-dopa, compared to on placebo, secured less earnings, while 10R/10R participants on L-dopa secured more earnings than when they were on placebo.

Given the complexity of this task, maximizing earnings likely reflects both learning about the behavior of the second player and using this information for strategic decision-making. Given the design of this study, these processes could not be disentangled. Nonetheless, in line with predictions, 9R carriers evidenced dopamine overdose effects that produced either impaired learning about behavior or deficient decision making. In contrast, 10R/10R participants benefitted from exogenous dopamine producing either improved learning or superior decision making.

Taken together, these studies suggest that 9R carriers are more sensitive to elicited pulsatile or phasic dopamine, particularly in the striatum, as well as in functional cortical partners. These effects have been noted during successful encoding and retrieval, as seen through enhanced

regional brain activity and functional connectivity. 9R carriers were also shown to be more sensitive to dopamine overdose.

1.9 Aims of the Present Study

The aim of the current study was to investigate how differences in DAT1 affect baseline memory encoding and retrieval performance in healthy elderly controls. Foremost, we planned to investigate how polymorphisms in this gene interact with PD pathophysiology and dopaminergic therapy to affect memory encoding and retrieval performance. We intended to implement a study similar to MacDonald and colleagues (2013) with separate encoding and recall measures, investigating these effects in both the ON and OFF states in PD.

This study was designed to investigate the role of a dopaminergic polymorphism (DAT1 40-base-pair VNTR) on memory encoding and retrieval in PD patients on and off medication as well as in healthy controls. Identifying gene-medication interactions for cognitive symptoms in PD patients would be important from both a clinical and basic science standpoint. Clinically, identifying genes that interact with medication in certain cognitive domains could lead to treatment paradigms that account for a wider spectrum of potential complications and side effects. Additionally, this study could yield valuable insights on the mechanisms of memory encoding and retrieval by taking into account variation in endogenous dopamine signaling and their potential interactions in the presence of exogenous dopamine.

1.10 Hypotheses/Predictions

In healthy controls, we predicted superior encoding scores in DAT1 9R carriers, but did not expect genotype to affect recall scores.

Overall, for PD patients off medication, we expect to see a similar pattern of effects as in the control group for encoding, with 9R participants outperforming 10R/10R participants. In addition, based on previous research (MacDonald et al., 2013; Grogan et al., 2015), we expect PD patients off medication to perform equivalently to controls in the encoding task. On medication, we further predict that 9R PD patients will be more sensitive to overdose from exogenous dopamine and, hence, will have greatest impairment in performance relative to off performance. For recall, we expected PD patients to perform more poorly than controls regardless of genotype, and further that all PD patients would recall more items in the on than off dopamine state.

2.0 Methods

2.1 Participants

Forty-five patients with PD participated in the study. Patients were diagnosed by a licensed neurologist and met the core assessment criteria for diagnosis of idiopathic PD for surgical interventional therapy and the UK Brain Bank criteria for PD. All patients who participated in this study were referred directly from licensed neurologists. Patients who were recruited were asked to bring a control participant (e.g., spouse, relative, friend) with them if possible who was of a similar age and had completed a similar number of years of education. Controls were also recruited from a pre-existing database if particular patients could not bring a control participant with them. Forty-two healthy control participants were tested as well. Patients and controls were excluded if they were previously diagnosed with dementia or mild cognitive impairment, if they reported loss of a

previous level of function related to cognitive problems, or if they scored less than 22/30 on the Montreal Cognitive Assessment (MOCA). Further, participants were excluded if they were abusing alcohol, prescription or street drugs, or taking medications such as donepezil, galantamine, rivastigmine, memantine, or methylphenidate. Participants were also excluded if they were depressed or anxious enough to require treatment from a psychiatrist or if they had any neurological illnesses. This study was approved by the ethics review board of both the Sudbury Regional Hospital (Sudbury, Ontario, Canada), and the University of Western Ontario (London, Ontario, Canada). All participants provided informed consent prior to testing according to the Declaration of Helsinki (1991).

Presence of disease as well as severity were assessed for all patients both on and off dopaminergic medication using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) by a licensed movement disorders neurologist. All controls were screened for signs of PD and a score was assigned to them on the UPDRS. None were judged to have PD. All patients and no controls were treated with dopamine replacement medications such as L-dopa and/or dopamine agonists. Eighteen Patients were taking dopamine agonist medication. Table 2.1 presents mean group demographic information, screening affective and cognitive measures, and daily dose of DA-replacement medications in L-dopa equivalents. Calculation of daily L-dopa equivalent dose for each patient was based on theoretical equivalence to L-dopa (Evans et al., 2004) as follows: L-dopa dose + L-dopa dose x 1/3 if on entacapone + bromocriptine (mg) x 10 + cabergoline or pramipexole (mg) x 67 + ropinirole (mg) x 20 + pergolide (mg) x 100 + apomorphine (mg) x 8.

Two participants from each group were excluded because of an inability to properly determine their genotypes for the DAT1 gene. As such, 43 PD patients and 40 controls were included in our subsequent analyses.

Table 2.1: Demographic and screening data for PD patients and controls separated by genotype

	PD		Control	
	10R/10R	9R	10R/10R	9R
<i>n</i>	29	14	26	14
Age	68.03 (1.40)	69.14 (1.80)	64.42 (1.13)	67.54 (2.02)
Education	15.17 (0.51)	14.35 (0.86)	14.50 (0.48)	13.46 (0.66)
Years Disease	6.83 (1.31)	6.27 (1.30)	-	-
LED (mg)	683.60 (63.69)	687.63 (86.87)	-	-
DA (n)	13	5	-	-
BDI-II (ON)	8.07 (1.16)	10.43 (1.34)	3.31 (0.72)	3.07 (1.22)
BDI-II (OFF)	8.44 (1.05)	10.93 (1.51)	3.81 (0.88)	4.21 (1.39)
BAI (ON)	8.59 (1.27)	12.00 (2.63)	3.19 (0.72)	3.43 (1.09)
BAI (OFF)	9.90 (1.52)	11.50 (1.92)	2.69 (0.67)	2.71 (0.70)
SAS (ON)	11.93 (1.01)	12.50 (1.42)	9.62 (0.82)	9.86 (1.32)
SAS (OFF)	11.41 (1.15)	11.50 (1.32)	9.69 (0.94)	9.21 (1.48)
ANART IQ	122.45 (1.53)	123.917 (2.40)	123.27 (1.51)	123.11 (2.00)
F-Words	13.45 (0.77)	16.62 (1.83)	14.35 (0.84)	14.93 (1.01)
A-Words	10.07 (0.81)	13.46 (1.66)	12.04 (0.81)	13.00 (1.37)
S-Words	13.41 (0.90)	17.92 (1.99)	15.15 (0.82)	15.07 (1.43)
Animals	19.03 (1.12)	19.69 (1.74)	20.64 (1.21)	21.00 (1.01)
MOCA	25.79 (0.43)	26.86 (0.61)	27.62 (0.52)	27.07 (0.62)

All values reported are group means (SEM). Education refers to the number of years spent in the education system. Controls were not given dopaminergic medication, but their data are presented to correspond to the ON-OFF order of the PD patient to whom they were matched. Elaboration of measures used in table follow below.

Education = years of education; **Years Disease** = years since diagnosis of PD; **LED** = daily L-DOPA equivalent dose in mg; **DA** = number of PD patients who were taking dopamine agonist drugs; **BDI-II** = Beck Depression Inventory II score; **BAI** = Beck Anxiety Inventory score; **SAS** = Starkstein Apathy Scale scores; **ANART IQ** = National Adult Reading Test (Nelson and Willison, 1991) IQ estimation (tested in the ON session only); **F-, A-, or S-Words** = number of words beginning with the letter F, A, or S, respectively, generated in 60 s (tested in the ON session only); **MOCA** = total score on the Montreal Cognitive Assessment.

