VERBAL MEMORY IN IDIOPATHIC NON-DEMENTED PARKINSON’S DISEASE: A STRUCTURAL MRI AND QUANTITATIVE WHITE MATTER TRACTOGRAPHY ANALYSIS

By

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To my wife Kristi and my children Anwyn, Lily, and Zachary
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By

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Introduction: While Parkinson’s disease (PD) is classified as a movement disorder, cognitive declines start early in the disease process. Difficulty with verbal memory is a common clinical complaint of non-demented individuals with idiopathic PD but research evidence of deficits is inconclusive. Parkinson’s disease pathology affects the medial temporal lobe (MTL) early in the disease process. While past studies have found some evidence of structural MTL changes in idiopathic PD, none to date have incorporated both gray and white matter of memory-related brain areas, particularly through brain MRI fiber tracking.

Methods: 40 non-demented individuals with idiopathic PD and 40 age, education, and gender matched peers participated in this study. Participants received brain MRI and verbal memory testing as part of a larger comprehensive neuropsychological evaluation. Semantic language measures were included as control variables. Magnetic resonance images were processed and analyzed using automated, semi-automated, and manual methods. Statistical analyses included analysis of variance and correlations.
Results: PD individuals had poorer list and story memory than age matched non-PD peers. Processing speed accounted for some variance in memory performance but did not fully explain deficits. There were no group language differences. While there was heterogeneity in memory performance, 20% of PD participants had significant deficits across two memory measures. There were also changes in left entorhinal volumes, when controlling for total intracranial volume, with PD participants having entorhinal volumes that were 11% smaller than Controls. Group differences were not seen in the connectivity of the cingulum between the entorhinal cortex and the retrosplenial cortex. Smaller entorhinal volumes related with poorer story memory recall and recognition. Decreased cingulum connectivity related with worse verbal list recognition performance.

Discussion: While a majority of non-demented individuals with PD have intact verbal memory, this study demonstrated that amnestic verbal memory declines occur early in the process of PD for a subset of individuals. Further, changes are seen in the medial temporal lobes (MTL) of individuals with PD, which adds to the evidence that amnestic deficits exist in PD and are more common than generally believed.
CHAPTER 1
INTRODUCTION

Parkinson’s Disease

Parkinson’s disease (PD) is classified as a movement disorder; the initial and typical clinical symptoms are most noticeably motoric with resting tremor, rigidity, akinesia, or postural instability. There are, however, a number of autonomic, cognitive, memory, and mood symptoms that are sometimes overlooked or are thought to be unrelated to PD. Cognitively and clinically, it is frequently noted that individuals diagnosed with PD self-report with bradyphrenia (reduced speed of thinking), difficulty retrieving words, and difficulty learning or recalling new information. Complications with memory and cognition in PD are documented throughout the literature (Naismith et al., 2010; Sawamoto et al., 2007; Uc et al., 2005; Cameron et al., 2010; Stepkina et al., 2010; Park & Stacy, 2009; Rodriguez-Ferreiro et al., 2010). Collectively, these symptoms of PD place a burden on quality of life above and beyond the burden of motoric symptoms (Hariz & Forsgren, 2010; Chen, 2010).

PD Prevalence and Impact

It is estimated that there are about 1 million individuals in the United States who currently have Parkinson’s disease and up to 10 million worldwide (Parkinson’s Disease Foundation, 2013). The lifetime risk of developing Parkinson’s disease is between 1-4% with men at greater risk than women (Elbaz et al., 2002). With access to better healthcare and nutrition, longevity has been increasing. It is expected that the number of individuals with Parkinson’s disease will grow as the number of older adults around the world increases due to increasing incidence of PD with age. Parkinson’s disease is likely caused by an amalgamation of factors. There is evidence from twin studies that
genetics explain a small but significant portion of the variance in developing PD (Wirdefeldt et al., 2011). While the precise cause of PD remains unknown researchers have made progress in understanding the etiology and course of the disease.

**PD Etiology**

While generally thought as a dopaminergic disorder, the hallmark pathology of Parkinson’s disease – Lewy neurites (LN) and Lewy bodies (LB) – forms first in the olfactory bulb and medulla oblongata. The LNs then spread upward and outward including the substantia nigra, basal forebrain, limbic system, and, in later stages, throughout the neocortex (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004). LNs and LBs increase in density as PD progresses as well as if dementia develops. However, severity of clinical symptoms does not correlate strongly with the severity of PD pathology; instead, worsening clinical symptoms in PD might be linked with an interaction between more Lewy neurites and greater neuronal loss (Halliday, Lees, & Stern, 2011). Nevertheless, relatively little is known about this interaction between cellular PD pathology and cellular loss. While PD pathology will not be directly addressed in the current study, cellular loss will be measured.

Some have proposed that, because the olfactory system is affected in PD, unknown environmental pathogens entering through the olfactory system play a role in the development of PD (Hawkes, Shephard, & Daniel, 1999; Hawkes, Del Tradici, & Braak, 2007). These pathogens might also enter the enteric nervous system via the stomach and progress to the lower brainstem via cell-to-cell transmission (Hawkes et al., 2007; Halliday et al., 2011). Even if specific environmental and biological factors resulting in PD are unknown, it is believed that a mixture of biological and environmental factors seems to play the largest role in who develops PD (Wirdefeldt et al., 2011).
Differences in mixtures of biological and environmental factors might lead to differences in presentation of Parkinson’s disease symptoms.

**Cognitive Considerations in PD**

In addition to the core motor, autonomic, emotional, and cognitive symptoms of Parkinson’s disease, many patients with PD go on to develop dementia. Parkinson’s disease patients are at up to a six fold risk compared to peers without PD for developing a comorbid dementia, such as Alzheimer’s disease, Lewy Body dementia, vascular dementia, or Parkinson’s disease dementia (Aarsland et al., 2001; Aarsland et al., 2005). There are estimates that more than 35 million individuals worldwide are currently living with dementia, with that number predicted to top 115 million in the next 40 years (Wimo & Prince, 2010). Because individuals with PD are at an increased risk of developing dementia, which worsens already impaired quality of life, it is imperative to gain greater understanding of cognitive and neurobiological changes in PD and the overlap between or comorbidity of PD and dementia.

