AN EXAMINATION OF CONCURRENT DISCRIMINATION LEARNING WITHIN INDIVIDUALS WITH PARKINSON'S DISEASE

by

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The main focus of this research is to further understand memory formation by examining the role of the basal ganglia in learning. Broadly, this study examines how the basal ganglia may play a role in a task that has been associated with declarative memory mechanisms, in this case the concurrent discrimination task (CDT). Specifically, we examine how performance is affected on the CDT when structures of the basal ganglia are compromised by recruiting individuals with Parkinson's disease (PD). Past work examining the performance of individuals with PD on a CDT have had contradicting results and have proposed that participants may adopt different strategies that rely variously either on declarative or non-declarative strategy (Moody et. al., 2010). We aimed to reduce strategy differences by making changes in stimuli, increasing the number of stimuli significantly, increasing the number of learning blocks, and making all participants explicitly aware of the task structure and goals. By making the goals explicit, we predicted that we would engage a declarative mechanism in both PD and control individuals. To examine declarative memory formation we used the Remember Know task (RK). However, since used a significantly larger set size of stimuli we hypothesized that individuals with PD would perform significantly worse on the CDT than control individuals. The current study reveals that there are no significant differences in performance between individuals with PD and control participants on both the CDT and RK task. We attribute these results to design of our paradigm and stimuli which may have influenced individuals to engage in declarative strategies to perform the CDT reasonably well.

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1.0 INTRODUCTION

Learning is a complex process that humans are able to perform in a remarkable manner. Different memory systems within the brain contribute to learning. Two such systems that are essential in the formation of memory are the declarative and non-declarative systems. Mapping the underlying neural structures responsible for learning is a difficult task; however, significant strides have been made within the field of cognitive neuroscience toward understanding the anatomical components involved in learning. For example, it is widely accepted that the hippocampus is associated with declarative memory, and the structures of the basal ganglia are associated with non-declarative memory (Squire, 1992; Seger, 2006). What has yet to be established is how standard memory tasks involve these anatomical structures. Gaining a better understanding of this issue is an important step to advancing research in this field.

Within the literature, there exists a lack of clear understanding concerning memory and learning processes. For years, this knowledge gap has spurred considerable research attempting to better understand how the formation of memory takes place. One important finding has been that the engagement of the hippocampus and basal ganglia is highly dependent on the type of task that is performed. For example, several studies have associated performing simple discrimination tasks with the hippocampus, and motor learning tasks with the basal ganglia (Zola-Morgan & Squire, 1986; Peigneux, Maquet, Meulemans, Destrebecqz, Laureys, Degueldre, & others, 2000). But the notion that only one neural structure is responsible for the performance of a given task has been challenged repeatedly (Knowlton, Mangels, & Squire,

1996; Aggleton, Nicol, Huston, & Fairbairn, 1988; Hood, Postle, & Corkin, 1999). For instance, it has been shown that the weather prediction task (WPT), which was traditionally categorized as a non-declarative task and related to the basal ganglia only, can also be learned in a declarative manner that involves contributions from the hippocampus (Shohamy, Myers, Onlaor, & Gluck, 2004; Poldrack, Clark, PareÂ-Blagoev, Shohamy, Moyano, Myers, & Gluck, 2001). The shift from a single memory type per task to a multiple memory systems perspective is a topic of great debate needing further examination.

To address this need, this thesis focuses on the structures of the basal ganglia, and the role they play in concurrent discrimination learning. The work will test the hypotheses that the learning of the concurrent discrimination task (CDT) involves complex interactions between both the hippocampus and basal ganglia. Before turning to an empirical examination of this question, the thesis will begin with a brief overview of: (1) the declarative and non-declarative memory systems, (2) the anatomical structures associated with these systems, (3) tasks that engage the structures of the basal ganglia, (4) tasks engaging the hippocampus, (5) tasks thought to engage multiple memory systems, and (6) the concurrent discrimination task.

1.1 BRIEF OVERVIEW OF DECLARATIVE AND NON-DECLARATIVE SYSTEMS

The two memory systems that are in focus are the declarative and non-declarative systems. The declarative memory system is associated with the formation of fact based memories that can be readily verbalized such as people, places, things, and events. There are a number of tasks that have been shown to activate this system, such as the delayed non-matching task in monkeys, the water maze task in rats, and the verbal paired associate task in humans (Zola-Morgan & Squire,

1986, Hood et al., 1999, Shimamura & Squire, 1984). Some of the declarative tasks are *deterministic* in nature, meaning that there is always a consistent association between a stimulus and a correct response.

In contrast, the non-declarative memory system is associated with learning complicated motor skills such as riding a bike (Squire & Zola, 1996). There are multiple types of non-declarative memory, one of which is procedural memory. Procedural memory is described as incremental learning through repetitive experiences. A defining characteristic of this type of memory is that the knowledge that underlies the skill cannot be readily verbalized (Squire & Zola, 1996). Some procedural memory tasks employ *probabilistic* learning, which means that the relationship between a stimulus, response, and outcome is not fixed. In other words, there is a probability of a reward, but it is not 100%. Generally, individuals learn the likelihood of an outcome through multiple experiences (Squire & Zola, 1996).

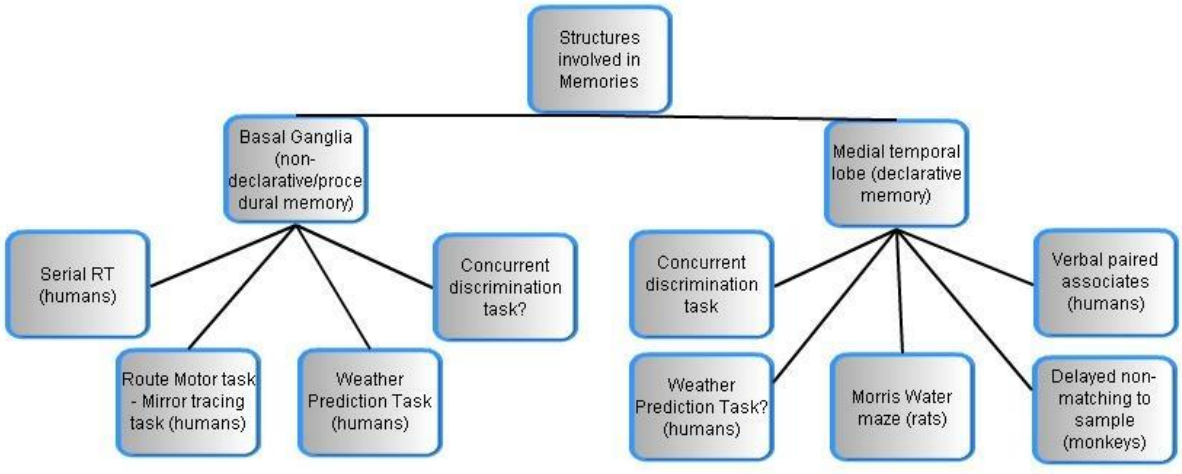

Figure 1: A summary of the memory systems and tasks associated with the systems

1.2 ANATOMICAL STRUCTURES

The declarative and non-declarative systems are each associated with neural structures within the brain, which include the medial temporal lobe and basal ganglia respectively. It is well established that the declarative system is associated with the MTL, primarily the hippocampus along with other supporting brain structures (Squire, 1992). When damage occurs to the MTL it greatly affects the capacity of memory formation and learning within an individual. Previous studies of humans and non-human primates have illustrated that individuals who have hippocampal damage find it difficult to create novel declarative memories and have considerable difficulty learning declarative memory tasks (Zola-Morgan & Squire, 1986; Hood et al., 1999).

Considerable research has provided evidence that the basal ganglia are crucial for some forms of procedural memory (Gabrieli et al., 1997; Jackson et al., 1995; Knopman & Nissen, 1991; Packard & Knowlton, 2002). The basal ganglia are composed of several structures, including the globus pallidus, subthalamic nucleus, substantia nigra, and the striatum (which consists of the caudate nucleus and putamen) (Packard & Knowlton, 2002). Multiple lines of patient work have provided evidence that structures of the basal ganglia are heavily engaged during certain non-declarative memory tasks. For instance, a study examining individuals with Huntington's disease, which is associated with degeneration of the basal ganglia, illustrated that the disease was associated with impaired performance on motor learning tasks such as the serial reaction time task (Gabrieli et al., 1997).