When examining the effect of DAT1 genotype on our demographic and screening measures within the PD patient and control groups, we found no significant differences in any measure in either

group (Table 2.1). We also noted a significant difference in both age ($t = -2.01$, $p = 0.05$) and MOCA scores ($t = 2.72$, $p < 0.01$) between our 10R/10R PD patients and 10R/10R controls. No statistically significant differences were seen between 9R carrier PD patients and controls. When collapsing across genotype, PD patients had higher scores than controls on the Beck Depression Inventory-II and Beck Anxiety Inventory during both the on and off medication sessions and on the Starkstein Apathy Scale during the on medication session. This is a common finding (Aarsland et al., 2011; Broen et al., 2016; den Brok et al., 2015). Despite these higher scores, no PD patients (or controls) were moderately or severely depressed or anxious. We used an a priori cutoff of 28 (i.e., moderate depression) for the BDI-II and BAI for exclusion, but no participants approached this cutoff for either inventory. Finally, PD patients had statistically significantly lower MOCA scores than healthy controls, though means for both groups were within normal limits.

2.2 Genotyping Procedure and Results

Saliva samples were collected from participants using Oragene 2 mL DNA collection kits (DNA Genotek, Ottawa, Ontario, Canada). A 40-base-pair VNTR located in the 3' -untranslated region of the DAT1 cDNA was amplified using polymerase chain reaction from genomic DNA using 5 U of Taq DNA polymerase. An initial denaturation was completed for 3 min at 95.1 °C. Afterward, 35 cycles of denaturing at 93.1 °C for 45 s, annealing at 67.5 °C for 45 s, and extension at 72.1 °C for 45 s were performed, all in the presence of primers 5'-TGT GGT GTA GGG AAC GGC CTG AG-3' and 5'-CTT CCT GGA GGT CAC GGC TCA AGG-3'. A final extension was then completed at 72.1 °C for 3 min. polymerase chain reaction amplification was carried out in a final volume of 25 µL consisting of 80 ng of genomic DNA, 250 µM of each deoxyribonucleotide, 10 pmol of sense and antisense primers, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, and 1.5 mM MgCl₂.

66.7% of participants were homozygous for the 10R allele and 33.3% of participants were carriers of a single 9R allele and a 10R allele. No participants were homozygous for the 9R allele. The DAT1 gene was shown to be in Hardy-Weinberg equilibrium (χ^2 test, $p = 0.067$). DAT1 genotypic frequency was similar for control (10R/10R: 65%, 9R: 35%) and PD patient (10R/10R: 68.2%, 9R: 31.8%) groups.

2.3 Design and Procedure

Participants performed two versions of the AFLT on two consecutive days. PD Patients completed the AFLT once while on their dopamine-replacement therapy and once while off dopamine-replacement therapy. We counterbalanced the ON-OFF order such that half the participants first completed the task while ON and the other half first completed the task while OFF. PD patients took their medication as per their neurologist's instruction in ON sessions. Patients were instructed to abstain from taking L-dopa 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 began in the OFF state. Control participants were also tested on two days, although control participants were not given any dopamine-replacement medication. By testing control participants on two consecutive days, and analyzing their data to correspond to the PD patient to whom they were matched, we controlled for any potential order, fatigue, or practice effects related to repeatedly performing different versions of our memory measures.

In each session, a set of 15 abstract symbols, List A, was presented to participants. These symbols were presented one at a time for 1000 ms in the centre of a computer monitor. Participants were

instructed to try to remember as many of these symbols as possible. After the entire list had been presented, the participant was given 60 s to draw all the symbols they could remember onto a piece of paper. This study-immediate recall procedure for List A was repeated five times in each version of the AFLT task.

A second set of 15 abstract symbols, List B, was then presented using parameters identical to those above, but List B was only presented a single time. Participants were then given 60 s to draw all the symbols they could remember after the presentation List B. Next, participants were asked to draw all the symbols that they could recall from List A again.

After a 30-minute period of delay, during which participants performed distractor tasks (a number comparison task not reported here), participants were asked to draw all the symbols that they could freely recall from Lists A and B.

Appendices 5.1-5.4 present Versions 1 and 2 of Lists A and B. Versions 1 of all lists was used on Day 1 and Versions 2 of all lists were used on Day 2, regardless of ON or OFF medication status. In this way, an equal number of PD patients performed Versions 1 and 2 lists in the ON and OFF states.

2.4 Data Analysis

The AFLT was scored by two researchers who were blinded to the identity of the participant (i.e., PD or Control) and session (i.e., ON or OFF state). A single point was awarded for each recalled item that could be unambiguously identified. Therefore, items were classified as correct if they

had minor distortions in their shape or orientation. Any discrepancies in scoring between the two scorers were addressed such that an agreement was reached concerning scoring of these items.

The difference in the number of correctly recalled items from the first and final study-immediate recall phases was used as our metric of memory encoding (Vakil et al., 1998, 2010; Mitrushina, et al., 2005; Vakil & Blachstein, 1993; Woodard et al, 1999; Crawford et al., 1989). That is, the number of items successfully recalled in the first study-immediate recall phase was subtracted from the number of items successfully recalled in the final study-immediate recall phase. This was to control for the effects of working memory and immediate recall abilities. This subtraction serves to better isolate the memory encoding performance. This strategy aims to eliminate effects related to retrieval ability on performance, as retrieval ability is expected to contribute to performance equally for the first and the last study-immediate recall phases, with differences across phases owing more to a participants' encoding (Vakil et al., 1998, 2010; Mitrushina, et al., 2005; Vakil & Blachstein, 1993; Woodard et al, 1999; Crawford et al., 1989).

We used the total number of items recalled from List A after the 30-minute delay divided by the total score achieved in the final study-immediate recall phase as our measure of memory recall. Unlike study-immediate recall phases, recall after delay is believed to preferentially index retrieval processes (Wixted and Ebbesen, 1991). Further, by correcting for the number of items recalled on the final study-immediate recall phase, retrieval can be assessed in a less biased manner, controlling for differences between individuals in encoding ability.

Encoding scores and weighted recall scores were used as dependent measures in two separate 2x2x2 mixed-design analyses of variance (ANOVA) with Group (PD vs. Control) and Genotype (DAT1 10R/10R vs. 9R carriers) as between-subject factors, and Session (ON vs. OFF) as the within-subject variable. Where warranted by significant interaction results, we followed up with subsequent 2x2 mixed ANOVAs with Group (PD vs. Control) or Genotype (DAT1 10R/10R vs. 9R carriers) as the between-subject factors and Session (ON vs. OFF) as the within-subject variable. If justified by the analyses described above, we investigated further in one-way ANOVAs with Session (ON vs. OFF) as the within-subject factor to explore the simple effects of Session within Group and/or Genotype.

3.0 Results

3.1 Encoding Phase

We examined encoding scores in the AFLT in a 2x2x2 mixed ANOVA with group (PD vs. Control) and DAT1 genotype (DAT1 10R/10R vs. 9R carriers) as between-subject factors, and Session (ON vs. OFF) as the within-subject variable (Table 3.1; Figure 3.1). We found a marginally significant main effect of Group with lower encoding scores for PD compared to Controls [$F(1, 79) = 3.327, MSE = 8.137, p = 0.072$]. Session x Group [$F(1, 79) = 4.311, MSE = 2.809, p < 0.05$] and Session x DAT1 [$F(1, 79) = 4.518, MSE = 2.809, p < 0.05$] interactions were significant.

To better understand these interactions, we next examined Group and Session effects for each of the DAT1 genotypes separately. For 9R carrier participants, there was a Session x Group interaction [$F(1, 26) = 4.101, MSE = 2.304, p = 0.053$] that did not quite reach significance, but no significant main effects. This interaction for 9R carriers resulted due to a significant ON-OFF

effect for PD patients but not controls ($F < 1$), with PD patients performing significantly more poorly ON relative to OFF medication [$F(1, 13) = 6.250$, $MSE = 2.286$, $p < 0.05$]. For 10R/10R participants, there was only a significant main effect of Group [$F(1, 53) = 5.844$, $MSE = 7.268$, $p < 0.025$] with controls outperforming PD patients.

In sum, we see overdose effects in the 9R carrier PD group and poorer performance in 10R/10R PD patients on medication compared to 10R/10R Controls.