Memory, cognitive, and functional impairments start relatively early in the disease process and worsen if a dementia develops. This places a burden on clinicians and researchers to detect these cognitive and memory problems early so that individuals with PD can receive necessary treatment that will improve their quality of life. The quality of life of PD patients is affected early by their motor symptoms, which are functionally impairing. Much is known about the neurobiology of motor symptoms in PD, however, not as much is known about the underlying neuroanatomical substrates of the cognitive and memory symptoms.

The motor symptoms of PD are associated with a loss of dopaminergic neurons in the substantia nigra pars compacta located in the mesencephalon, which is a
phylogenetically ancient area of the brain located in the brainstem. This loss of dopamine affects many areas of the brain, including deep brain nuclei, such as the caudate and putamen, which are part of the basal ganglia and are involved in motor functions among other abilities. Cortical areas are also affected. Although dopamine plays a dominant role in motor and cognitive slowing in PD, there are other neurotransmitters and brain regions to consider in addition to dopamine and the basal ganglia (i.e., the nigrostriatal pathway). Some of the other affected systems include noradrenergic, serotonergic, and cholinergic structures and pathways (Jellinger, 1991). A significant amount of serotonin is produced in the brainstem and much acetylcholine is produced in the basal forebrain; both brainstem and basal forebrain are affected early in the Parkinson’s disease process. In fact, serotonin and acetylcholine deficits can occur earlier than or concurrently with dopamine deficits (Halliday et al., 2011). Serotonin and acetylcholine are important in such functions as emotional regulation and cognition. Not all individuals with PD experience the same amount of pathological changes. There is growing evidence that Parkinson’s disease is not entirely a homogenous disease but one with a range of affected autonomic, motor, cognitive, and memory symptoms (Kehgia et al., 2010; Kim et al., 2009).

**Memory for Verbal Information**

Clinically, individuals with PD often report concern about memory and word retrieval problems. While deficits in other cognitive functions might be interpreted by individuals with Parkinson’s disease as “memory problems”, empirical studies show that verbal memory impairments do occur early in the course of idiopathic PD (Baran et al., 2009; Davidson et al., 2006); however, reasons for these difficulties remain unclear. When assessed clinically, verbal memory difficulty in patients with PD is not
homogenous. Some patients do not report any significant memory problems while others report difficulty remembering names or conversations or items on a “to-do” list. This variability in memory difficulty has also been seen in research populations (Filoteo et al., 1997; Weintraub et al., 2004).

Part of the reason that there can be variability in memory difficulties is the complexity of memory. In order to remember verbal information, an individual needs to pay attention, understand what is being said or read, and process information quickly (particularly if the information is unstructured) while simultaneously organizing and consolidating the information into intact storage systems. Faulty memory can occur when there are problems in any of these areas. This also means that disentangling what might be ‘pure’ memory difficulties from memory difficulties due to other processes is difficult. A better understanding of the foundations and concepts of memory can elucidate the nature of memory deficits when they occur.

**Cognitive and Biological Substrates of Memory**

Memory is a multi-faceted and high level component of brain function. The ability to learn and remember starts at a basic level in the brain; each neuron changes in response to use (Hebb, 1949). The phrase “neurons that fire together wire together” explains that learning and memory have a biological foundation at the neuronal level; this type of neuronal change with experience has been termed Hebbian learning after its main proponent. When two or more neurons fire in response to a stimulus, this paired association is strengthened, making it more likely that the next time one of them fires, the other one will fire as well. It can thus be said that the neurons ‘learn’ and ‘remember’. This type of cellular learning is the foundation of neuroplasticity, which simply means that the brain changes with experience. This plasticity of the brain is the
neurobiological reason humans and all other animals with a nervous system can learn and remember.

In order to understand memory better, a few terms will be provided and defined. Learning is the process of acquiring novel information whereas memory is the persistence of that acquired information over time with the goal that it can be accessed for further use. In order for information to be learned and become a memory, there are three general processes worth noting: encoding, storage, and retrieval. Encoding is the process of transferring information to memory. During the encoding phase, information is acquired – perceived and manipulated – and consolidated – information is stored and processed further such that its representation in storage is strengthened. There is considerable evidence that the encoding, particularly the consolidation, of memory occurs in the medial temporal lobe (MTL) with the entorhinal cortex and hippocampus the chief structures of this area (Sara, 2000). There is, however, evidence that other brain regions – such as the frontal lobes – are active during and important for memory encoding (Stebbins et al., 2002).

Storage is thus the ‘library’ that holds all of the encoded information for permanent retention. Storage of memories is believed to be widely distributed throughout the cerebral cortex including the frontal lobes but is still largely dependent on the medial temporal lobe (Smith & Squire, 2009).

The last part of the process of the memory system is retrieval, which is acquiring information from storage for active use (Gazzaniga, Ivry, & Mangun, 2002). While diverse brain structures are involved in retrieval, including the medial temporal lobe, prefrontal cortex, and parietal regions (Clement, Belleville, & Mellah, 2010), memory
retrieval is mediated by and most strongly dependent upon the hippocampus and entorhinal cortex (Muzzio et al., 2009; Meulenbroek et al., 2010; Hoscheidt et al., 2010).

Memory is often further reduced into three temporal types of memory: sensory, short-term, and long-term (Anderson, 1976). Sensory memory is essentially everything that the senses (e.g., vision or hearing) register in any given instant; this type of memory lasts milliseconds to seconds. Information from sensory memory that is attended to and selected for retention then moves into short-term memory, which lasts seconds to minutes. Information can then be further consolidated into long-term memory, which lasts minutes to an indefinite period. While important parts of the overall memory process, sensory and short-term memory will not be discussed further because they are not directly applicable to this project. It should be noted that there are competing views and contradictory evidence for this model of the memory system but addressing controversy in memory models is beyond the scope of the current project (review for more information on models of memory: Aggleton & Brown, 2006; Markowitsch et al., 1999; Cave & Squire, 1992).