1.3 TASKS ENGAGING THE HIPPOCAMPUS

Tasks associated with declarative memory involve the formation of memories for facts and events. For instance, it has been shown in non-human primate studies that the MTL is highly associated with performance on the delayed non-matching task (Zola-Morgan & Squire, 1986). To perform the task successfully, monkeys must recognize a novel object in order to receive a food reward. The monkeys are initially presented with a sample object that is followed by a delay. Two objects, the sample and a novel object, are then presented and the monkey must choose the novel object. This task requires that the monkeys learn and remember which object was initially presented. In a study by Zola-Morgan & Squire (1986) monkeys were trained to perform the task until it was learned successfully. The structures of the MTL were then lesioned and the monkeys were tested on the task again. The lesioned monkeys are unable to perform the task, strongly supporting the argument that the MTL is heavily associated with successful performance on the delayed non-match to sample task.

The engagement of the MTL for tasks associated with declarative memory is found in other animal species (Broadbent, Squire, & Clark, 2006; Hood et al., 1999). Rats are unable to perform well on the Morris water maze when the MTL is damaged. This task requires rats to swim around in an opaque pool and find a hidden platform. To successfully perform the task, rats must remember external cues, in this case shapes, that are placed around the pool and which guide the rats to the platform (Broadbent et al., 2006). The delayed non-match to sample task and the Morris water maze task appear to require the animals to form declarative memories by learning and remembering specific cues to perform the task successfully. If the MTL is damaged, the performance on these tasks drops considerably, thus supporting the claim that the MTL is strongly associated with declarative tasks (Broadbent et al., 2006; Hood et al., 1999).

1.4 TASKS ENGAGING THE BASAL GANGLIA

There are also tasks that are associated with the non-declarative system, including some that are thought to specifically engage the basal ganglia structures (Gabrieli, Corkin, Mickel, & Growden, 1993; Jackson et al., 1995; Knopman & Nissen, 1991; Packard & Knowlton, 2002). Tasks that are connected with non-declarative memory mechanisms require the formation of memories that are performance-based, but the memories cannot be easily verbalized. The mirror-tracing task is a prime example of how a memory can be formed without verbally expressible knowledge. This task is difficult to perform because individuals are looking at a reversed image and must trace it accurately. As individuals repeatedly perform the task they become faster at completing the tracing (Gabrieli et al., 1993). The serial reaction time task involves learning a sequence of key-strokes without most participants acquiring conscious knowledge of the sequence. Once again, as the participants repeat the task the speed at which they perform it becomes faster (Jackson, Jackson, Harrison, Henderson & Kennard, 1995). Individuals with Huntington's disease and individuals with Parkinson's disease (PD) perform poorly on these non-declarative tasks (Gabrieli et al., 1993; Knopman & Nissen, 1991; Jackson et al., 1995). Both of these diseases cause structures of the basal ganglia to be damaged (Gabrieli et al., 1993; Jackson et al., 1995). Therefore, the patients' inability to successfully perform the mirror tracing and serial reaction time tasks provides evidence that the structures of the basal ganglia are heavily associated with these non-declarative tasks.

1.5 TASKS ENGAGING MULTIPLE MEMORY STRUCTURES

Historically, certain cognitive tasks have been developed in an attempt to recruit a single memory system. Specifically, researchers have attempted to develop cognitive tasks that only engage either the declarative or a non-declarative memory system. There has been a shift in this approach as the literature has provided evidence that even these focused tasks can involve more than one memory system (Knowlton et al., 1996). This has led to increasing realization that there may be complex interactions between the two memory systems. The weather prediction task illustrates this complexity.

The WPT is a probabilistic category learning task, and as such it was initially described as a task that relies heavily on non-declarative memory mechanisms (Gluck, 2002). The task requires participants to predict whether it will rain or be sunny based on a set of cues. These cues are in the form of cards, four in total, which are presented in one, two, three, and four card combinations during a trial. Each of four cue cards is associated with a fixed probability of rain or sunshine. After making a decision, participants press a key to indicate their prediction and they are given immediate feedback whether the choice was correct or incorrect (Gluck, 2002). The task is probabilistic in nature, meaning that the cues do not have a single outcome directly mapped onto them throughout the trials. This makes it very difficult to learn patterns that associate cues to an outcome.

It has been argued that the WPT heavily relies upon the basal ganglia to develop non-declarative memories. Knowlton and colleagues (1996) examined two patient populations using the WPT. The first group consisted of patients with severe declarative memory impairments presumably resulting from damage to the MTL. The other group consisted of individuals with

Parkinson's disease (PD). Knowlton found that patients with PD had impaired performance on the task. The deficit was more pronounced in more progressed stages of the disease (Knowlton et al., 1996). In contrasts, patients with amnesia and damage to the MTL, which is associated with impairment in declarative memory, performed as well as controls. Interestingly, the performance examining declarative memory of both patient groups showed the opposite pattern to that found for the WPT. In other words, the patients with amnesia were unable to recall specific details about the task and the stimuli while patients with PD were able to do so. The ability to recall certain facts may not play a direct role in improving task performance, but it is pertinent to note that it is still intact. This suggests that patients with amnesia use the basal ganglia system to perform the task. Although the performance of patients with PD was impaired, these findings suggest that they were engaging the declarative memory system.

Shohamy, Myers, Onlaor, & Gluck (2004) provided evidence that the declarative memory system may actually be used to support successful performance on probabilistic category learning tasks. This study investigated a variation of the WPT, with individuals with PD as participants. Instead of the traditional cue cards used in the WPT, a Mr. Potato head® doll was used. Like the original task, four cues were assigned probabilities, as were the combinations of the cues. Unlike the WPT, the cues were not cards with shapes but facial features and accessories of a Mr. Potato head® doll. Another difference was that the outcome prediction was whether the doll would choose chocolate or vanilla ice cream. Two conditions were examined: one that included performing with feedback, and one that was based on observation. The feedback-based version was how the original WPT was performed, with participants given feedback on whether each decision was correct or incorrect. The observational protocol contained two phases. The first phase required individuals to look at images of Mr. Potato head

and the outcomes. In the second phase the participants performed the task but they were not given feedback on their decision (Shohamy et al., 2004). Like the Knowlton (1996) study, it was found that PD individuals perform significantly worse than controls in the original task. This outcome could be attributed to the idea that when feedback is available, basal ganglia learning is facilitated in a probabilistic category task. On the other hand, when structures of the basal ganglia are compromised such as in PD, learning cannot take place as efficiently. The observational conditional results were revealing: the PD subjects performed just as well as the controls. This is compelling evidence that probabilistic learning tasks thought to heavily rely upon the basal ganglia may also be performed by other structures. Also, there is neuroimaging evidence that complex interactions may occur between the basal ganglia and MTL when performing probabilistic category tasks (Poldrack & Rodriguez, 2004). The imaging studies lend support to the idea that the MTL also plays a role in non-declarative tasks.

An interesting question that arises from this line of research is whether a declarative memory task can be performed by the basal ganglia. There is a gap in the literature examining declarative memory tasks and how the basal ganglia may play a role. There have been a multitude of studies examining individuals who have a damaged hippocampus and their ability to perform declarative and non-declarative tasks. Furthermore, individuals with damage to the basal ganglia have been tested repeatedly on procedural tasks such as motor learning tasks like the mirror tracing task. However, there have not been many studies observing how individuals with basal ganglia damage perform on declarative memory tasks that involve feedback.

1.6 THE CONCURRENT DISCRIMINATION TASK

The CDT is an experimental paradigm that is strongly associated as a declarative memory task. To perform the CDT successfully, participants must learn multiple stimuli simultaneously during a single session. The stimuli are presented in pairs with one of the items within the pair being assigned as the correct one. Participants are asked to select the correct stimulus. Following every response there is feedback given on whether the selection was correct or incorrect. Unlike the WPT, the CDT is deterministic in nature, meaning that there is always a consistent, correct response to each stimulus pair.

There is some evidence that traditional declarative memory tasks such as the CDT, which is hypothesized to rely on the hippocampus, may also utilize the basal ganglia to support learning. For instance, Squire and colleagues (1988) examined individuals with alcoholism, and a second group with amnesia. Specifically, the patients with amnesia specifically had Korsakoff's syndrome, which is characterized by a vitamin deficiency and is associated with damage to the MTL. Symptoms include amnesia and general cognitive deficits. The patients with alcoholism were able to successfully perform the task and retain the memories formed from the CDT even after a 24-hour delay. The individuals with amnesia were significantly worse in performance both on the CDT and in retaining the knowledge after a 24-hour delay. These results provided further support to the argument that the MTL plays a vital role in the CDT. But, an interesting finding from this study was that even with damage to the hippocampus, patients with amnesia gradually improved, albeit ever so slightly, their performance on the CDT. These results suggest that the CDT is robust to a loss of declarative memory, and potentially that it can be successfully supported by the basal ganglia.