Table 3.1: Final study-immediate recall, encoding scores, and weighted recall scores for PD patients and controls separated by DAT1 genotype

	PD		Control	
	10R/10R	9R	10R/10R	9R
<i>n</i>	29	14	26	14
Final Recall (ON)	7.45 (0.41)	7.14 (0.78)	9.73 (0.44)	8.14 (0.91)
Final Recall (OFF)	7.93 (0.42)	7.71 (0.79)	9.65 (0.53)	8.14 (0.69)
Encoding (ON)	5.24 (0.41)	4.43 (0.55)	6.81 (0.38)	5.71 (0.70)
Encoding (OFF)	5.00 (0.43)	5.86 (0.75)	5.92 (0.50)	5.50 (0.63)
Weighted Recall (ON)	1.14 (0.05)	1.22 (0.15)	1.08 (0.03)	1.03 (0.06)
Weighted Recall (OFF)	0.97 (0.05)	1.03 (0.09)	1.16 (0.07)	1.08 (0.04)

All values reported are group means (SEM). First trial values correspond to the mean number of items recalled by each group in the first study-immediate recall trial. Final recall values correspond to the mean number of items recalled by each group in the final study-immediate recall trial. Encoding scores were calculated for each participant by subtracting the first recall score from the final recall score. Weighted recall scores were calculated by dividing the number of items recalled after a 30-minute delay by the number of items recalled during the final study-immediate recall trial. 10R/10R groups are composed of those who were homozygous for the 10R DAT1 VNTR allele. 9R groups are composed of those who were heterozygous for the 9R DAT1 VNTR allele.

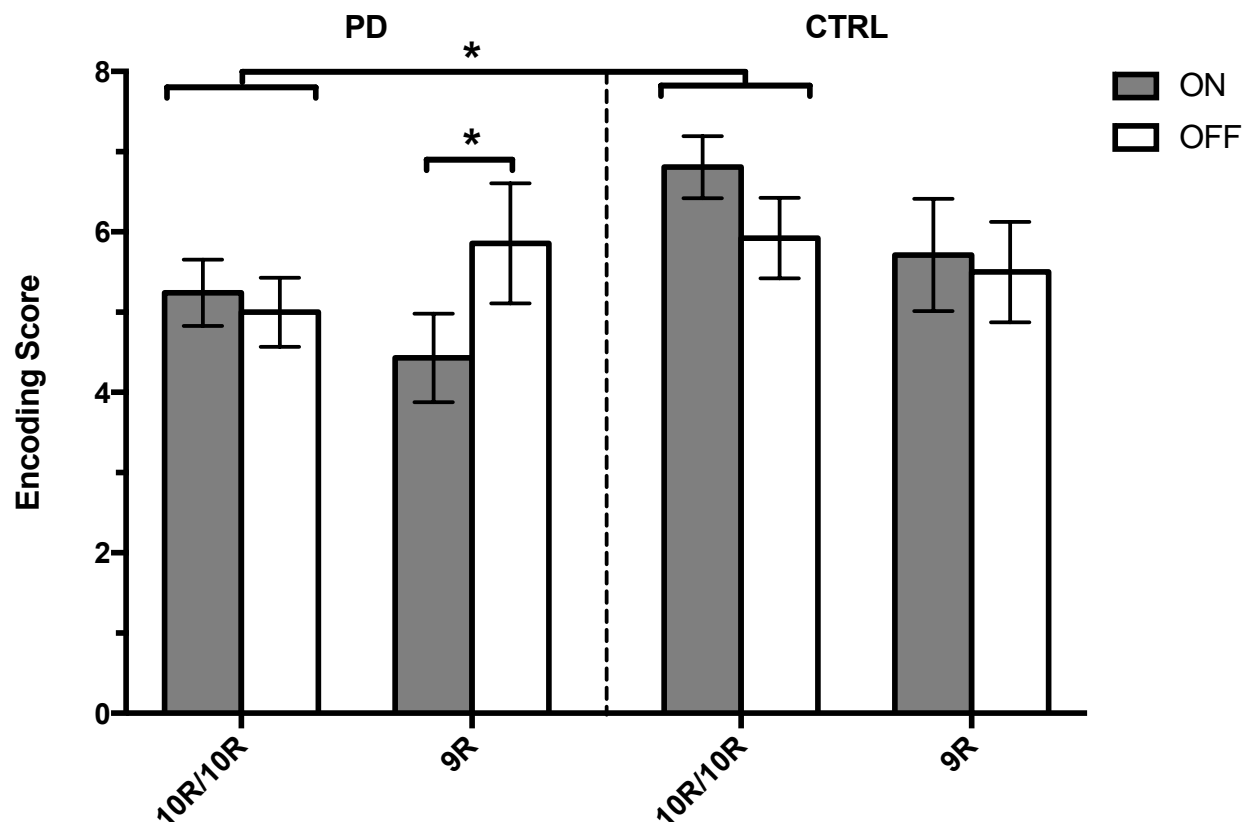


Figure 3.1. Encoding Scores. Mean encoding scores (\pm SEM) during the AFLT for PD patients and controls, on and off medication, separated into 9R carriers ($n_{(PD)} = 14$; $n_{(CTRL)} = 14$) and 10R/10R homozygotes ($n_{(PD)} = 26$; $n_{(CTRL)} = 29$) of the DAT1 40-bp VNTR polymorphism. A single asterisk represents $p < 0.05$.

3.2 Recall Phase

We examined recall performance in the AFLT in a 2x2x2 mixed ANOVA with group (PD vs. Control) and DAT1 genotype (DAT1 10R/10R vs. 9R carriers) as between-subject factors and Session (ON vs. OFF) as the within-subject variable (Table 3.1; Figure 3.2). There was no main effect of Group or DAT1. There was a significant Session x Group interaction [$F(1, 79) = 6.737$, $MSE = 0.085$, $p < 0.025$]. Exploring this interaction further, in PD patients, we found a significant main effect of Session [$F(1, 41) = 5.411$, $MSE = 0.119$, $p = 0.025$], reflecting better recall performance when on relative to off medication with no effect of Session in controls [$F(1, 38) = 1.539$, $MSE = 0.058$, $p > 0.20$].

In summary, we found that the administration of dopamine replacement medication improved recall scores in all PD patients. There were no differential effects related to DAT1 genotype. There were no differences in performance in the control participants based on Session, as expected given that they did not receive dopaminergic therapy nor with respect to DAT1 genotype.