Long-term memory (see Figure 1-1) is complex with at least two main distinctions – declarative and non-declarative. These memory systems are separate and can be separately affected by pathology or other damage (e.g., Roediger, 1990). Declarative memory is memory for facts, figures, people, faces, names, events, and objects, among other information. This is information that is usually explicitly learned and can thus be actively and intentionally recalled. Even though there are both verbal (names, shopping lists; Shallice & Warrington, 1970) and non-verbal (object or face recognition) components of declarative memory, even non-verbal memory can be expressed, or
translated, into language and thus declared. For example, memory for faces is non-verbal but an individual could describe a face using words, hence its classification under declarative memory. Non-declarative memory is, among other things, memory for motor skills such as playing tennis or the piano (procedural memory). Usually it is tasks and skills that are implicitly learned and to which we generally do not have conscious access. Components of this memory system usually cannot be expressed in words.

While various memory systems were briefly reviewed, the focus of this study is on verbal memory so other types will not be explored further. Because memory is multi-faceted, memory deficits can develop in a number of ways. In order to assess verbal memory deficits, verbal memory tests were developed by researchers and clinicians. Two common types of verbal memory tests are list-learning and story memory.

**Tests of Verbal Memory**

*Verbal list-learning measures.* Verbal list learning tests, such as the Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt & Benedict, 2001), the California Verbal Learning Test – II (CVLT-II; Delis et al., 2000), or the Philadelphia (repeatable) Verbal Learning Test (PrVLT; Price et al., 2009) are used both clinically and in research settings. The tests are complex in that they include a set of indices used to decipher whether learning problems are associated with working memory, encoding and/or retrieval difficulties. Regardless of the specific test name (HVLT, CVLT, PrVLT) each list-learning test includes three main components: a set of list learning trials (immediate recall), a delayed recall trial, and a recognition component.

List learning trials allow for researchers and clinicians to assess encoding of the test information. Specifically, researchers can look at the number of words retained over the learning trials, or they can assess improvement over the trials to see if individuals
benefit from repeated exposure. Damage to the MTL has been associated with poorer learning and encoding. In one study, researchers found that atrophy of the medial temporal lobe, including the hippocampus, was correlated with total learning performance even within a group of Alzheimer’s disease patients; those who had smaller hippocampi and more medial temporal lobe atrophy consistently learned fewer total words on a list-learning test (Wolk et al., 2011). Testing for information after a delay (delayed recall) allows researchers to evaluate the consolidation and persistence of learned information. The number of words recalled after a delay can be assessed; it can also be compared to the number of words learned on any given learning trial. Doing so provides a measure of the persistence of information in storage. Delis and colleagues (2005) demonstrated that by looking at delayed recall performance, taking into account how many extra words a person gives, it is possible to reliably differentiate between people with more MTL and cortical atrophy (e.g., Alzheimer’s disease) and those with subcortical atrophy (e.g., Huntington’s disease). People with better memory not only remember more information but they are also able to inhibit incorrect responses and thus not produce as many extra words (intrusions) during recall. In other words, people with better memory not only recall more words but also make fewer errors during a recall task. This is an ability that is heavily dependent on the MTL.

It has been demonstrated that the thickness of the cortex of the MTL is positively correlated with delayed memory performance in Alzheimer’s patients. While the cortical thickness of other temporal and frontal areas relates with working memory performance, the thickness of cortical areas other than the MTL do not reliably correlate with delayed memory performance (Wolk et al., 2011). This provides additional evidence that the
MTL is the key area of the brain responsible for the transfer of information into storage as well as the later retrieval of that information from storage. Other researchers have found that Alzheimer’s patients who have smaller left entorhinal cortices do worse on delayed list-learning recall (Di Paola et al., 2007). Smaller hippocampal volumes have also been associated with poorer delayed recall in non-demented, healthy older adults (Price et al., 2010; Tupler et al., 2007). This is important evidence that gross volume changes help explain variability in memory performance; that variability is linked with gross volume changes is true within groups of healthy individuals or within groups of neurologically compromised individuals.

The third main component of list learning measures is recognition testing. For the recognition test, a larger group of words is read to participants, from which they need to select the words they heard previously. Recognition tests are also heavily dependent on the MTL; individuals who have Alzheimer’s disease and who have thinner MTL cortex (with the implication of more atrophy) perform more poorly on recognition testing (Wolk et al., 2011). There is, however, some controversy over the role the MTL, and specifically the hippocampus, plays in recognition testing (Kramer et al., 2005) but the preponderance of evidence (Brown, Warburton, & Aggleton, 2010; Gold & Squire, 2006) supports the role of the hippocampus and related structures, such as the entorhinal cortex, as necessary (but not necessarily sufficient) for the encoding and consolidation (and retrieval) of information.

While the MTL structures are necessary for verbal memory, they are not sufficient to explain all memory functioning. Brain areas, such as the frontal lobes, play important roles in verbal memory. Damage to the frontal lobes or frontal connections often result
in working memory and executive (planning, organization, inhibition) deficits. On list-learning tests, performance on initial learning trials is strongly affected by working memory whereas later ones are more affected by long-term memory (Vakil & Blachstein, 1993). Thus, even though the MTL is vital for memory performance, damage or disruption to other brain areas will also affect memory. Individuals experiencing memory deficits due mainly to MTL (and closely connected brain regions) damage (e.g., encoding and consolidation deficits) are said to have an amnestic disorder. In contrast, individuals who experience memory problems due to frontal-subcortical areas and connections (e.g., processing speed, working memory, and organizational deficits) are described as having dysexecutive memory problems. These memory profiles will be discussed more in depth later.

With typical clinical scores such as total learning, delayed recall, and recognition, it is possible to start to investigate and differentiate amnestic and dysexecutive profiles. Delayed recall and recognition scores are particularly sensitive to changes in the MTL (Wolk et al., 2011; Brown, Warburton, & Aggleton, 2010; Gold & Squire, 2006). There is evidence that initial learning is not as affected by hippocampal atrophy as delayed recall and recognition are in individuals with dementia (Tanner et al., 2011) because it is more dependent on working memory abilities (Vakil & Blachstein, 1993), which are widely distributed throughout the brain.

Some verbal memory measures like the CVLT and PrVLT allow for in-depth analysis of amnestic patterns. Specifically, both the CVLT and PrVLT contain five learning trials, a separate interference trial where a new list of words is presented, a short delayed free recall trial (e.g., “Tell me all the words you can remember from the
first list; the one I read several times to you.")], a short delayed cued recall trial, long delayed (after 20-30 minutes) free and cued recall trials, and a recognition component that includes foils from the interference trial. Whereas the CVLT was designed for broad clinical and research use, the PrVLT was developed specifically for use with older adults (Price et al., 2009).