There have been two studies that have examined the ability of individuals with damage to the basal ganglia to perform the CDT (Moody, Change, Vanek, & Knowlton, 2010; Shohamy, Meyers, Geghman, Sage, & Gluck, 2006). Both of these studies found that medicated individuals with PD performed significantly worse than individuals in a control group. In a follow-up analysis, however, Moody and colleagues (2010) found that the performance of the PD participants was significantly affected by whether they were explicitly aware of the goal of the task. Participants were labeled as being "aware" of the goal according to their performance on a post-test questionnaire, in which participants were asked to recognize the shapes that were rewarded in the CDT. Participants were classified as aware if they could select the rewarded shapes. The implication of being aware in this study is that the declarative system was involved in learning the task. When the study was conducted, participants were not explicitly aware of what the goal of the task was, which was to pick the object that contained the smiley face. The task involved object pairs that could not be easily verbalized. The participants were instructed to go with their "gut feeling" to where they believed the smiley face was located. The results illustrated that for controls there were no significant differences in performance from being aware and not aware. In contrast, aware participants with PD demonstrated a significant improvement in performance compared to those that were not aware. In addition, when individuals with PD were aware their performance was comparable to the control participants. The results bring forth an intriguing implication of how both the declarative and non-declarative system can play a role with success on the CDT (Moody et. al., 2010).

The findings of Moody and colleagues (2010) demonstrated that individuals without known damage to their central nervous system are able to perform the CDT whether they are aware or not aware. When aware, these individuals are able to successfully pick out specific

examples from the task on the post-test questionnaire. It is possible that these individuals relied upon their declarative memory system to learn the task, which allowed them to later use their declarative memories to pick out the exemplars. The not-aware control group was unable to pick out exemplars, yet they were still able to perform the task as well as the aware group. This suggests for these individuals the task was learned by utilizing non-declarative memory mechanisms, without engaging the declarative memory system enough to form declarative memories of the rewarded exemplars. A compelling result from this study is that only the patients with PD that were aware could perform the task successfully. This strongly suggests that the declarative system was most likely being used for the CDT when participants were knowledgeable about the task. The poor performance of the not-aware PD group can be attributed first to their damaged basal ganglia, which may mean that they were unable to use this system to perform the task, and also to the fact that they failed to engage the MTL system to support their task performance by relying upon declarative memory mechanisms (Moody et al., 2010). These results lead to the interpretation that the CDT can involve a basal ganglia non-declarative memory system, but it can also be performed using the declarative system. We further explore this concept in the present study.

1.7 PURPOSE OF THIS STUDY

The main focus of this research is to further understand memory formation by examining the role of the basal ganglia in learning. Specifically, we hope to further understand the process of forming procedural memories. In the proposed study, we will replicate Moody's study by also examining individuals with PD and using the CDT paradigm; however the proposed protocol reflects a few key differences. Because the work of Moody et al. (2010) indicated that

participants may adopt different strategies for performing the task, relying variously upon either a declarative or non-declarative strategy, we aimed to reduce strategy differences by using verbal stimuli and by making all participants explicitly aware of the task structure and goals. As part of our instructions, we explained that each pair would have one item that would always be the correct time to select, and we emphasized that the goal was to learn the correct item through trial-and-error. By making the goals explicit, we predicted that we would engage the declarative system in all participants. If this is the case, then the PD participants should be able to learn the task as well as control participants, and be able to recall the correct stimuli just as well as the control participants after learning. However, as another difference from the Moody et al. study, we use a larger set size of stimuli. We hypothesized that individuals with PD would perform significantly worse on the CDT than control individuals. We believe that a larger set size should make the task more difficult for the declarative system to handle, and therefore the workload may be shared by using both the MTL and basal ganglia memory systems. Thus, this increase in set size, and corresponding increase in the use of the basal ganglia, may lead PD participants to perform our version of the CDT more poorly the control participants, even though all participants are aware of the task structure and goals.

2.0 METHODS

2.1 PARTICIPANTS

A total of 42 participants completed the research study. Twenty were recruited into a Parkinson's disease (PD) group, and 22 were recruited into a control (Ctrl) group. Five of the individuals with PD were not used in the analyses (one participant had a DBS and did not tell us until later in the study, one subject could not complete the study due to cognitive deficits, and three subjects did not complete the study since they were falling asleep). Seven of the control individuals were not included in the analyses. One subject was excluded due to lack of effort which was determined after receiving oral confirmation that she was not trying to succeed on the task. Another individual was excluded due to a low MMSE score, and five subjects were excluded since their yoked partner in the PD group was excluded. All participants were screened for neurological diseases, head injury, and substance abuse. To rule out depression, all participants were administered the Beck Depression Inventory–II (BDI-II). If individuals scored higher than 16 they were omitted from the study. In addition, all participants had to score at least a 26 on the Mini Mental State Exam (MMSE) to be eligible. All participants gave informed consent according to the procedures of the Institutional Review Board at the University of Pittsburgh and were compensated for their time. All participants were paid $15.00 an hour. The two groups were specifically matched on gender (seven females, nine males), age, and education level (see Table 1).

Participants in the control group were recruited in two ways: (1) by dispersing flyers into the community and receiving responses from interested individuals or (2) inviting the spouses of patient participants to participate in the study. Participants with PD were recruited from the Pittsburgh Institute for Neurodegenerative Diseases (PIND) Movement Disorders Center Research Registry at the University of Pittsburgh Medical Center and local support groups in the Pittsburgh area. All of the PD participants were on some form of dopamine replacement therapy. Two patients were on a monotherapy regimen specifically targeting D2 receptors. Eight participants were on some type of combination therapy, which included the drugs Entacapone, a Monoamine oxidase (MAO) inhibitor, or a cholinesterase inhibitor. Patients were excluded from participation if they were on antipsychotics, anti-dementia agents, D3 receptor antagonists, or any of the above listed medications in patch form. In addition, patients were excluded if they were undergoing deep brain stimulation. The Hoehn and Yahr scale (Goetz et al, 2004), which is a tool to stage the progression of Parkinson's disease (PD), was used to determine the patient's disease severity. The Hoehn and Yahr scale is a 5-point scale ranging from 1 to 5. Stage 1 is associated minimal Parkinson's disease symptoms, and stage 5 with the most severe symptoms. Five participants were mildly progressed (stage 1), nine patients were mild-moderately progressed (stage 2), and one patients were moderately progressed (stage 3).

Table 1. Participant Information for the Participants with Parkinson's Disease and Controls

Group	Age	Education	BDI – II	MMSE	Hoehn and Yahr Scale	Disease Duration
Parkinson's disease	63.75	16.1	11.5	29.75	2	6.375
Controls	65.95	15.45	5.05	29.14	-	-

Age, education, and disease duration are in years. BDI – II = Beck Depression Inventory – second edition, MMSE = Mini Mental State Exam.

2.2 APPARATUS AND MATERIALS

A general battery of neuropsychological measures was used to screen and examine participants' overall memory, general cognition, and mental state. Measures included the Visual Recognition task from the Weschler Memory Scale, Third edition (WMS-III; Weschler, 1997), Matrix Reasoning task from the Weschler Abbreviated Intelligence Scale, Third edition (WAIS-III; Weschler, 1997), the MMSE (Folstein, 1987), and the BDI-II (Beck, Steer & Brown 1996). The Unified Parkinson's Disease Rating Scale (UPDRS) was used to determine the progression of PD within the patients (Goetz et. al, 2004). The control participants were administered the Neuroticism Extroversion Openness – Personality Inventory - Revised (NEO PI-R; Costa & McCrae,1992). Table 2 provides a list and description of the questionnaires, tests, and subtests.