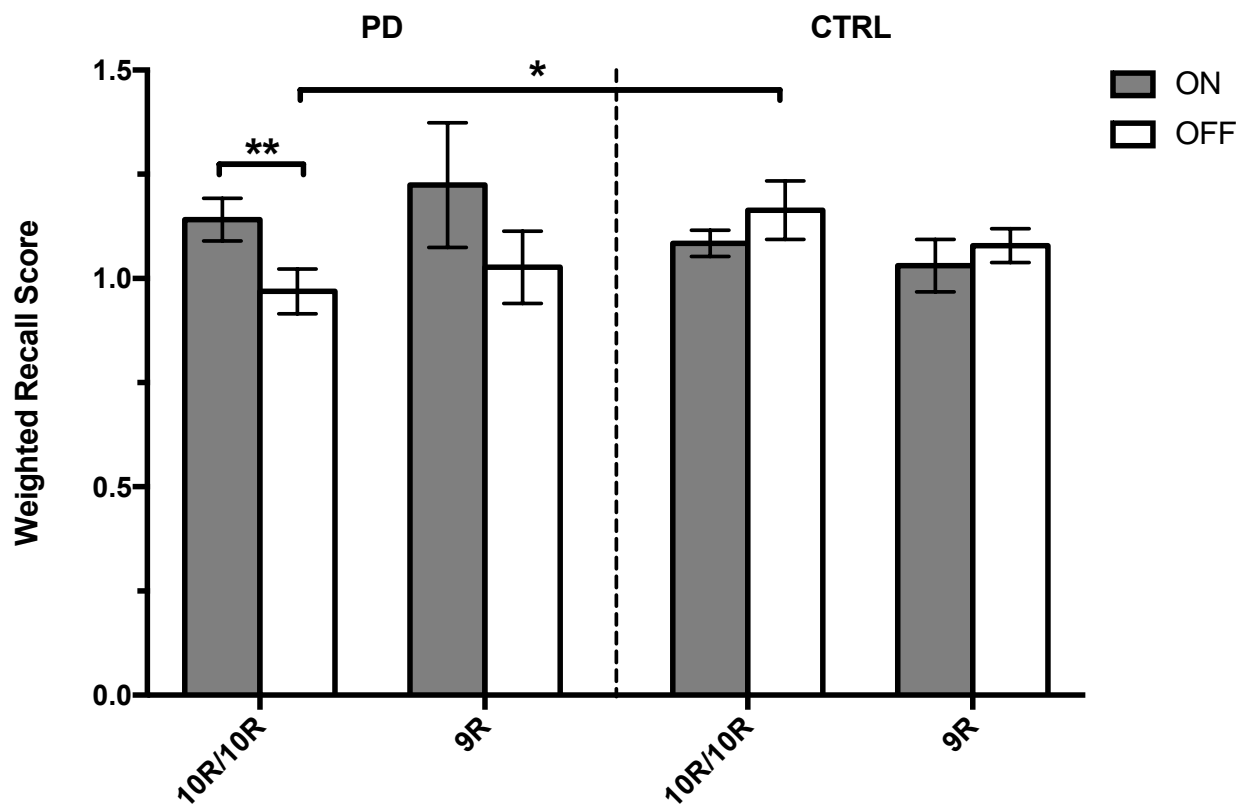


Figure 3.2. Recall Scores. Mean recall scores (\pm SEM) during the AFLT for PD patients and controls, on and off medication, separated into 9R carriers ($n_{(PD)} = 14$; $n_{(CTRL)} = 14$) and 10R/10R homozygotes ($n_{(PD)} = 26$; $n_{(CTRL)} = 29$) of the DAT 40-bp VNTR polymorphism. A double asterisk represents $p < 0.01$. A single asterisk represents $p < 0.05$.

4.0 Discussion

4.1 Summary of Results

We investigated the impact of DAT1 polymorphisms on encoding and retrieval in healthy, elderly controls as well as in PD patients. We further explored the effect of dopaminergic therapy on performance in our PD patients. With respect to encoding, we found no main effects of DAT1 polymorphisms overall or in either group. In 9R carriers, however, PD patients had lower encoding scores on, relative to off, medication, though no ON-OFF effect was noted in 10R/10R homozygotes. Finally, we also found that 10R/10R controls outperformed 10R/10R PD patients, though 9R PD patients performed statistically equivalently to 9R controls.

Turning to our measure of retrieval, we found that DAT1 polymorphisms did not yield main effects overall, or in either group, and this variable did not interact Group or Session. We found that the administration of dopaminergic medication enhanced memory retrieval in PD patients, though there was no effect of Session in the control group.

4.2 Memory Encoding and Retrieval in PD

This study is only the third designed to investigate explicit memory encoding and retrieval processes separately in PD patients, both on and off dopaminergic therapy. Performance on each study-immediate recall trial reflected the combined influences of encoding and retrieval from long-term memory, as well as of immediate or working memory processes. However, the number of items transferred to long-term memory was expected to systematically increase across study-immediate recall trials, with less clearly predictable effects on other processes. Consequently, subtracting performance in the final from the first stimulus-recall trial provided a less confounded estimate of encoding or learning (Vakil et al., 1998, 2010; Mitrushina, et al., 2005; Vakil & Blachstein, 1993; Woodard et al, 1999; Crawford et al., 1989). Conversely, by weighting delayed

recall performance relative to the number of items recalled on the final study-immediate recall condition, we could assess retrieval processes, discounting differences in encoding ability across participants (MacDonald et al., 2013; Wixted and Ebbesen, 1991).

Our findings are essentially in line with those of both previous studies, obtaining poorer encoding scores on than off medication for 9R PD carriers and improved recall performance for PD patients, irrespective of genotype, on relative to off medication. MacDonald and colleagues (2013) and Grogan and colleagues (2015) similarly found that encoding in PD is superior at baseline and is worsened by dopaminergic medication. In contrast, retrieval was found to be impaired in the OFF state and was improved by dopamine supplementation. This pattern of findings is easily explained relating the different brain regions that are implicated in encoding and retrieval to known PD pathophysiology.

4.3 Interpretation of Memory Encoding Results

Encoding is consistently shown to recruit and depend upon VTA-innervated brain regions. Early studies in patients with temporal lobectomies revealed an inability to encode new explicit information (Milner, 1968, 1972; Scoville and Milner, 1957). Using neuroimaging techniques, explicit memory encoding has also been shown to preferentially engage the VTA-innervated medial temporal structures, such as the hippocampus (Schrager et al., 2008). An influential model proposed by Lisman and Grace (2005) describes a novelty-dependent loop responsible for long-term memory encoding which includes hippocampus, subiculum, pallidum, VS, and VTA. The hippocampus is described as the gate to this loop. It detects novel information and sends a downstream signal through the subiculum and pallidum to VS, where connections to the VTA

arise, eliciting dopamine release from the VTA to the hippocampus. Dopamine release from the VTA to the hippocampus is postulated to facilitate memory encoding. Hippocampus activity has been noted during the presentation of novel stimuli and during memory studies of intentional encoding using a variety of neuroimaging as well as molecular techniques, including single-unit recordings (Fyhn et al., 2002) PET (Tulving et al., 1996), fMRI (Strange and Dolan, 2001; Yamaguchi et al., 2004; Spaniol et al., 2009) and c-Fos quantification (Jenkins et al., 2004).

Another brain region that receives dopaminergic innervation from VTA and has been implicated in learning and encoding is the OFC. OFC is bi-directionally connected to medial temporal regions such as the hippocampus (Barbas, 1993; Barbas and Blatt, 1995; Catenoix et al., 2005; Cavada et al., 2000). OFC activity is elicited during the presentation of novel visual stimuli in non-human primates (Rolls et al., 2005). OFC activity is also correlated with subsequent successful recall performance (Frey and Petrides, 2003). Given that OFC has been found previously to be activated during the presentation of deviant visual stimuli (Petrides et al., 2002), OFC may be implicated in the encoding process of the AFLT. OFC may be engaged during the presentation of a symbol that was incorrectly recalled during a previous recall phase because the presented symbol will appear deviant relative to the participant's incorrect memory of it. Therefore, deficient functioning of VTA-innervated OFC may contribute to deficient encoding.

In addition to its proposed role in the novelty-dependent encoding loop proposed by Lisman and Grace (2005), VS, another VTA-innervated brain region, seems to be implicated in learning and memory encoding (Atallah et al., 2007; Hiebert et al., 2014; MacDonald et al., 2013; Spaniol et al., 2009). Early theories suggested that VS is specialized for reward learning and processing

(Camara et al., 2010; Cools et al., 2002; Delgado et al., 2000, 2007; Knutson and Cooper, 2005; O'Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010). However, a role for VS in learning situations where no reward, punishment, or even feedback is present has been described in many recent studies (Feigin et al., 2003; Ghiladri et al., 2007; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2006; Tremblay et al., 2010).

Characteristic of a region implicated in learning and encoding, VS activity noted using neuroimaging is greatest early in a task, when rules and strategies are being acquired (Seger, 2006, 2010; Delgado 2005; Filoteo et al., 2005) and decreases as performance asymptotes (Reiss et al., 2005; Hiebert et al., 2014). Once learning is established, VS activity only peaks after salient events occur, such as the reception of unexpected rewards (Bray et al., 2007; Breiter et al., 2001; Rodriguez et al., 2006; Ullsperger et al., 2003; Hampton et al., 2007) or negative feedback after errors (Simoes-Franklin et al., 2010).