Other list-learning indices have been associated with MTL changes. One index has been referred to as a savings index (Lamberty, Kennedy, & Flashman, 1995; Welsh et al., 1994). The savings index is a measure of information retained from the immediate learning to the delayed time period (Lamberty et al., 1995). It is a measure of an individual’s ability to retain learned information when factoring in how much the individual initially learned (Filoteo et al., 2009). This savings score has been shown to be sensitive to early memory changes in dementia (Welsh et al., 1994). Individuals who ‘save’ less learned information have a relatively rapid rate of forgetting. This quick forgetting is largely affected by MTL pathology (Squire, Stark, & Clark, 2004) but might also be affected by other brain regions (Filoteo et al., 2009). Overall though, how much information is retained, or ‘saved’, is affected by the integrity of the MTL and as such, the savings index is sensitive to MTL atrophy.

Scores from individual list-learning trials or indices can be used to differentiate between MTL and frontal effects on memory. While the following index scores will not be used for the main analyses of the present study, they are presented as examples of the utility of using various list-learning index scores for differentiating between types of memory impairment. For example, two of the trials on the CLVT and PrVLT can be particularly useful for assessing for the presence or absence of amnestic difficulties:
cued recall and an interference trial. Following a free (non-cued) delayed recall trial, on the CVLT and PrVLT, the participant is given a cued recall trial. Many list-learning tests include words from different semantic categories, for example, places, animals, or vegetables. On the cued recall trial, an individual is thus asked to tell the examiner all the words that were in a particular semantic category. This serves as a cue that provides context and structure to help organize memory recall. This can enhance recall in situations where information is stored but there is difficulty retrieving it (Craik & Tulving, 1975).

The interference trial is a learning trial with a novel list of words. It is usually given just after the five learning trials for the first list and before a short delayed recall. Giving this trial allows one to probe for the effects of working memory and the ability to inhibit inappropriate responses. Thus structuring a list-learning test to include cued recall, an interference trial, and improved recognition testing can be particularly helpful and allow researchers and clinicians to better assess for the presence or absence of amnestic difficulties (Davis et al., 2002). Specifically, individuals with medial temporal lobe pathology make more intrusion errors on free and cued recall as well as during recognition testing (Delis et al., 1991). This means that they have more of an indiscriminant response set – they cannot differentiate between words from the learning trials and distracter words. Assessing participants’ recognition discriminability is particularly salient to the current study. This type of memory pattern (an indiscriminant response set) occurs when there is more disruption or damage to the MTL. Price and colleagues (2009) found that individuals with dementia with little evidence of subcortical vascular disease (i.e., their dementia is thought to be mainly cortical and
neurodegenerative in nature) produced more cued recall intrusions as well as false
positives on recognition testing. While more is known about memory patterns in
dementia, particularly Alzheimer’s disease, within PD, relatively little is known about the
medial temporal lobe, particularly the entorhinal cortex, and associated white matter
pathways as they relate with verbal memory performance. A discussion of this will occur
later in this manuscript.

List-learning tests are sensitive to memory changes because they are generally
free from contextual and other associative information that can serve as semantic
support from which to pull information during recall (Lezak et al. 2004). There are,
however, at least two prominent problems with list-learning verbal memory tests for
assessing memory deficits in PD. One problem is that they are affected by speed of
processing (see for example, Diamond, Johnson, Kaufman, & Graves, 2008). Because
Parkinson’s disease typically results in bradyphrenia (Huber, Shuttleworth, &
Freidenberg, 1989; Rogers et al., 1987) – cognitive slowing – what looks like a verbal
memory encoding deficit might simply be caused by reduced processing speed and
working memory (Foster et al., 2010). This means that on memory measures that are
strongly affected by processing speed, such as list-learning tests, if there are
processing speed deficits, ‘pure’ memory difficulties might be overstated. One proposed
solution is to use multiple memory measures, especially ones that might not be as
affected by processing speed, such as story memory measures (Zahodne et al., 2011).

Another problem with using list-learning tests – and any neuropsychological test
for that matter – is that norms developed for the tests are not usually targeted to a
particular population, such as PD. This is an issue because the extent to which findings
can be generalized from one population to another can be limited by the nature of the normative sample (Greenaway et al., 2009). When applying normative data from broader samples of individuals who are not necessarily similar to the targeted sample, it is possible to either overestimate or underestimate impairment. This is a problem that is easily solved. A useful solution to alleviate this problem that minimizes unexplained variance between groups is using matched control groups for the derivation of normative data.

**Story learning measures.** In addition to list-learning measures, there are other ways to assess verbal memory. Another common way to assess verbal memory is by use of a story memory test. Briefly, a paragraph of prose is read to an individual who is then asked to tell it immediately back to the examiner and then again after a 20-30 minute delay. Story memory tasks also include a recognition component where the individual is asked to answer a series of simple yes/no questions about the story. Performance on story memory tests is thought to be less affected by processing speed and executive deficits than list-learning tests are; it has also been linked to the MTL with more atrophy and pathology of the MTL associated with poorer story memory performance on all indices of the tests – immediate recall (learning), delayed recall (retention), and recognition (Jokinen et al., 2004; Berlingeri et al., 2008; see also Price et al., 2010). Some have argued that it is important to have multiple measures of verbal memory when assessing for memory impairment (Loewenstein et al., 2009). Having impairment on both list-learning and story tasks provides stronger evidence of actual memory difficulty than does having impairment on either alone (Zahodne et al., 2011;
Janecek et al., 2011). Both list-learning and story memory tests are useful for assessing memory of individuals with Parkinson’s disease, particularly when combined.

**Is there a Verbal Memory Impairment in Parkinson’s Disease?**

It is believed that many verbal memory deficits in PD are associated with impairments involving frontal system functions (attention, processing speed, and/or working memory). These deficits are linked to dysfunction of circuits between the basal ganglia and the frontal lobes (Tinaz et al., 2008; Saint-Cyr, 2003). These circuits were first described in depth by Alexander, DeLong, and Strick (1986) as connecting the basal ganglia with different parts of the frontal lobes with an organization dependent on the function of the circuit; the different circuits are involved in motor, cognitive, and emotional processes. It is believed that dysfunction in these circuits reduces memory performance due to a deficit of processing speed and executive abilities (e.g., set shifting, ordering; Zahodne et al., 2011).