Participants also completed a battery of experimental tasks. The experimental protocol was designed to examine concurrent discrimination learning and to test declarative and procedural memories for the learned items. The experimental protocol consisted of three computer tasks. The major task was the concurrent discrimination task (CDT). The two other experimental tasks were a remember-know recognition memory test (RK) task and a lexical decision task (LDT). An Intel Personal Computer with a 50 cm color monitor was used to

administer the tasks and record the responses using E Prime (Psychological Software Tools, Inc., Pittsburgh, PA). A post-test questionnaire was administered at the end of the experimental task. The questionnaire consisted of nine statements that asked about strategy in reference to the CDT. All experimental tasks on the computer used words and non-words as stimuli. All words that were used in the experimental tasks were of the same frequency range of 7.015 to 13.02 log HAL. The lexical statistical parameters established at elexicon.wustil.edu and http://www.psy.uwa.edu.au/MRCDataBase/mrc2.html were used to create the words that were implemented in the tasks (Balota, Yap, Cortese, Hutchison, Kessle, Loftis, Neely, Nelson, Simpson & Treiman 2007). The CDT consisted of 150 word items, in which half of the words (positive words) were associated with positive feedback following their selection (three green checks) and the other half (negative words) were associated with negative feedback (three red x's). A Microsoft Excel macro randomly assigned which words were positive and negative within the word pair for every participant. The Microsoft Excel macro was also used to divide the 150 words items into 75 word pairs for every participant. The RK task consisted of 100 word items, drawn from the 150 presented in the initial CD task, along with 100 additional novel word items. For the 100 word items drawn from the CDT task, half of the selected items were positive words and half were negative words. The final experimental task, the LDT, was composed of fifty words from the CDT (twenty-five positive and twenty-five negative words), twenty-five non-words, and twenty-five novel words.

Table 2. Neuropsychological Test Information for Parkinson's disease and Controls

Tests	Subtest	Description	Purpose of testing
WMS-III	Visual Reproduction I – recall	Individuals studied figures in a testing booklet for ten seconds. The figures were then covered and the individuals were asked to reproduce the figures from memory in a testing booklet.	This test examines memory; specifically the ability to recall visual objects immediately.
	Visual Reproduction II-recall	A 30 to 40 minute delay was implemented. During the delay, participants were asked to fill out the UPDRS or NEO-PI-R. After completion of the task, participants were asked to reproduce the figures from Visual Reproduction I from memory.	This test examines memory by looking at the participants abilities to recall visual objects after a delay.
	Visual Reproduction II-recognition	Participants were shown figures and asked to determine which figures were from Visual Reproduction I and which were not.	This test examines memory via asking participants to recognize visual objects.
	Visual Reproduction II-copy	The initial figures that were presented in Visual Reproduction I were presented again to participants. Participants were asked to copy the figures into the answer booklet.	To examine participants' abilities to copy figures.
	Visual Reproduction II-discrimination	Participants were presented with a figure from the Visual Reproduction I. Six additional figures were presented simultaneously. One of these six figures matched the figure from the Visual Reproduction I task. The participant was asked to identify the figure that matched. They did this a total of 7 times.	To examine the participants ability to discriminate figures.
UPDRS		A four part interview that consists of questionnaires, interview, and then a physical examination of motor symptoms.	To determine the severity of PD
NEO-PI-R	N/A	A personality inventory containing 240 statements. Only the comparison participants performed this inventory.	To have a similar testing experience to the individuals with PD. Specifically when the individuals with PD are taking the UPDRS. In addition, it also gives the time delay needed for the Visual Reproduction tasks.
BDI-II	N/A	A questionnaire containing 21 statements with 4 answer choices below each statement.	A quick screening tool for depression.
Health History Questionnaire	N/A	A questionnaire collecting information on participants' health background. Additionally the questionnaire focuses on diagnosis date for individuals with PD and PD medications for the participants with PD.	Provides health history of participants.
MMSE	N/A	A quick examination that tests orientation, registration, attention and calculation, recall, language, and the ability to copy complex figures.	A quick screening tool assessing an individual's cognitive state.
WAIS	Matrix Reasoning	Participants were given visual patterns and asked to decipher the pattern.	A quick test for IQ.

2.3 Procedure

Each participant was tested individually in a quiet room. At the beginning the testing session all participants were consented. The first task administered was the Visual Reproduction I task, which was followed by the administration of the UPDRS by a certified rater. The UPDRS was followed by the administration of the Visual Reproduction II task, the BDI-II, MMSE, Health History questionnaire, and the Matrix reasoning task, the CDT and post-learning assessment tasks (RK and LDT). The control participants also followed the same protocol; however, instead of taking the UPDRS the NEO-PI-R was administered to create a testing experience similar to that experience of the patient group.

The first task administered on the computer was the CDT. Following the CDT the participants performed the RK task. The final computer task administered was the LDT. We employed a deterministic CDT with feedback to investigate learning in individuals with PD and matched controls. The aim for every participant was to learn which word was correct for each of the 75 word pairs. Each of the trials consisted of a fixation cross in the middle of the screen for a duration of 1500 ms, followed by the simultaneous presentation of a word pair displayed for 5 seconds. Participants were instructed to pick either the top or bottom word by pressing the number 1 or 2 on the keyboard. The "1" and "2" button presses were designated for the top and the bottom word respectively. After a participant's response was recorded, feedback was given. Three green checks on the monitor indicated a correct decision and three red x's indicated an incorrect decision. Figure 2.3 below illustrates how the stimuli were presented. After the first round, where the entire list of 75 pairs was administered, the list cycled through again for another 8 rounds. There was always the option of having a break in between the rounds. The orders of the trials were randomized for every round as were the positions of the words in each trial.

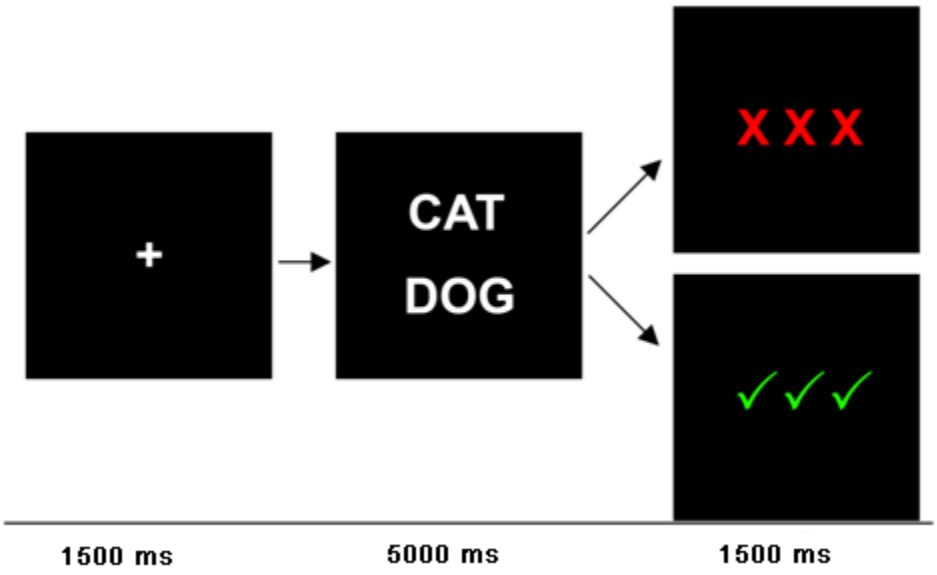

Figure 2: Presentation and Timeline for the Concurrent Discrimination Task *ms = millisecond

We examined the participants' declarative memory for the CDT items by implementing a RK task. A trial in the RK task consisted of a single word presented on the screen. This word could either be a word from the previous CDT or a novel word. Participants had four options to classify the stimulus; they could either press "1" if they definitively knew that the word was a word from the CDT, "2" if they believed the word was from the previous list, "3" if it was a new word that had not been presented before, or "4" if they did not know. If the participants determined it was a word from the previous task a "+/-" appeared above the word prompting the individual to judge whether the word was paired with three green checks (positive) or three red x's (negative). If participants believed the word was the positive item in the pair they pressed "1", if they believed it was the negative item in the pair for the CDT items they pressed "2"; finally, if they did not know, they pressed "3."

The final computer task, a lexical decision task (LDT), further probed procedural memory by examining response time and accuracy to old and new stimuli. A single word was

displayed on the screen and participants were instructed to decide whether the word was a real word or a non-word as quickly as possible. If the word was real participants were asked to press "1" and if it was a non-word to press "2." Presentation of the stimuli was randomized.

3.0 STATISTICAL ANALYSES

3.1 DATA EXCLUSION

Of the twenty participants with PD recruited for the study, four participants with PD were not included in the data analyses due to exclusion criteria. One participant was excluded due to having a deep brain stimulator (DBS), another participant was excluded due to a pre-existing basal ganglia condition, and three other participants were unable to complete the study due to fatigue and excessive sleepiness. The data from the 15 PD participants who qualified and completed testing were used for analyses.