Though the examples in the preceding paragraph relate to situations in which encoding occurs implicitly or unconsciously, VS was identified as a region in a meta-analysis of explicit memory encoding (Spaniol et al., 2009). Further, Goldenberg and colleagues (1999) documented an inability to intentionally learn new verbal material in a patient following a focal, left nucleus accumbens (i.e., VS) bleed. In contrast, this patient performed normally on measures that demanded retrieval of previously-learned verbal information, or tests of divided and shifting attention, working memory, language, as well as of encoding and retrieval of non-verbal information. Finally, Mizuta and Motomura (2006) investigated explicit word list learning in three patients with infarcts owing to left recurrent artery of Heubner (RAH) occlusions—the artery that

specifically and exclusively supplies VS—documented during neurosurgical intervention for anterior communicating artery (AComm) aneurysms, relative to two patients with right RAH occlusions and three patients treated for AComm aneurysms without RAH impairment or consequent VS infarction. Patients with left but not right VS infarcts were specifically impaired in word list learning. Taken together, these results seem to implicate VS in explicitly learning new information, with left VS lateralized for verbal materials.

The VTA is relatively spared in PD, particularly at early stages of disease (Kish et al., 1988). Administration of exogenous dopamine, titrated to motor symptoms mediated by the significantly dopamine-depleted DS, reliably impairs functions performed by VTA-innervated brain regions, such as VS, limbic, and prefrontal cortical regions, through dopamine overdose (Gotham, 1988; Cools et al., 2006; MacDonald and Monchi, 2011). This includes explicit memory encoding (Chiaravalloti et al., 2014; Ellfolk et al., 2013; Knoke et al., 1998; MacDonald et al., 2013; Grogan et al., 2015). In addition to increased dopamine concentrations in VTA-innervated regions relative to DS, particular cytoarchitectonic aspects of VS are likely to predispose this region to disruption from dopamine overdose. VS MSNs are smaller relative to other MSN populations, have fewer dendrites and spines, and have sparser dopaminergic input than DS (Wickens et al., 2007). As such, receptor stimulation in VS is slower and more sensitive to dopaminergic input intensity (Wickens et al., 2007). Indeed, VS MSNs show graded, incremental, and more finely-tuned responses affected to a greater degree by the intensities or frequencies of dopamine impulses than DS (Zhang et al., 2009). Additionally, VS has a lower DAT concentration than DS, which, through decreased synaptic clearance, results in a longer duration response to dopamine stimulation (Wickens et al., 2007). Given these cytoarchitectonic features—independent of the fact that it

receives more ample dopaminergic supply at baseline due to its innervation from spared VTA—VS seems more susceptible to exogenous dopamine overdose and disruption of its function than DS.

4.4 Interpretation of Memory Retrieval Results

Explicit retrieval processes (e.g., recall and recognition memory processes) have been less well researched, but seem to implicate more distributed brain regions, including DS and cortical regions to which DS is reciprocally connected, in addition to medial temporal structures (Spaniol et al., 2009). Frontal lobe lesions, particularly in dlPFC (Gershberg and Shimamura, 1995; Eslinger and Grattan, 1994; Stuss et al., 1994) impair free recall, and these brain regions as well as a dorsal frontoparietal network (Kragel and Polyn, 2013) are engaged preferentially using neuroimaging during free recall and recognition memory testing. A meta-analysis of 30 neuroimaging studies investigating retrieval in a recognition memory performance revealed large clusters of preferential activation in DS, dorsal frontal regions such as dlPFC, and other cortical partners of DS, including frontal eye fields and motor cortices (Spaniol et al., 2009). In other studies, DS is preferentially activated in neuroimaging studies when recognizing previously-presented items in an episodic recognition test (Kim, 2010) as well as during remembering of category membership (Seger et al., 2010; Helie et al., 2010).

In addition to explicit memory retrieval tests, DS is implicated in implicit forms of remembering. DS is engaged when performing previously-learned motor sequences relative to the performance of random motor sequences (Reiss et al., 2005). DS is instrumental in navigating the Morris Water Maze (MWM)—a task that requires the unconscious retrieval and application of previously-

learned information (Miranda et al., 2006; Miyoshi et al., 2012). Increased oxidative metabolism, an indirect measure of cellular activity, is observed in DS in experimental animals performing tasks that require retrieval of previously-learned spatial information (Mendez-Couz et al., 2015; Miranda et al., 2006; Miyoshi et al., 2012). In humans, participants deemed to be more accurate spatial navigators have been shown to have higher hippocampal and caudate activations when following a well-learned route in a familiar environment (Hartley et al., 2003). These findings support the notion that DS plays a role in tasks that require the retrieval of previously-learned information both explicitly and implicitly.

DS is most often implicated in decision making and response or action selection (Grahn et al., 2008; Hiebert et al., 2014). Studies of DS lesions in humans and non-human primates have shown deficits in shifting attention between stimuli, especially away from more salient ones (Benke et al., 2003; Cools et al., 2003, 2010; Thoma et al., 2008), in flexibly altering decision-making strategies or response sets (Benke et al., 2003; Cameron et al., 2010; Ell et al., 2006; Grahn et al., 2008; Leber et al., 2008; Yehene et al., 2008), suppressing more automatic responses (Benke et al., 2003; Cameron et al., 2010; MacDonald et al., 2011; White, 2009; Robertson et al., 2015), and in updating goals when the parameters for decisions have changed (Grahn et al., 2008; Hazy et al., 2006; Vakil et al., 2004). Reviewing this extensive literature, DS is implicated in flexible decision-making and selecting, particularly in ambiguous or high-competition contexts (Ali et al. 2010; Grinband et al., 2006; MacDonald et al., 2011; Monchi et al., 2001, 2006; Robertson et al., 2015; Rogers et al., 2000; van Schouwenburg et al., 2010). DS promotes selection of responses or actions in the motor system and of sensory stimuli via attentional systems (Ali et al., 2010, Leung et al., 2000, Pardo et al., 1990, Pinel et al., 2004, Peterson et al., 1999, 2002; MacDonald et al., 2011).

We speculate that analogously, DS's role in retrieval is to facilitate selection among internally generated stimuli.

DS is seriously dopamine restricted in PD in the OFF state, even at early stages of disease. Consequently, functions mediated by DS, such as movements and cognitions, are impaired when PD patients are tested off dopaminergic therapy. Functional neuroimaging has also revealed that cortical networks implicating DS are dysfunctional in PD patients in the OFF state (MacDonald and Monchi, 2011). Consistent with this literature, delayed recall in the AFLT was impaired in PD patients off medication relative to performance of healthy controls (MacDonald et al., 2013). Functions performed by DS and by its cortical partners are consistently improved by dopaminergic supplementation. In line with this, we found that in PD patients, recall after delay, weighted relative to number of items recalled in the final study-immediate recall phase, was improved by dopaminergic therapy.

The cytoarchitectonics of DS are quite different than those of VS. As such, it is expected that dopamine replacement medication will affect DS in a different manner than is expected in VS. DS is supplied by very dense dopamine inputs from the SN. This high density of dopamine inputs and the numerous dendrites and spines on DS MSNs (Wickens et al., 2007) cause rapid and maximal responses in DS through a wide range of SN firing frequencies and intensities (Wickens et al., 2007; Zhang et al., 2009). Further, DS is invested with high concentrations of DAT1, resulting in dopamine being rapidly cleared after release from presynaptic terminals. This results in short periods of dopaminergic stimulation for DS MSNs (Wickens et al., 2007). When all the above is considered, dopaminergic stimulation in DS is precisely-timed, brief, and seemingly binary

because maximal responding occurs over wide ranges of stimulation. DS seems attuned for rapid, flexible, and more absolute responding that would be advantageous for a brain region implicated in deciding between alternatives. These characteristics also suggest that DS is more likely to benefit from exogenous dopamine, as finely-tuned or graded responses are not observed, and this region seems less likely to experience dopamine overdose.