When these frontal-subcortical circuits are disrupted, which occurs in PD, this can affect the encoding and storage of information from an organizational level. Retrieval of information from storage is also reduced; however, because information was encoded (not necessarily as well as in an individual without PD but also not necessarily at an impaired level) the information was processed and stored. With difficulty freely retrieving information, an individual with frontal-subcortical dysfunction benefits from cuing because the information was stored but the processes of searching and retrieving from storage are not working flawlessly. In other words, when prompted with a cue (e.g., “Which of the following words did I previously read to you?” – a recognition task), someone with frontal-subcortical dysfunction will typically benefit from that cue because, in part, it reduces the effort needed to retrieve information. This has been interpreted as
indicative of a primary self-retrieval problem rather than one of primary encoding (Stone et al., 1998; Kramer et al., 2005; Dobbins, Simons, & Schacter, 2004). In other words, frontal-subcortical dysfunction disrupts memory more by reducing the ease of retrieval than it does by reducing the ability to store and retain information, although the efficiency of such processes are likely reduced.

On formal clinical testing such as with word list-learning, which is devoid of significant structure, being able to impose structure through grouping similar words together (semantic clustering) or applying mnemonic devices (memory strategies) during the encoding phase improves performance (Weintraub et al., 2004). Individuals with PD can learn information, just not as efficiently or as quickly as people without PD. This pattern of memory deficit is a dysexecutive memory profile, which is believed to be due to frontal network (frontal lobes plus connected subcortical structures) dysfunction, slowed speed of processing, or executive control shortcomings (Baddeley & Wilson, 1988; Baddeley, Della Sala, & Spinnler, 1991; Stuss & Alexander, 2007).

Conversely, while frontal systems are involved in verbal memory performance of individuals with PD, it is possible that frontal system dysfunction does not fully explain memory deficits seen in individuals with PD; there is an argument that some of the verbal memory deficits in PD patients might be related to compromised storage of verbal information (Lee et al., 2010). This means, in part, that there is a breakdown in the encoding process; thus, some information is not transferred to storage. This breakdown in encoding goes beyond a reduction in the efficiency of the encoding process – some information is simply not processed and maintained in storage. This is what happens in disorders such as Alzheimer’s disease, which initially and primarily
affects the MTL (entorhinal cortex, hippocampus, and surrounding areas). People with pure encoding deficits will have difficulty retrieving information from storage because the information never was stored and so there is nothing to retrieve, or at least not as much information as with healthy individuals. Additionally, learned information can rapidly leave storage, which reduces the amount of information in storage that can be later retrieved. With memory deficits, when cued with a recognition task there is little to no benefit and performance is at or near chance level. This type of memory profile – poor encoding, storage, and hence, retrieval because there is little information to draw from storage – has been termed an amnestic profile (Delis et al., 1991).

**Parkinson’s Disease is Heterogeneous**

There is evidence that PD patients experience amnestic memory difficulties as well as dysexecutive memory deficits or even no memory difficulties. When looking at the progression of PD, there are PD patients who never develop dementia, some who develop Parkinson’s disease dementia, Lewy body dementia, small vessel vascular disease dementia, Alzheimer’s disease, or some other variety or mixture of dementia pathologies and etiologies. While PD is not a dementia, individuals with PD are at an increased risk of developing dementia (Aarsland et al., 2001). Even those who are non-demented can start exhibiting cognitive and memory deficits early in the disease process (Baran et al., 2009). It follows that because memory is multi-faceted and dementias are varied, those with PD who will progress and eventually develop some form of dementia will have cognitive deficits that progress along different paths and with different trajectories.

Thus, it is not likely that all Parkinson’s patients, even ones who will not develop dementia at some point, will exhibit the same memory deficits or even any significant
memory deficits, at least until late in the progression of PD. There is evidence that supports this heterogeneity in memory; not all PD patients exhibit a primary retrieval (dysexecutive) memory deficit pattern. There is evidence that a subset of individuals with PD show evidence of an amnestic profile, such as is typical in damage to or pathology of the MTL (Weintraub et al., 2004; Filoteo et al., 1997). Other idiopathic PD patients also might have a mixture of amnestic and dysexecutive difficulties while others might not have any obvious verbal memory deficits.

In one study where researchers used a list-learning test to classify types of memory deficit in individuals with PD, the researchers found that 50% of PD patients did not have significant memory deficits, 26% of PD patients had a dysexecutive profile similar to that of Huntington's disease and 23% had memory problems more similar to the amnestic profile that patients with Alzheimer's disease typically display (Filoteo et al., 1997). These memory profile classifications were based on performance on the 16 item list-learning test (California Verbal Learning Test {CVLT}). Specifically, the researchers looked at the number of words individuals learned, the number of errors they made during recall (stating words not on the list), and how well individuals did on recognition relative to free recall (to see if participants benefited from the recognition trial). These particular scores were shown previously to be sensitive to memory deficit differences between patients with Alzheimer's disease and those with a prototypical subcortical disease – Huntington’s disease. Individuals with Alzheimer's disease do not learn many words, they quickly forget the words they do learn, “recall” a number of words that were not on the list, and do no better on recognition than they did on free
recall of words. Patients with Huntington’s disease, however, while doing poorly in total learning, benefit from the recognition trial (Massman et al., 1992).

In the study by Filoteo et al. (1997), the researchers investigated whether or not PD patients with amnestic (23% of their PD group) versus dysexecutive (26% of their PD group) memory profiles also differed on other neuropsychological measures. There was no between-group difference in language, verbal fluency, or frontal organizational functions. The only test for which there was a difference was on a test commonly associated with degraded semantic memory (semantic fluency), which is often impaired in Alzheimer’s disease; PD patients with an amnestic memory profile produced fewer words than PD patients with a dysexecutive profile produced. Even though there was a reduction in semantic fluency in the amnestic group, there were no differences in language, verbal (non-semantic) fluency, or frontal organizational skills. The researchers interpreted their results as providing evidence that the amnestic PD patients did not also have Alzheimer’s pathology. Thus, memory dysfunction within idiopathic PD possibly varies independently of comorbid Alzheimer’s pathology.