One control subject was excluded due to not meeting the criteria for the MMSE score. The other participant was excluded due to lack of effort. The participant stated that she was not trying to learn the task or putting forth effort into doing well on the task. The data from the 15 control participants who qualified and completed testing were used for analyses.

All analyses were performed with statistical package SPSS version 19 for PC.

3.2 CDT ANALYSES

To examine learning patterns in the current study we implemented ANOVA models. Specifically, these were mixed 2 x 9 models with group (PD, control) as a between subject factor and block (blocks 1-9) as a within subject measure. One of the ANOVAs examined mean

accuracy per block and the other looked at mean RT per block. Significant ANOVA results were followed by post hoc pairwise t-tests to examine the group differences in more detail. If PD impairs CDT learning, main effects of both factors, as well as an interaction between them, would be expected. In other words, individuals should improve in response speed and accuracy with repeated exposure to the items, but this learning should be reduced in the individuals with PD.

3.3 RK TASK ANALYSES

The data from the RK task were used to examine group differences in declarative memory formation for the items in the CDT by performing three analyses. First, to examine whether there was an overall difference in recognition memory between the two groups in recognizing words that were or were not used as CDT items (old vs. new words), a student's t-test was used to compare the proportion of correct responses across the two groups. Second, to probe reward contingency effects on recognition memory, we examined whether the recognition accuracy and response speed for old words varied across the two groups depending upon whether the items were rewarded or non-rewarded words in the CDT task. This was accomplished with 2 (group: PD, control) x 2 (reward contingency: rewarded, not-rewarded) ANOVA models. Based on previous work, we expected that recognition memory would be better for rewarded versus unrewarded items; if this item type effect reflects a contribution from a basal ganglia reinforcement learning system, then group differences in the effects of item type might be observed.

Third, we examined what we will call fact memory, by measuring how well participants could recall whether a correctly recognized old word was a rewarded or non-rewarded item in

the CDT task. For this analysis we selected trials with correctly recognized old words from the initial recognition memory judgment, and then investigated whether there were group and reward contingency effects on fact recall accuracy and response speed for these trials. This was accomplished with 2 (group: PD, control) x 2 (reward contingency: rewarded, non-rewarded) ANOVA models that examine differences in fact memory accuracy and response speed across the two groups. If the basal ganglia contribute to the formation of this fact memory, especially for rewarded items, main effects of group and an interaction between group and item type would be expected.

4.0 RESULTS

4.1 PARTICIPANTS

We examined if there were any differences between individuals with PD and controls in age, education, BDI, MMSE, and matrix reasoning by performing a two-tailed independent t-tests (Table 3). No significant differences were found for age, education, MMSE, and matrix reasoning. There was a significant difference between the two groups for BDI scores. This is consistent with previous research, since depression is often comorbid with PD, although our patients with PD only reported mild depression (Jasinska-Myga, Putzke, Wider, Wszolek, Uitti, 2010; Poewe, 2007). For individuals with PD the average time since they were diagnosed with PD was 6.27 (SD: 3.17) years.

Table 3. An examination of age, years of education, BDI scores, and performance on the MMSE and matrix reasoning between PD and Controls

	Parkinson's Disease	Control	t-test	p-value
Age in years	63.47 (6.41)	64.4 (5.38)	-.580	.566
Education in years	16.2(3.36)	16.03(3.51)	.281	.781
BDI	11.13(6.5)	4.87(5.34)	2.793	.009
MMSE	29.8(0.41)	29.53(0.64)	1.464	.154
Matrix Reasoning	17.53(4.49)	15.53(5.85)	.850	.402

Standard deviations are in parenthesis

*BDI = Beck Depression Inventory, MMSE = Mini Mental State Exam

4.2 CONCURRENT DISCRIMINATION TASK

4.2.1 Accuracy

We examined the performance of the two groups on the CDT by performing a 2 (group: PD, Control) x 9 (block) ANOVA for both accuracy and reaction time data. As expected there was a main effect of block, which reflected the fact that participants performed better with successive repetitions of the CDT item pairs ($F= 50.36$, $p < 0.05$, partial eta squared = .643). The effect of group, ($F = .04$, $p > .05$, partial eta squared = .001) and the interaction between group and block was not significant ($F = .44$, $p > .05$, partial eta squared = .015) This suggests that the individuals with PD learned at a similar rat e as the matched controls (Figure 3.)

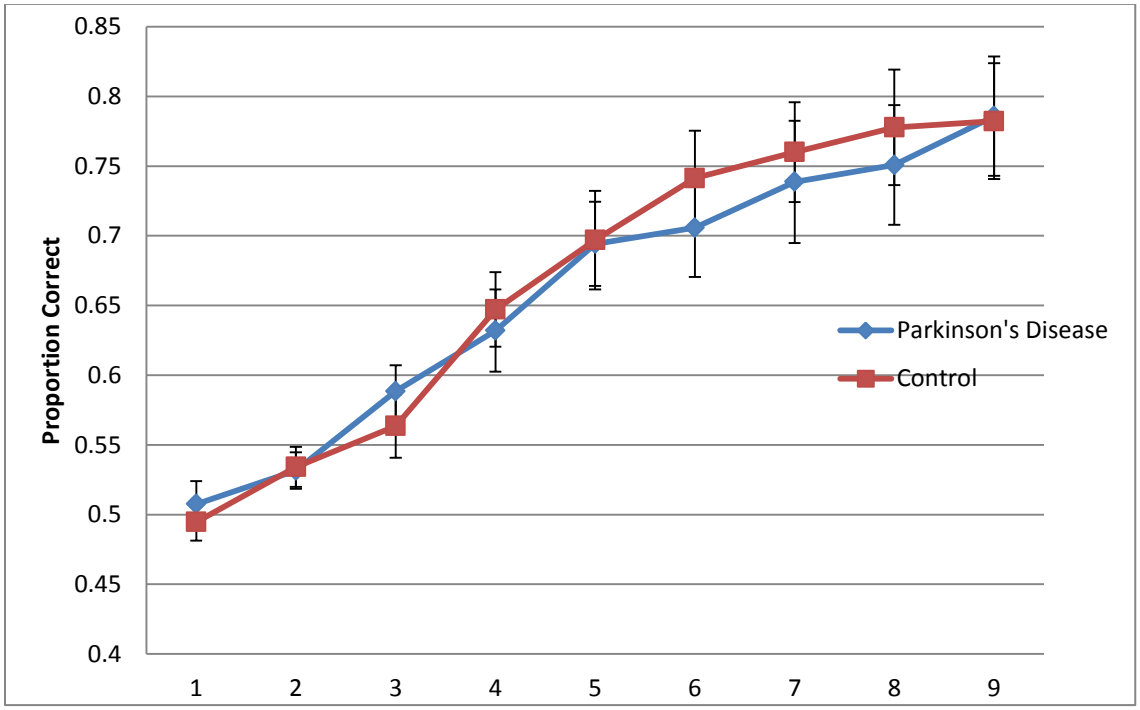

Figure 3. Mean accuracy of individuals with PD and controls across blocks of the concurrent discrimination task. Error bars indicate standard error mean in performance within the group for the particular round

4.2.2 Reaction time

We examined the mean reaction times with a 2 (group: PD, control) x 9 (block) ANOVA to see if there were differences between the two groups. There was a significant effect of block, $F = 4.83$, $p<0.05$, partial eta squared = .147. As shown in Figure 4.2.2, both individuals with PD and controls slow down the second and third rounds and then become faster in later rounds. This is most likely because the participants are learning the correct word items during the second and third round, and become faster with repetition of their correct responses. All individual with PD were slower on average than the individuals in the control group, the effect of group, $F = 3.51$, $p > .05$, partial eta squared = .111 and the interaction between group and block, $F = .298$, $p > .05$, partial eta squared = .011 were not significant (Figure 4). Although figure 4.2.2 illustrates that there is no overlap with the standard error bars between the two groups the ANOVA did not find any significance. The ANOVA fails to find significant differences since it takes account sample size. It is most likely the case that our sample size is too low and does not have enough statistical power hence there is no significant differences between the two groups (Belia, Fidler, Williams, & Cummings, 2005; Lazante, 2005; Cumming & Finch, 2005; Cumming, Fidler & Vaux, 2007;)