4.5 Relevance of Current Study to Memory Function in PD

The current study, along with those that have employed a similar approach, provide a framework for beginning to understand the significant inconsistency that arises in the PD memory literature (Chiaravalloti et al., 2014; Ellfolk et al., 2013; Knoke et al., 1998; Pirogovsky-Turk et al., 2015; Ellfolk et al., 2012; Higginson et al., 2005; Ibarretxe-Bilbai et al., 2011; Vingerhoets et al., 2005). Most previous investigations of memory have tested PD patients either on or off dopaminergic therapy, not both, obtaining memory measures influenced by combined encoding and retrieval processes. Performance in these studies, therefore, reflects the summed effects, in unknown proportions, of a) some deficient and b) other spared memory processes in PD, as well as of c) medication-induced improvements in some operations and d) impairments in others. To elaborate, accounting for the considerable variability in the PD memory literature, even small methodological changes across studies could greatly affect the estimates of memory that are obtained. Procedures that emphasize encoding will have contrary effects on performance to methods that accentuate retrieval processes. Adding further to the inconsistency, dopaminergic therapy exerts opposite effects on encoding and retrieval processes, as shown in our study.

4.6 DAT1 Effects on Memory Function in PD

The most novel aspect of our study was that we investigated the impact of differences in DAT1 polymorphisms on performance in PD. Our study constitutes the first to investigate the effect of 9R versus 10R/10R polymorphisms in the DAT1 gene on explicit memory encoding and retrieval, in healthy elderly controls compared to PD patients.

4.6.1 Encoding Effects

DAT1 controls clearance and re-uptake of synaptic and extrasynaptic dopamine, particularly in striatum and hippocampus. Recent meta-analyses have concluded that expression of DAT1 9R allele is higher than the 10R/10R homozygotes (Costa et al., 2011; Faraone et al., 2014), despite previous studies that have concluded the opposite (Jacobsen et al., 2000; van de Giessen et al., 2009; van Dyck et al., 2005). As such, 9R carriers are predicted to have lower concentrations of synaptic and extra-synaptic DA compared to 10R/10R participants at baseline. Lower baseline dopamine concentrations were hypothesized to yield higher signal-to-noise ratio, with more impact of teaching signals in the form of event-related, phasic, and pulsatile dopamine bursts relative to tonic or basal dopamine levels. Consequently, we expected 9R carriers to evidence improved encoding relative to 10R/10R participants.

There were no main effects of DAT1 genotype on encoding overall or in either group separately. Though we predicted differences on the basis of DAT1 genotype, failure to find significant differences was not inconsistent with the literature in healthy participants. To this point, standard behavioural measures have not clearly revealed differences in performance based on DAT1 genotypes (Congdon et al., 2009; Eisenegger et al., 2013; Garcia-Garcia et al., 2010; Kasparbauer et al., 2015; Schott et al., 2006). Neuroimaging measures appear to be more sensitive to these

differences, however. In healthy participants, larger activations are elicited in the midbrain dopaminergic reward system in 9R carriers compared to 10R/10R homozygotes (Dreher et al., 2009; Forbes et al., 2009; Hariri et al., 2006). Further, enhanced activity in VS, inferior PFC, and anterior cingulate cortex have been noted in 9R carrier healthy participants during successful encoding of list items (Schott et al., 2006). In addition to the possibility that our behavioural measures were too insensitive to detect differences in encoding performance across genotype that have been noted previously in terms of neural activity using functional neuroimaging, our current experiment was underpowered with 28 9R carriers and 55 10R/10R homozygotes overall (14 9R carrier PD patients, 14 9R carrier controls, 29 10R/10R PD patients, and 26 10R/10R controls).

Contrasting PD and Control groups on encoding for each genotype independently, we found poorer performance for PD patients relative to controls for the 10R/10R genotype only. Taken at face value, this could suggest that for 10R/10R PD homozygotes, higher basal dopamine decreased efficiency of event or reward-related pulsatile dopamine to achieve the necessary phasic-to-basal ratio to produce downstream signaling. Due to even *minor* dopamine depletion in VTA-innervated regions, PDs could have been more affected than controls by the inefficiency in reaching critical signal-to-noise differences, through generation of sufficiently large phasic dopamine bursts relative to the higher basal dopamine levels in the 10R/10R homozygotes. Previous research suggests that exceeding a given signal-to-noise (i.e., phasic-to-basal dopamine) threshold triggers activation of D1 receptor neurons and learning (Frank, 2005; Kerr and Wickens, 2001; Kravitz et al., 2012; Reynolds et al., 2001; Shen et al., 2008; Wickens et al., 2003). Further, PD lessens DAT1 levels further (Booij et al., 1997), potentially further increasing tonic, basal dopamine in 10R/10R PD patients in the OFF as well as in the ON dopaminergic therapy state. Finally, repeated and

chronic exposure to dopaminergic therapy could yield receptor changes that exacerbate these inefficiencies (Aquino et al., 2015).

The above interpretation of the finding that encoding was less effective in PD 10R/10R relative to control 10R/10R is constrained by the fact that 9R and 10R/10R PDs did not differ in encoding performance. Further, this differential effect for PD 10R/10R and PD 9R carriers relative to their respective control groups must be viewed in the light of the fact that we obtained more 10R/10R homozygotes than 9R allele carriers in this study. In this way, power to detect statistical differences for contrasts involving the former group was increased compared to those including the latter group.

Based on previous research (MacDonald et al., 2013; Grogan et al., 2015), we expected encoding to be impaired in PD patients tested on relative to off dopaminergic therapy. This is due to the fact that encoding is mediated by brain structures that receive dopamine supply from the relatively-spared VTA. These brain regions are sensitive to overdose from exogenous dopamine therapy that is titrated to DS-depletion levels and overdose has been reliably shown in many functions mediated by VTA-innervated brain regions (Cools et al., 2006; MacDonald & Monchi 2011). Further, we predicted that 9R PD patients will be more sensitive to overdose from exogenous dopamine and, therefore, will have greatest impairment for on relative to off performance. 9R PD patients have lower tonic dopamine levels due to increased DAT1 expression and consequently more rapid synaptic clearance and reuptake of dopamine. This results in a more optimized signal-to-noise ratio. When dopamine is delivered in a non-physiological way, it is expected that DAT1 reuptake mechanisms are exceeded, resulting in higher tonic dopamine levels and a decreased signal-to-

noise ratio to which these 9R individuals are unaccustomed. For the ON 10R/10R PD, exogenous dopamine is expected to have lesser detrimental effect on learning performance given that larger fluctuations in basal dopamine are experienced and tolerated by these individuals in their baseline state. That is, in the context of already elevated tonic dopamine levels at the synapse in this 10R/10R PD group in the off state, dopamine supplementation will alter the relative magnitude of the phasic-to-tonic dopamine ratio (i.e., signal-to-noise) to a lesser extent. Potentially higher phasic dopamine responses will actually occur in the 10R/10R PD group in the ON state compensating for any changes in tonic dopamine, with lesser effect ultimately on downstream signaling. Effects bolstering these expectations were seen in a study examining the effects of DAT1 genotype on learning about the prosociality of others in a healthy control group (Eisenegger et al., 2013). That is, in line with these predictions, in a previous study, healthy 9R carriers who were given L-dopa were less able to learn about the playing style of a partner in an interactive experimental task and could not, therefore, adopt an adaptive strategy to maximize their winnings (Eisenegger et al., 2013).

In line with our expectations, 9R carrier PD patients had lower encoding scores on medication relative to off medication. This group is expected to experience a greater perturbation on their signal-to-noise ratio produced by phasic relative to tonic dopamine levels at the synapse. However, no ON-OFF differences in encoding performance occurred for our 10R/10R homozygotes. This is the first study to investigate the effect DAT1 and exogenous dopamine on a cognitive function mediated by a VTA-innervated brain region. Previous studies look only a mixed genotype group effects. We speculate that overdose effects were absent in the 10R/10R PD group because the relative increase in synaptic dopamine concentrations from baseline to ON medication state would

be of a smaller magnitude in this group than in the 9R group. Experience with and tolerance to higher tonic dopamine levels at baseline in this group might have been protective to overdose effects. However, again it is important to consider that these investigations were performed in small numbers of participants and that the reliability of this pattern of findings will be enhanced by testing with larger sample sizes.