However, this research has some limitations. The authors did not produce enough evidence to entirely rule out early Alzheimer’s disease processes in the amnestic PD patients. This is not necessarily a problem but it is unclear whether or not this heterogeneity in memory performance in PD is due to PD pathology or concomitant Alzheimer’s or other pathology. However, this is an issue that can only be addressed through brain tissue biopsy. An additional limitation is that the authors did not include story memory performance in their analyses, which would have helped their argument if the amnestic PD group also had story memory deficits. In spite of these limitations,
these results provide evidence that there might be heterogeneity of memory deficits in PD.

Another study revealed a similar memory pattern in PD patients with 48% with unimpaired memory, 33% with impaired retrieval (i.e., dysexecutive memory), and 17% with impaired encoding (i.e., amnestic deficits; Weintraub et al., 2004). Weintraub and colleagues found that in a group of non-demented PD patients, those with dysexecutive and amnestic memory profiles had similar free recall performance on the HVLT-R but the dysexecutive group had significantly higher recognition scores and fewer intrusion errors than the amnestic group had. Additionally, Weintraub and colleagues found a significant association between a measure of executive function and impaired retrieval – meaning that those who benefitted from the recognition component of the verbal memory task tended to have more problems with their ability to organize, shift set, and perform other executive tasks.

While verbal memory for word lists is thought to be more affected in patients with PD, there is evidence that story memory performance is also affected in non-demented PD participants (Beatty et al., 2003). Beatty and colleagues showed that non-demented PD participants performed as poorly on a story memory test as they did a list-learning test. Also in this study, the poor performance on story memory was found even when controlling for a possible floor effect in test performance. Deficits in story memory are more typical of amnestic verbal memory difficulties than of dysexecutive ones.

There is further evidence for amnestic memory problems in PD patients: researchers have found recognition impairments in PD patients relative to controls (Beatty et al., 2003; Beatty et al., 1989; Helkala et al., 1988). This means that verbal
memory deficits in non-demented PD patients might not be solely related to problems with retrieval or executive dysfunction. That is a conclusion supported by the findings of Filoteo et al. (1997) and Weintraub et al. (2004). Thus, while executive deficits affect verbal memory performance in a proportion of PD participants, some verbal memory deficits might also be attributed to other neuronal or neurodegenerative processes.

This concept of multiple memory profiles in non-demented idiopathic PD patients is not without controversy but there is building evidence of heterogeneity of motor, cognitive, and emotional symptoms in Parkinson’s disease (see for example, Hardy, 2010). Verbal memory is only one of the cognitive functions affected by Parkinson’s disease. A look at some broader areas of cognition will provide additional evidence of heterogeneity in Parkinson’s disease.

**A Growing Concern: Mild Cognitive Impairment and Parkinson’s disease.**

There is growing concern for the development of dementia in PD. It is widely accepted that mild cognitive impairment (MCI) places individuals at greater risk of developing dementia (Gauthier et al., 2006). Additionally, MCI is a heterogeneous condition with some individuals having more memory (amnestic) difficulties, some having more executive difficulties, some converting to dementia over time, others staying with mild impairment, and others converting back to normal cognition (Douaud et al., 2011). It is generally believed that those with amnestic MCI are more likely to develop Alzheimer’s disease, those with dysexecutive MCI are more likely to develop a subcortical or vascular dementia, and those with mixed presentations could develop either dementia or a mixed presentation of dementias (Gauthier et al., 2006). There continues to be a debate regarding the significance or relevance of mild cognitive impairment in PD.
In Alzheimer’s disease, there is evidence that memory difficulties and disruptions to language are related. Individuals who have Alzheimer’s disease often have word-finding difficulties, which difficulties are known as a fluent, anomic aphasia (Price et al., 1993). While it is possible to have language difficulties without memory impairment, it is common to have disruption to the language as well as the memory system with the cortical atrophy common in pathologies such as Alzheimer’s disease or other amnestic disorders (Cummings, 1986; Galton et al., 2000). It is thus reasonable to expect changes to language (e.g., difficulty naming or reductions in semantic abilities) to be comorbid with amnestic memory difficulties. While there can be disruptions to the access of the semantic storage system with damage to subcortical systems such as is common in Huntington’s disease and Parkinson’s disease, individuals with more cortical changes have a breakdown in the semantic storage system itself, rather than difficulty with accessing it (Randolph et al., 1993). This is due to the changes to the cortex, including the temporal lobe. There can be, however, heterogeneity in cognitive deficits in populations with neurological disorders.

There have been attempts to classify subgroups of PD with mild cognitive impairment (MCI). Caviness and colleagues (2007) used a cut point of 1.5 standard deviations when compared to age matched peers to classify PD participants as having MCI. A deficit of 1.5 standard deviations on a neuropsychological test using a normally distributed (Gaussian) curve, places an individual at about the 7th percentile. This means that 93% of age-matched peers perform as well as or better than someone with a score at least a 1.5 standard deviation deficit. A 1.5 standard deviation deficit is also a typical clinical cutoff for classifying impairment.
Using this cutoff, Caviness and colleagues (2007) looked at five broad cognitive domains: frontal/executive, amnestic (memory), visuospatial, attention, and language. They found that 62% of participants had normal cognition in all domains, 21% had mild cognitive impairment, and 17% had dementia. A clinical classification of dementia, from a neuropsychological standpoint, usually requires impairments in activities of daily living as well as cognitive and memory impairments. Of the 21% classified as PD-MCI, 22% of those had only an amnestic deficit and 11% had multiple domains including amnestic deficit (39% had only frontal/executive dysfunction and an additional 22% had multiple domains but no amnestic memory difficulties). Thus, the authors found that there is variability in cognitive and memory profiles of individuals with PD.