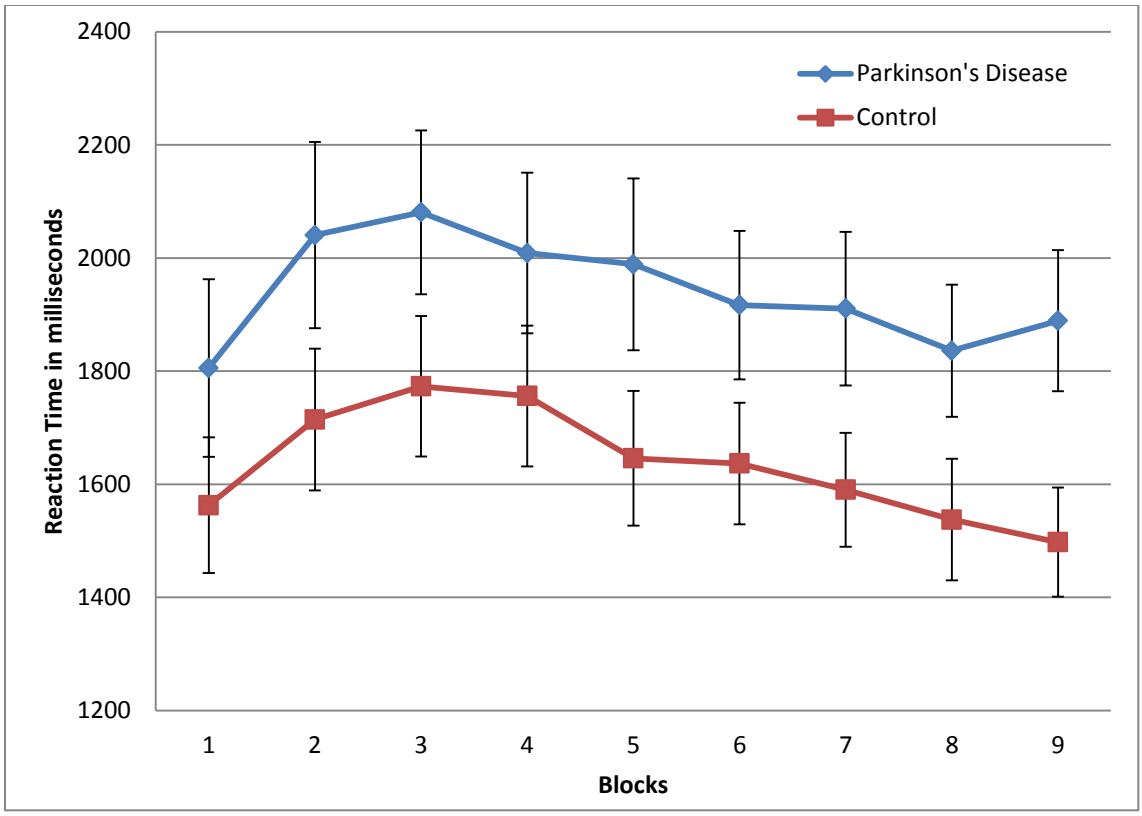

Figure 4. Mean reaction times of individuals with PD and controls across blocks the concurrent task. Error bars indicate standard error of mean within the group for the particular round.

4.3 POST-TESTS

4.3.1 Remember-Know: Recognition Memory

We examined if there were any differences in performance between the two groups (PD and controls) on the RK task with independent t-tests. There were no significant differences in accuracy, $t(28) = -.469$, $p > .05$ (Figure 5), or reaction time, $t(28) = .386$, $p > .05$ (Figure 6).

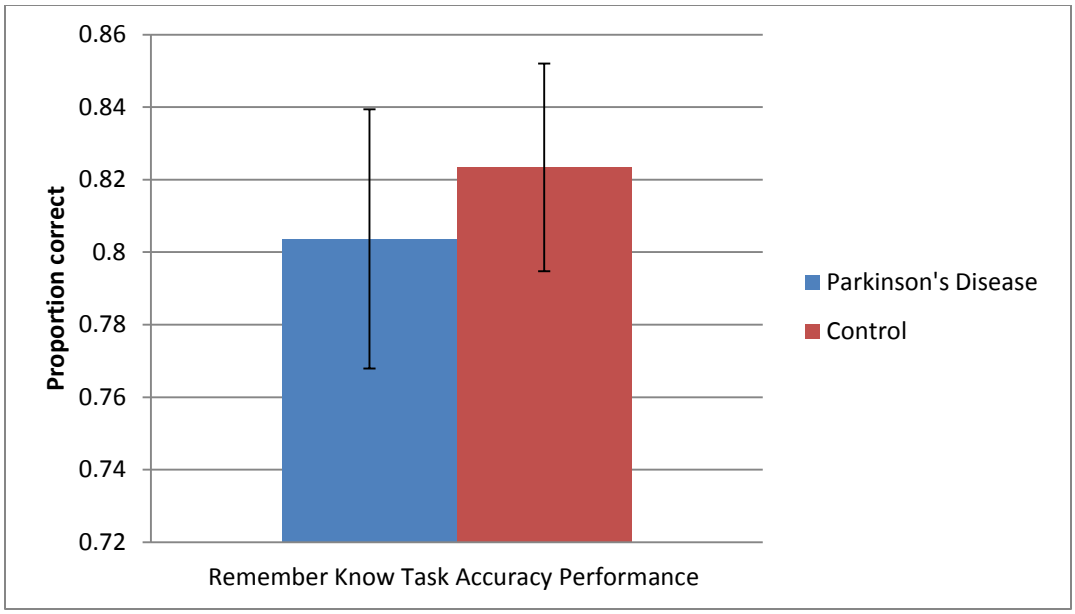

Figure 5. Mean accuracy of overall performance on the Remember-Know task within individuals with PD and controls. Error bars indicate standard error of the mean within the group

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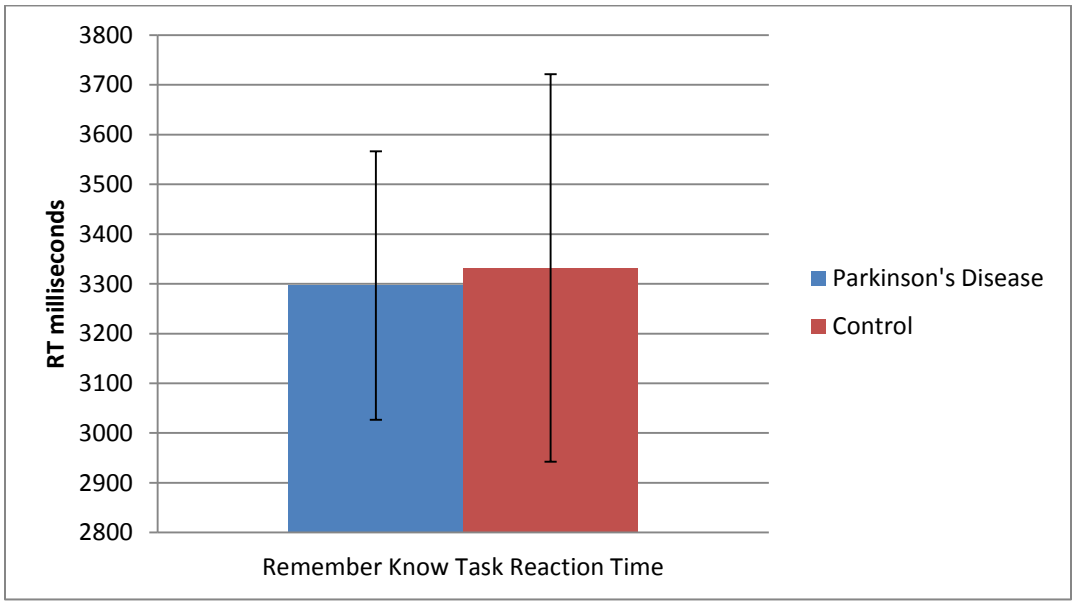

Figure 6. Mean reaction times of individuals with PD and controls on the Remember-Know task. Error bars indicate standard error of the mean in performance within the group.

4.3.2 Remember-Know: Effect of reward contingency on recognition memory

We further examined whether reward contingency had an effect on recognition of CDT items, by conducting a 2 (group: PD, control) x 2 (item type: rewarded, non-rewarded) ANOVA. There were no significant differences in group, $F = .39$, $p > .05$, or interaction between the group and item type, $F = .02$, $p > .05$ (Figure 7). However, there was an effect of item type, $F = 24.13$, $p < 0.05$. For both groups, words that were rewarded were correctly recognized more as a word from the CDT than non-rewarded words. We also examined reaction time using the same 2 x 2 ANOVA model and found no effect of group, $F=.04$, $p > .05$, item type $F = 1.21$, $p > .05$, or interaction, $F = .47$, $p > .05$ (Figure 8).