4.6.2 Retrieval Effects

For recall, we speculated that DAT1 9R carriers might reveal superior performance as well, due to a more optimized signal-to-noise ratio in selecting among internal stimuli to produce recall responses. However, retrieval has been shown to implicate DS and DS-involving cortical networks (Spaniol et al., 2009) and the cytoarchitectonics of DS adapt it to easily achieve maximal firing or responsivity, for very brief durations (Wickens et al., 2007), based on a broad range of SN firing frequencies and intensities (Wickens et al., 2007; Zhang et al., 2009). In this way, differences in baseline or tonic dopamine levels in DS were speculated to potentially have lesser impact on success of event-related, phasic dopamine to achieve successful D1 and D2 receptor stimulation and signal transduction. Decreased effect of these phasic-to-tonic ratios across participants, on activity levels in DS (Zhang et al., 2009) ultimately translates to less influence on activation in DS's cortical partners via facilitation of the direct pathway and inhibition of the indirect pathway. In this way, we expected that 9R and 10R/10R genotypic backgrounds might have less influence on recall performance than we expected for encoding. Recall implicates broader brain regions including DS and cortical networks involving DS (Spaniol et al., 2009). In PD, DS is significantly dopamine depleted even at the earliest stages of disease, and motor and cognitive functions mediated by DS are impaired (Cools, 2006; Cools and D'Esposito, 2011; Cools et al., 2001, 2003;

Frank, 2005; Frank et al., 2004; Hood et al., 2007; Lewis et al., 2005; MacDonald and Monchi, 2011; MacDonald et al., 2011; Moustafa et al., 2008a, 2008b; Shook et al., 2005; Slaboz et al., 2006; Tremblay et al., 2010). Consequently, we expected PD patients to perform more poorly than controls regardless of genotype, and further that all PD patients would recall more items in the on than off dopamine state. Finally, it seemed less likely that exogenous dopamine therapy would have differential effects on PD patients based on DAT1 genotypic differences.

Indeed, we found no main effect of DAT1 genotype on recall performance overall or within each of our groups. Further, DAT1 genotype did not interact significantly with Group or with Medication Session. As predicted, we found that PD patients recall was improved on dopaminergic medication relative to off, replicating previous research (MacDonald et al., 2013; Grogan et al., 2015, but see Bronnick et al., 2011). This pattern is entirely predictable because DS is severely dopamine depleted in PD.

4.7 Limitations of the Current Study

We acknowledge a number of limitations of the current study. Foremost, the interpretation of our findings related to effects of DAT1 polymorphisms and dopaminergic therapy on encoding and retrieval remains speculative given that the present study is merely behavioural. Without integrating functional neuroimaging into our protocols or examining these processes in patients with focal lesions, our explanations remain provisional. Going forward, we will confirm our interpretations by coupling our behavioural paradigm in PD patients and healthy controls, on and off dopaminergic therapy using functional neuroimaging.

Further, despite promising and predicted patterns, our study remains underpowered due to small sample sizes, particularly in our 9R carrier participants. This led to differences in age and MOCA in our 10R/10R PD group relative to its control group, which could potentially influence our findings. Critically, our main finding related to DAT1 polymorphisms resulted from a within-subject comparison, which would not be influenced by these demographic group differences. The reliability and generalizability of our results are also questioned by this small sample size. Recruitment is currently underway to address this issue and boost our statistical power.

Lastly, we recognize the limitations of examining polymorphisms in a single gene influencing dopamine regulation in the brain. This is an ongoing project, and we plan to investigate the effects of additional dopaminergic gene polymorphism such as in COMT, the D2 receptor, and dopamine- and cAMP-regulated phosphoprotein. These polymorphisms will affect dopamine clearance in the PFC, hippocampus, as well as in the direct and indirect signaling pathways. The inclusion of these polymorphisms will allow us to investigate interactive effects, rather than assessing the effects of a single gene polymorphism in isolation. Several studies of the effects of dopaminergic polymorphisms have found interactive effects or have shown that it is necessary to control for some polymorphisms on others (e.g., Cockburn et al., 2014; Nikolova et al., 2011; Smith et al., 2013; Yacubian et al., 2007).

4.8 Conclusion

We found that dopaminergic therapy had differential effects on explicit memory encoding and retrieval in PD patients relative to healthy age-matched controls, essentially replicating findings of the only two previous studies that have examined memory in PD in this manner (MacDonald et

al., 2013; Grogan et al., 2015). We found that dopaminergic therapy worsened encoding, for a subset of our PD patients based on genotype, and improved retrieval in PD. These results contribute to a greater understanding of memory impairments in PD, helping to clarify significant inconsistencies that occur in this literature to date.

We further explored the effect of DAT1 genotypic variations on memory performance in healthy, elderly volunteers and in PD patients. At a behavioural level, there were no differences in encoding or recall performance based on DAT1 genotype within the PD or control groups. Only, 9R PD patients experienced overdose effects with poorer encoding on relative to off dopaminergic therapy. This was explained on the basis of differences in phasic-to-tonic dopamine ratio for this group compared to 10R/10R homozygotes. Understanding how genetic background influences cognition and response to dopaminergic therapy in PD could lead to more tailored treatment regimens that attempt to remediate DS-mediated motor and cognitive functions while minimizing detrimental effects on other cognitive functions. Caution, however, should be exercised in these interpretations until patterns can be explored in a larger dataset. Future studies will aim to correlate our findings with regional brain activation using neuroimaging to confirm our interpretation of our findings.

4.9 References

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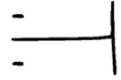

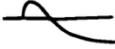


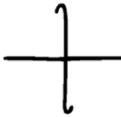

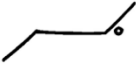







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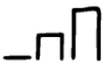
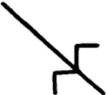






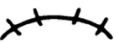


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5.0 Appendices








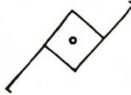





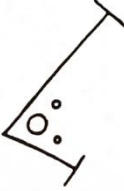

5.1 List A symbols used on Day 1 of testing.













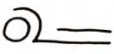


5.2 List B symbols used on Day 1 of testing.

5.3 List A symbols used on Day 2 of testing.

5.4 List B symbols used on Day 2 of testing.

5.5 Ethics approval notice from the Sudbury Regional Hospital



Health Sciences North
Horizon Santé-Nord

Research Services Office
1st Floor Clinical Research, Northeast Cancer Centre
41 Ramsey Lake Road
Sudbury, ON P3E 5J1
t: 705-523-7100, ext. 2409
email: reb@hsnsudbury.ca

To: Dr. Penny A. MacDonald

Study Title: The Role of Basal Ganglia in Cognition

Sponsor/Funding Agency: CRC/CFI/NSERC/Lawson Internal Research Fund/Academic Medical Organization of Southwestern Ontario/London Hospital Association

REB Review Type: Full Board

Date of Meeting: May 2, 2016

Notification of Study Re-Approval

Expiry Date: May 02 2017

Project Number: 746

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

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

The maximum duration of approval is one year. As Principal Investigator, you are responsible for renewing the approval for this study prior to the expiry date by submitting an Annual Renewal Form or if the study is complete, a Final Report form. Please add **March 21 2017** to your calendar as a reminder to complete and submit the appropriate form six weeks prior to the expiry date. There is no grace period.

PLEASE NOTE: Research participants cannot be enrolled into a study if ethics approval has lapsed. If this occurs, it will be considered a serious protocol violation and you will be asked to complete and submit an Unanticipated Problem Form and to report the violation to your Sponsor/Funding Agency.

The forms and guidelines can be found on the HSN intranet or by emailing the Research Ethics Office at reb@hsnsudbury.ca should you not have access to same.