However, there are a number of potential criticisms of Caviness and colleagues’ study. First, there were only 18 individuals in the PD-MCI group (total sample N = 86), which resulted in just 4 being diagnosed as having amnestic MCI (with an additional 2 who had amnestic MCI plus difficulty in one or more other domains). This works out to 7% of the broader sample being diagnosed with amnestic MCI (or amnestic MCI plus other deficits). It is difficult to draw firm conclusions with a limited number of PD patients having MCI and a smaller sample of those with amnestic MCI. It is possible that this estimate is low because the authors assessed verbal memory using the auditory verbal learning test (AVLT), which was not designed specifically for use with older adults (Lezak et al., 2004) and might not be a particularly sensitive measure to assess for an amnestic memory profile. Nevertheless, there is compelling evidence that there are some PD patients who have amnestic memory problems (Janecek et al., 2011); however, the extent to which amnestic deficits occur in PD is not fully clear.
Another limitation is the test indices used to examine MCI in PD. Caviness and colleagues (2007) investigated only immediate and delayed recall, which might provide a limited view of list learning (Price et al., 2009). They did not include recognition memory, which might have changed some of the classifications away from amnestic (i.e., if there were substantial improvements in recognition from recall or if there were no deficits in recognition compared to controls). Further, the researchers used literature-based normative values, which they state might offer better reliability and generalizability but conversely, using literature-based norms rather than a closely matched normative sample can limit the sensitivity and specificity of findings and introduce uncontrolled variance into the results. In addition to this, Caviness et al. (2007) did not include a story memory task, which when combined with list-learning tasks, can improve classification of mild cognitive impairment (Rabin et al., 2009; Loewenstein et al., 2009). In short, the study potentially has serious limitations but does support the idea of memory deficit heterogeneity in PD.

Even given these limitations, we can tentatively conclude that in non-demented PD patients, there is variability in cognitive deficits; this is clear when we compare the results of the study by Caviness et al. (2007) to other similar studies (see for example, Foltynie et al., 2004; Aarsland et al., 2010). There is further evidence that a significant portion of PD patients might have amnestic memory difficulties. Other researchers found in a large and well-controlled study that 14% of individuals with PD could be classified as having amnestic MCI (Aarsland et al., 2010). Overall, while the precise proportion remains unknown, this review of the literature establishes that it is likely that between 7-22% of non-demented individuals with PD experience amnestic memory
deficits with somewhat higher proportions of individuals experiencing dysexecutive MCI (e.g., Caviness et al., 2007; Filoteo et al., 1997). The variability in that range could be due to different memory measures used, different cut-off points and criteria for defining types of memory difficulties, different sample sizes, or differences in study inclusion and exclusion criteria. Using more specific analyses targeted on drawing out amnestic difficulties should allow for stronger conclusions to be made about how disruption to the MTL affects memory in PD patients. In summary, there has been considerable and building evidence in recent years to suggest heterogeneity in how Parkinson’s disease affects cognition and memory (Jellinger, 2010).

**Language and Semantic Knowledge in Parkinson’s Disease**

Semantic knowledge is one component of language that has been shown to be relatively intact in old age and even in some neurological disorders such as Parkinson’s disease (Portin, Laatu, Revonsuo, & Rinne, 2000). Semantic knowledge, however, is impaired in Alzheimer’s disease (Della Sala et al., 2004; Carew, Lamar, Cloud, Grossman, & Libon, 1997). It has also been shown to be impaired in cognitively compromised individuals with Parkinson’s disease (Portin et al., 2000; Bayles et al., 2000). Wide networks of brain regions subserve semantic abilities (Catani & Jones, 2005; Friederici, 2009). For most individuals, such language functions are largely lateralized to the left cerebral hemisphere, particularly to the perisylvian region (Catani & Jones, 2005). Damage to any of these diverse brain regions can result in reduced semantic functioning.

Focus on localized cortical regions started in the 1800s with case studies published by Broca and Wernicke demonstrating deficits in language resulting from left hemisphere brain damage (Geschwind, 1972; Geschwind, 1971). From these case
studies we learned that damage to left inferior frontal and temporal-parietal regions resulted in language deficiencies of differing presentation. In brief, it is believed that language comprehension is mediated primarily by the temporal lobe whereas language production is more frontally mediated. However, that summary understates the complexity of language and the brain networks that support language functions including semantic knowledge.

While many aspects of language are preserved in the early stages of PD, there is evidence that some language functions are affected in PD. Holtgraves and McNamara (2010) found a deficit in pragmatic comprehension, which is language use in social contexts. They found that these deficits (specifically, a deficit in speech act comprehension, implying greater difficulty understanding the speech of others in social contexts) were related to poorer performance on an executive function measure (Stroop Color-Word interference task) and could not be fully explained by slowed processing speed. Additionally, these social language difficulties were correlated with disease severity. Pragmatic comprehension, however, is a complex form of language, involving a number of other cognitive functions. As such, pragmatic comprehension is not considered a pure language task (Zurif, 1980), especially compared to a simple semantic retrieval task.

Grossman (1999) found that sentence comprehension deficits occur in PD. These deficits were linked with selective attention difficulties, which are believed to rely heavily on affected frontostriatal circuitry. Sentence comprehension requires holding in mind a phrase including the connection between a subject, verb, object, and location. Thus, sentence comprehension has a large demand on working memory. Sentence
comprehension is thus a fairly complicated form of language, affected by other cognitive functions. Simpler forms of language, however, might also be affected in PD.

There is evidence of impaired confrontation naming in PD. Matison and colleagues (1982) found a slight deficit on the Boston Naming Test in a group of 22 PD patients. They called this a “tip of the tongue” syndrome or a “word production anomia”. Cooper and colleagues (1991) found language, including confrontation naming, deficits in individuals with PD; however, these only occurred in individuals with global cognitive deficits. In other studies, however, researchers have not found impairments on semantic knowledge tasks, such as confrontation naming, in idiopathic, non-demented PD (Tröster, Stalp, Paolo, Fields, & Koller, 1995; Pagonabarraga et al., 2008).

Generally, the accepted view about PD is that any language difficulties observed in PD are not similar to aphasias seen with focal or diffuse left hemisphere lesions (Grossman, 1999) or those that occur with cortical dementias, such as semantic dementia or Alzheimer’s disease. Thus, it is believed that most language difficulties in non-demented PD are due to frontal-striatal network deficiencies, which result in slowed processing speed, attention deficits, working memory difficulties, and executive dysfunction (see Bastiaanse & Leenders, 2009 for a review). This implies that brain regions and networks directly supporting language functions including semantic knowledge are likely not affected in PD, at least early in the disease process.