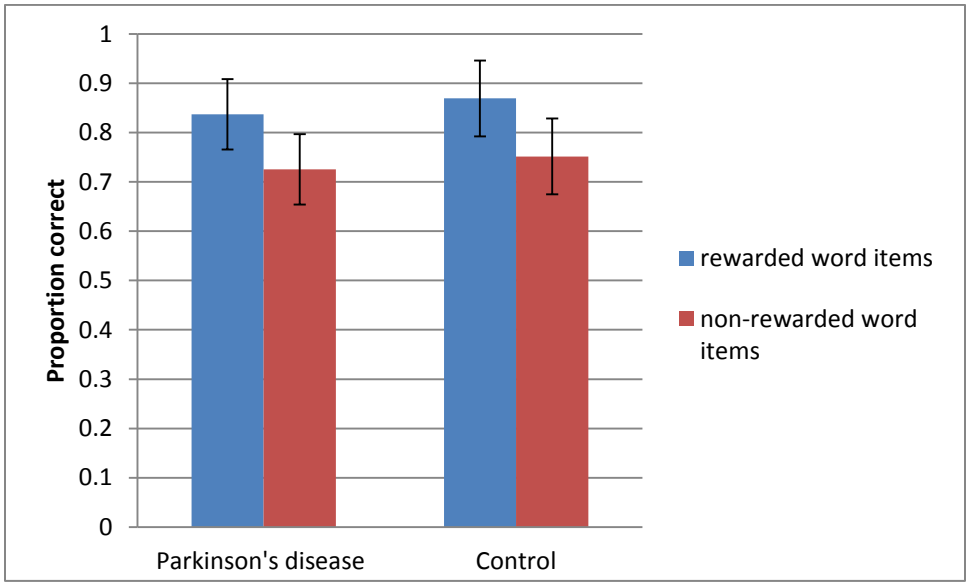

Figure 7. Mean accuracy of rewarded and non-rewarded word items by group (PD and control.) Error bars indicated standard error of the mean for each item type for each group

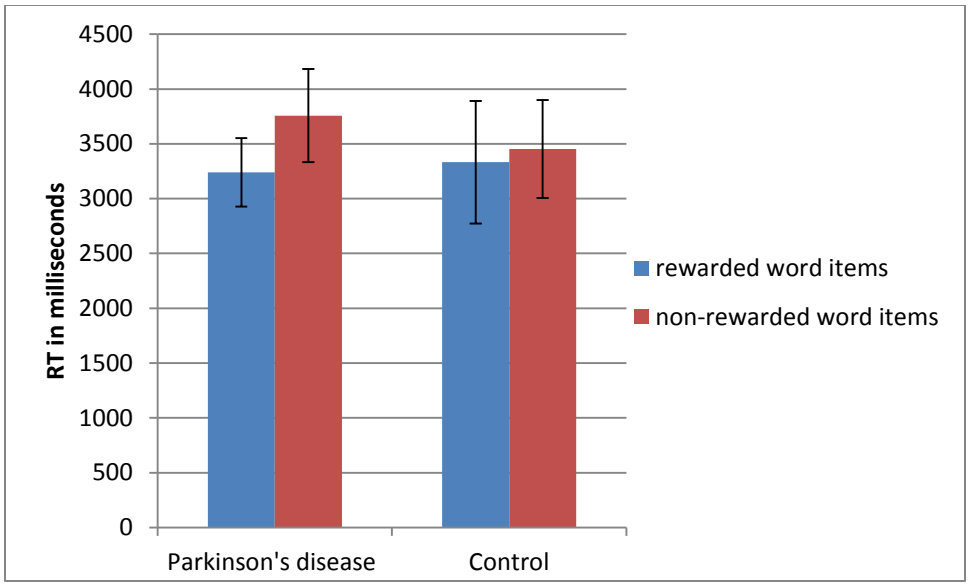

Figure 8. Mean reaction time of reward and non-rewarded word items by group (PD and control.) Error bars indicate standard error of the mean for each item type for each group

4.3.3 Recognition Memory: Fact memory

Finally, we examined how well participants were able to recall whether the words from the CDT were rewarded or not using a 2 (group: PD, control) x 2 (item type: rewarded, not-rewarded) ANOVA. There was a significant effect of item type, $F = 6.78$, $p < 0.05$. Rewarded words were classified more accurately than non-rewarded words. However, the main effect of group, $F=.124$, $p > .05$, and the interaction between group and item type, $F = .148$, $p > .05$, were not significant (Figure 9). We examined reaction time using the same 2 x 2 ANOVA model and found that there was no effect of group, $F = .32$, $p > .05$, interaction, $F = 2.70$, $p > .05$, or item type, $F= .000$, $p > .05$.

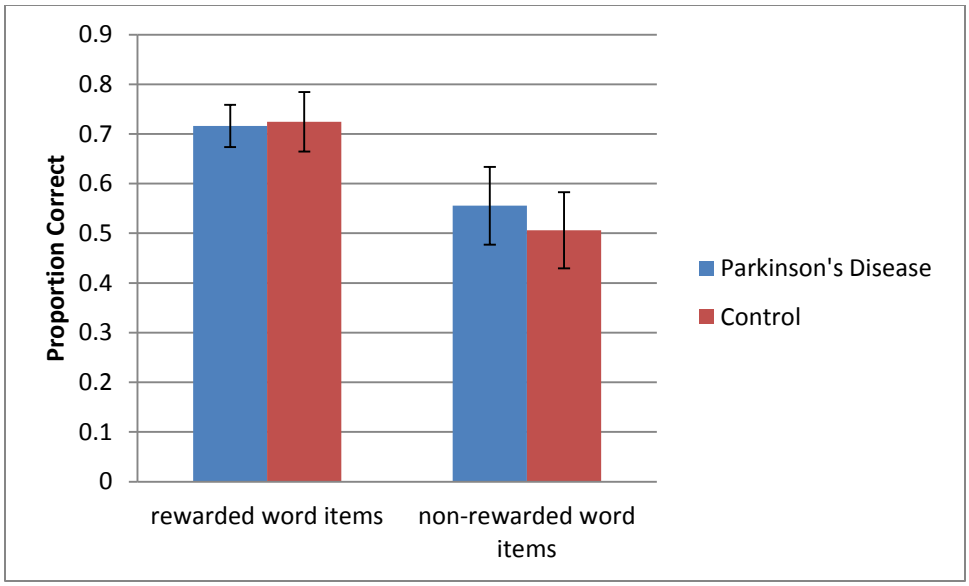

Figure 9. Mean accuracy of the ability to recall reward contingency by group (PD and control.) Error bars indicate standard error of the mean for each group and item type

5.0 DISCUSSION

5.1 CAN INDIVIDUALS WITH PD LEARN THE CDT TASK AS WELL AS CONTROLS?

Our study finds that individuals with PD do not perform significantly different than controls on the CDT. This contradicts previous studies, where individuals with PD on medication performed, as a group, significantly worse than a group of control individuals on the CDT (Moody et. al., 2010; Shohamy et. al., 2006). We found that both individuals with PD and control participants were able to perform the CDT and there were no significant differences between the two groups.

Before the participants performed our task, we explicitly stated that one of the items within the pair would always have a reward associated with it and their job was to learn which item in each pair had the reward by the end of nine blocks. Past studies did not make it explicitly clear to the research participants that there was always a reward associated with one (and only one) of the items within the pair. They simply instructed participants to find the smiley face (the reward) for each item pair (Moody et. al., 2010, Shohamy et. al., 2006). Being aware of the goal for a task, which is the realization that there is a reward associated with a particular item in each trial (stimulus-outcome contingency), may play a pivotal role on how well an individual performs (Shohamy et. al., 2004; Moody, 2010.) Since we made the directions and stimulus-outcome contingency of the CDT explicitly clear at the beginning of the task, we hypothesized

that individuals might be guided to a strategy that was more declarative in nature, and this would contribute to both PD participants and controls being able to perform the task.