Sincerely,

Mac Sinclair, Chair, Health Sciences North Research Ethics Board

5.6 Ethics approval from the University of Western Ontario



Research Ethics

**Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice**

Principal Investigator: Dr. Penny MacDonald

Department & Institution: Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, London Health Sciences Centre

Review Type: Full Board

HSREB File Number: 102018

Study Title: Distinguishing the roles of ventral and dorsal striatum in cognition (REB #18517)

Sponsor: Canadian Excellence Research Chair

HSREB Amendment Approval Date: December 18, 2015

HSREB Expiry Date: November 29, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Amendment	List of changes to ethics protocol and consent form	2015/11/19
Revised Western University Protocol	Marked version of updated ethics protocol	2015/11/19
Instruments	UPPS-P Impulsive Behavior Scale	2015/11/19
Instruments	Domain Specific Risk Taking Scale DOSPERT	2015/11/19
Instruments	Behavioral Inhibition/Approach Scale BIS/BAS Scale	2015/11/19
Revised Letter of Information & Consent		2015/11/19
Revised Western University Protocol		2015/11/19

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

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

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Nicole Kaniki Grace Kelly ___ Mina Mekhail ___ Vikki Tran ___

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

6.0 Curriculum Vitae

University Educational Background

Masters of Science, Physiology/Pharmacology Expected Graduation 09/2015 – ongoing
 University of Western Ontario
 Master's Thesis: *Pharmacogenetics of non-motor symptoms in Parkinson's disease*
 Supervisors: Drs. Penny MacDonald and Adrian Owen

Bachelor of Medical Sciences, Hons. Spec. Phys/Pharm 09/2010 – 04/2015
 University of Western Ontario
 Undergraduate Thesis: *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*
 Supervisor: Dr. Penny MacDonald

Research-specific Honours, Scholarships, and Awards

Ontario Graduate Scholarship 04/2015 – 04/2016

Research Experience

Master's Student, Department of Physiology and Pharmacology 09/2015 – ongoing
 University of Western Ontario
 Supervisors: Drs. Penny MacDonald and Adrian Owen

- Designed and implemented protocol for testing multiple aspects of cognition in Parkinson's disease patients using computerized tasks
- Spearheaded recruitment and scheduling of participants
- Administered neurological assessments and collected genetic samples from patients

Undergraduate Research Assistant, Department of Psychology 09/2014 – 04/2015
 University of Western Ontario
 Supervisor: Dr. Scott MacDougall-Shackleton

- Designed and implemented protocol for manipulating serum glucocorticoid levels with subcutaneous implants in songbirds
- Performed weekly blood collections and stress tests, and quantitative magnetic resonance imaging

Undergraduate Thesis Student, Department of Phys/Pharm 09/2014 – 04/2015
 University of Western Ontario
 Supervisor: Dr. Penny MacDonald

- Tested cognitive abilities of healthy undergraduates in 3T MRI machine
- Used MATLAB to create scripts for analyses of blood-oxygenation-dependent-level signal
- Performed statistical analyses on behavioural datasets

Undergraduate Research Assistant, Department of Psychology 01/2014 – 08/2014
University of Western Ontario

Supervisor: Dr. Scott MacDougall-Shackleton

- Immunohistological study examining the effects of photoperiod on volume of song-control brain regions and migration of immature neurons in a songbird species
- Determined adult neurogenesis can occur in the absence of sex steroids in this species

Undergraduate Independent Research 09/2013 – ongoing
University of Western Ontario

Supervisor: Dr. Mike Atkinson

- Organized, oversaw, and analyzed data testing efficacy of proprietary study aid website (CanYouRecall) on first-year undergraduate students
- Integrated CanYouRecall into second-year Biochemistry course (Biochem2280) for assessment of efficacy in larger sample of undergraduate students

Publications, Presentations and Abstracts

Publications

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. 2015. Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study. *NeuroImage* 114: 170–184.

- Delineated the role of the dorsal striatum in decision-making using a number Stroop task with simultaneous blood-oxygenation-level-dependent (BOLD) signal
- Found that BOLD signal in the dorsal striatum only correlated with decision-making during situations requiring increased cognitive control
- Addressed and resolved a pervasive confound in the literature of striatum-mediated cognition

Robertson BD, Hasstedt MR, Vandermeer CL, MacDougall-Shackleton SA. 2014. Sex steroid-independent effects of photostimulation on the song-control system of white-throated sparrows (*Zonotrichia albicollis*). *General and Comparative Endocrinology* 204: 116–172.

- Manipulated the photoperiod and presence of gonadal steroids of adult, male white-throated sparrows to elucidate the regulatory mechanisms of seasonal neurogenesis
- Brains were extracted and immunohistological techniques were applied to determine volume and recruitment of immature neurons to brain regions of interest
- Found that seasonal neurogenesis can occur in the absence of sex steroids and provided a potential mechanism by which neurogenesis may occur in this circumstance

Publications in Preparation

Robertson BD, Farrell TM, MacDougall-Shackleton SA. Perils and pitfalls of manipulating glucocorticoids with silicone implants.

- Implanted subcutaneous glucocorticoids to replicate and expand upon previous findings that these implants only increase serum glucocorticoid concentrations for several days post-implantation
- Investigated hypothalamic-pituitary-adrenal (HPA) axis reactivity and body composition using quantitative magnetic resonance
- Successfully replicated our previous findings and found differences in HPA axis reactivity between treatment groups

Martow JM, Robertson BD, Meadows KN, Atkinson ML. The effects of self-generated questions on delayed recall of newly learned facts.

- Designed a study aid website (CanYouRecall.com) that uses timed recall of self-generated questions
- Tested the efficacy of CanYouRecall in a sample of first-year undergraduate psychology students and found that low-achieving students benefitted
- Integrated CanYouRecall into a second-year biochemistry course (Biochem2280) at UWO to investigate the efficacy of CanYouRecall in a larger sample of undergraduate students

Presentations

Poster presentation 09/2015

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Inaugural Brain and Mind Institute Symposium. London, ON.

Platform presentation 06/2015

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. 50th Congress of the Canadian Neurological Sciences Federation. Toronto, ON.

Paper presented 03/2015

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. 12th International Conference on Alzheimer's and Parkinson's Diseases. Nice, France.

Platform presentation 02/2015

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Annual Schulich Medicine and Dentistry Clinical Neurological Sciences Departmental Research Day. London, ON.

Research presented 01/2015

Robertson BD, Newman AEM, MacDougall-Shackleton SA. *Perils and pitfalls of manipulating glucocorticoids with silicone implants*. Annual meeting of the Society for Integrative and Comparative Biology. West Palm Beach, FL.

Poster presentation 11/2014

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Annual UWO Physiology and Pharmacology Departmental Research Day. London, ON.

Paper presented 08/2014

MacDougall-Shackleton SA, Hall ZH, Vandermeer CL, Hasstedt MR, Robertson BD. *Gonad-dependent and gonad-independent regulation of neural and behavioural plasticity in songbirds*. 26th International Ornithological Congress. Tokyo, Japan.

Poster presentation 05/2014

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Annual meeting of the Southern Ontario Neuroscience Association. London, ON.

Poster presentation 03/2014

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Annual London Health Research Day. London, ON.

Poster presentation 03/2014

Robertson BD, Hiebert NM, Seergobin KN, Owen AM, MacDonald PA. *Dorsal striatum mediates cognitive control, not cognitive effort per se, in decision-making: An event-related fMRI study*. Annual Schulich Medicine and Dentistry Clinical Neurological Sciences Departmental Research Day. London, ON.

Poster presentation 01/2014

Hasstedt MR, Robertson BD, Vandermeer CL, MacDougall-Shackleton SA. *Sex steroid-independent effects of photostimulation on the song-control system of white-throated sparrows (*Zonotrichia albicollis*)*. Annual meeting of the Society for Integrative and Comparative Biology. Austin, TX.

Abstracts

Robertson BD, Newman AEM, MacDougall-Shackleton SA. 2015. *Perils and pitfalls of manipulating glucocorticoids with silicone implants*. Integrative and Comparative Biology 55: E154.

Hasstedt MR, Robertson BD, Vandermeer CL, MacDougall-Shackleton SA. 2014. *Sex steroid-independent effects of photostimulation on the song-control system of white-throated sparrows (Zonotrichia albicollis)*. Integrative and Comparative Biology 54: E285.

Teaching experience

Graduate Teaching Assistant 09/2015 – 12/2015
Department of Physiology and Pharmacology, University of Western Ontario

- Taught fourth-year undergraduate sensory physiology course
- Designed and taught online and in-class tutorials, held office hours

Graduate Teaching Assistant 09/2014 – 04/2015
Department of Physiology and Pharmacology, University of Western Ontario

- Taught a third-year undergraduate physiology lab course
- Supervised laboratory experiments, designed and taught tutorial sessions, met with students outside of laboratory