We reasoned that a second difference in our paradigm might impede the ability to use the declarative memory system, even when participants are explicitly aware of the task structure. In past studies, the largest number of object pairs participants with PD had to learn on a CDT was 30 pairs of items (Moody et. al, 2010). We dramatically increased the number of item pairs to 75 in our paradigm. By increasing the set size of object pairs we speculated that the task would be more difficult for the declarative system to handle, and therefore individuals might begin to disperse the workload by also relying on the non-declarative, procedural system. To further encourage individuals to specifically rely more on non-declarative memory mechanisms, the CDT item pairs were repeated across nine blocks, whereas prior studies have given fewer exposures. If the increase in object pairs and exposures encourages individuals to rely on the non-declarative, procedural system associated with the structures of the basal ganglia, then individuals with PD should perform poorly on our CDT paradigm even when they are aware of the task goals. Our results do not support this prediction.

Our use of verbal stimuli may have made it easier for participants to learn the large number of items. We used word items as the object pairs, whereas past studies ((Moody et. al., 2010, Shohamy et. al., 2006) have used shapes that were hard to verbalize. The use of verbal stimuli may have played a role in allowing our participants to make associations that aided in the formation of declarative memories, even when there were a large number of items to be learned.

5.2 POST-TEST ASSESSMENT OF RECOGNITION MEMORY

As a component of our paradigm, we examined declarative memories for the CDT items. To do this, we used a remember know task following the CDT to probe possible declarative memory formation. We believed that both declarative and non-declarative memory systems would be engaged. However, we hypothesized that individuals with PD would rely more on the declarative system in order to perform the task and that control individuals would rely on the non-declarative system. As a result individuals with PD would form stronger declarative memories about the specific word pairs than control individuals. We found that there were no significant differences between the two groups. Once again, this may be due to the fact that all of our participants were aware of the reward contingencies of the CDT hence all participants were guided to rely on a more declarative strategy. Moody et al. (2004) found similar results, in that individuals who were aware of the reward contingencies of the task were able to successfully recognize the rewarded items on a post-test, regardless of whether they had PD or not. This supports the idea that the MTL may be playing a key role in being able to perform the CDT in both individuals with PD and controls when the task is performed in a more declarative manner.

An assessment of fact memory was embedded in the RK task, by examining how well participants were able to remember whether words correctly judged as old based on reward contingency (items that were rewarded or not rewarded). We expected that individuals with PD would be heavily relying on the declarative system, and therefore they would perform significantly better than the controls. There was no such difference. This could be again because both groups were given explicit directions to learn the items and reward contingencies hence both groups were relying more on the declarative system allowing the ability to perform comparably on the task.

5.3 OTHER CONSIDERATIONS

Our results indicate that even if individuals have atypical function within structures of the basal ganglia, they are able to perform our variant in the CDT. There were a few differences in our paradigm from past studies that may have contributed to the success of our individuals with PD, as compared to those in past studies. We believe that one critical difference is that we made it explicitly clear what the instructions and the goals of the task were to the participants. Other differences that might have also affected the results also warrant consideration. These lie outside of the task design, and in other aspects of the study such as the sample size and the nature of the recruited participant group.

Two important aspects to consider are sample size and effect size. While Moody and colleagues (2010) had a sample size of 20 individuals for the PD group, when examining whether they were aware or unaware there were only nine individuals in aware group and 11 in the minimally aware group. Shohamy and colleagues (2006) study examining PD on the CDT had a respectable sample size of 24 individuals with PD; but she was interested in examining how they performed when they were ON and OFF medication. This split the group in half, leaving only 12 people ON medication and 12 people OFF medication. In addition, seven individuals in the ON medication group and one individual in the OFF medication group were unable to reach criterion on the CDT which excluded them from further statistical analyses looking at whether individuals with PD are able to learn features of the CDT. These exclusions left only five people with PD ON medication and 10 individuals OFF medication, which is quite a small population. Unfortunately, the effect sizes for these studies were not reported. It would have been insightful to have the effect sizes reported in order to determine whether the effects occurring in these studies do in fact exist. With both Moody and Shohamy's studies having

small sample sizes, coupled with no reported effect sizes, as a reader one should take these findings with caution. Our study has a sample size of 15 for both controls and individuals with PD which is a larger than those used in past studies that have found group differences. Our study found no significant effects between the two groups; the effect sizes found were large for the main effect of block for both accuracy and RT on the CDT. However, the effect sizes were small for group and interaction of group and block.

Our study also worked with a special population of individuals with PD. We recruited participants from support groups and a Parkinson Disease research registry. The individuals from these recruitment sources were willing to participate and highly motivated in order to help the understanding of the disease that they had. This may have made them more motivated to perform well than our control individuals.

In addition, all our participants with PD were on a wide range of combination therapy drugs to alleviate the symptoms of the disease. Our study did not differentiate between the type of drug classes, which has become a relevant issue in the PD literature (Frank, Seeberger, & O'Reilly, 2004; Cools, Barker, Sahakian, & Robbins, 2001). It has been observed that specific medications and drug classes can affect tasks differently (Cools et. al., 2001). Our recruiting criteria did not require participants to be on a monotherapy (strictly one type of medication class) regimen. Therefore it is hard to draw any conclusion on individuals with PD based on drug class.

Another aspect to consider when interpreting these results is disease severity. For our study, we recruited individuals who had mild to moderate severity of PD. It is possible that the progression of the disease had not yet affected the structures of the basal ganglia to the point where they were unable to perform the task. It may be that the structures of the basal ganglia were still at operative levels therefore allowing participants with PD perform comparably to the

controls participants. Yet, it may the case that PD has detrimental effects to the structures of the basal ganglia. The results of this study may imply that perhaps the medication regimen is working for the individuals with PD. It could be quite possible that the medication combination that individuals with PD are prescribed are working quite well therefore allowing them to operate just as well as the control individuals.

It is also plausible that we did not cover the entire window of learning. In the later blocks, blocks 6-8, there is suggestive evidence that the control group is beginning to perform better than the individuals with PD. It may be that the contributions of procedural memory may become more apparent in later stages of learning. Individuals with damage to the MTL appear to have gradual improvement when performing the CDT with an extended number of blocks suggesting that the contributions of the procedural system emerge towards later blocks (Hood et. al, 1999). If the current study had extended for more blocks, more pronounced differences between the two groups may have emerged.

5.4 FUTURE WORK

In order to strengthen the findings from this study, one dimension that is worth looking at with greater detail is the medication classes prescribed to individuals with PD and how they may play a role on performance on the CDT. It is also important to note that we are medicating these individuals so we may not see effects of the damaged basal ganglia. Therefore it may be worthwhile to examine how well individuals with PD are able to perform when they are OFF medication to see if there are any differences in performances.

In future studies it may be interesting to examine how well the target items are retained within both groups of participants. One way to do this is to test recognition memory a week of

the initial testing (Tricomi & Fiez, 2008). This might better reveal differences between the two groups, since declarative and non-declarative memories may have different rates of decay, allowing group differences in the formation of different memory types to be revealed more clearly.

Another aspect that could reveal knowledge about the multiple memory systems and PD is to examine effects of the progression of PD on the CDT. This could be done by conducting a larger study looking at different stages of individuals with PD and see if disease progression plays a role in performance. It is possible that as individuals progress farther into PD, cognition becomes more affected due to the pathology of the disease. By examining the progression of PD and the possible effects on CDT performance we may be able to discover how and the rate at which PD affects cognition in addition to how anatomical structures may be affected. Finally, in order to reveal the anatomical processes of individuals with PD on the CDT an fMRI study must be implemented. Having imaging data would allow investigators to draw stronger conclusions to the behavioral data by linking the anatomical components that are involved for both individuals with PD and controls.

5.5 CONCLUSIONS

Within the field of multiple memory research, well established tasks (i.e. WPT, CDT) have been traditionally associated as declarative and non-declarative. However, these tasks can be re-designed and manipulated to test a different memory mechanism than originally designed. It is clear that task paradigm design plays a critical role in influencing which memory systems an individual recruits to perform the task. The behavioral evidence in this study contradicts findings

in similar studies examining PD and the CDT (Moody et. al., 2004; Shohamy et. al., 2006). The evidence in our study appears to support prior claims that declarative memory mechanisms are engaged to perform the task in both individuals with PD and controls. It is difficult to draw a strong conclusion about what memory systems and strategies that may be used for each group without imaging data. However, one critical component may be whether explicit instruction is provided about the goals and reward structure of a task. Therefore how a task is presented and designed may contribute to the differences in performances. This supports that task design plays a crucial role on strategies that may be implemented which ultimately affects the outcome of how individuals perform the tasks.

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