**Language and semantic brain networks.** Production of spoken words, or even a single vowel or consonant sound, requires a broad network within the brain (Sörös et al., 2009). This network relies heavily on cortical and white matter areas surrounding the left Sylvian fissure for most right-handed individuals (Catani, Jones, & ffytche, 2005;
Turken & Dronkers, 2011). It involves frontal, parietal, and temporal cortical regions with underlying white matter as well as subcortical structures, such as the thalamus, also playing a role (Crosson, 1999). The long temporal to frontal white matter circuit that serves as a major language pathway is called the superior longitudinal fasciculus (SLF) / arcuate fasciculus (AF). There is some controversy whether or not the arcuate fasciculus is merely part of the SLF or if it is a separate, but closely related pathway (Duffau, 2008; Bernal & Ardila, 2009; Catani & Thiebaut de Schotten, 2008). For simplicity, the SLF and AF will be grouped together for this paper and referred simply as the arcuate fasciculus because the term fits the curved nature of the white matter bundle in the perisylvian region.

The AF can be separated into three regions – an anterior, which connects the frontal (Broca’s territory) with parietal regions (Geschwind’s area), a posterior segment, which connects parietal (Geschwind’s territory) and temporal cortex (Wernicke’s territory), and a long segment, connecting frontal cortex with temporal cortex (Catani et al., 2005). The AF is believed to be important for aspects of language functioning and disruptions to any part of the network can result in changes to language functions. It is, however, a complex fiber pathway with bidirectional connections between frontal – parietal and frontal – temporal regions (Duffau, 2008). While gross changes to the AF are not reported in Parkinson’s disease, there is evidence of microstructural white matter changes in the superior longitudinal fasciculus relatively early in the Parkinson’s disease process (Gattellaro et al., 2009), although these changes were not specifically localized to the AF portion of the superior longitudinal fasciculus. The AF and its function will be discussed more in depth later in this document.
Considerations for Neuroanatomical Predictors of Verbal Memory Impairment in PD

Idiopathic Parkinson’s disease (PD) affects not just the functions (e.g., cognition, memory, movement, and emotion) produced by the brain but also the structure of the brain. Neuroimaging, especially magnetic resonance imaging (MRI), allows for the investigation of the structure of the gray and white matter of the brain. Magnetic resonance image analyses allow us to better understand the neuroanatomical correlates or predictors of cognitive and memory processes. One type of magnetic resonance imaging that has grown considerably in research and clinical use is diffusion weighted imaging. Diffusion MRI data can be used for elegant visualization and quantification of the white matter in the brain. This permits better understanding of not just the discrete and localized neuronal areas involved in memory and cognitive processes but also the distributed networks connecting these areas. In other words, no part of the human brain is an island just as no function of the brain is completely independent of other functions.

The focus of this study is on how memory performance relates to the structure of both gray and white matter regions of the brain. Gray matter regions implicated in memory include the entorhinal cortex, which is part of the medial temporal lobe. White matter regions involved in memory processes are widely distributed but include, among other areas, the cingulum bundle. The focus in the present discussion will first be on the entorhinal cortex and then on the cingulum, particularly the posterior portion of the cingulum that connects to the entorhinal region.
Entorhinal Cortex and Medial Temporal Lobe

In idiopathic, non-demented Parkinson’s disease, there is evidence for hippocampal atrophy relative to controls (Laakso et al., 1996; Jokinen et al., 2009). The hippocampus is heavily connected with the entorhinal cortex, which has been shown to atrophy prior to the hippocampus in PD and Alzheimer’s patients (Jokinen et al., 2009; Choo et al., 2010). In general, the entorhinal cortex is the site of the earliest disruption in MTL atrophy and is possibly the cause of most of the memory changes seen in amnestic disorders because it disconnects the hippocampus from the neocortex (Insausti, 1993). This makes the entorhinal cortex an important structure for detecting early changes that can result in memory deficits. Both structures are part of the MTL (see Figure 1-2).

Historically, little was known about the functions of the MTL until James Papez (1937) proposed that the MTL was involved in emotion. This created additional interest in the MTL but relatively little was discovered about its role in cognitive and memory (or emotion, for that matter) processes until the 1950s. The medial temporal lobe became a focus for memory research following the seminal article by Scoville and Milner (1957) about Scoville’s patient Henry Molaisson (H.M.), who had his most of his hippocampi and amygdala plus surrounding parahippocampal gyri removed bilaterally as part of an experimental treatment for epilepsy. Following the procedure he experienced severe anterograde amnesia. This study and numerous subsequent studies demonstrated the importance of the MTL for the formation of semantic memory (Wolk et al., 2010), which is a form of declarative (explicit) memory. Patients with focal MTL damage have intact attention, working memory, visoperceptual skills, implicit memory, language, semantic knowledge, and global intelligence (Squire et al., 2006).
The medial temporal lobe is comprised of the hippocampal complex – the subiculum (the main output of the hippocampus), dentate gyrus, CA1 and CA3 fields of the hippocampus (regions CA2 and CA4 also exist but those are generally not included in connectional mappings of the hippocampus) – as well as the entorhinal, perirhinal, and parahippocampal cortices.

As is shown in Figure 1-3, the entorhinal cortex is the main afferent and efferent cortex of the MTL. It essentially controls the flow of information to and from the hippocampus (Schwarcz & Witter, 2002). The main white matter pathway from the entorhinal cortex into the body of the hippocampus (mainly the molecular layer of the dentate gyrus; Insausti, 1993) is called the perforant path, which has been shown to show degradation in older individuals with and without dementia (Yassa, Muftuler, & Stark, 2010). Disruption to any part of these circuits has the potential to affect all parts of the circuit.

Medial temporal lobe neuropathology in PD. Braak et al. (2004) proposed a series of stages of PD pathology. They stated that Lewy neurites are initially found in the medulla oblongata and olfactory bulb. From the medulla, the Lewy neurites spread upward into the substantia nigra and then to the allocortical areas of the medial temporal lobe and basal forebrain, disrupting both the dopaminergic and acetylcholinergic systems of the brain. Most of these pathological changes occur prior to phenotypical and clinical expression of motor symptoms. As symptom severity progresses, Lewy neurites and Lewy bodies continue to aggregate in affected areas while also spreading throughout the rest of the cortex, focusing particularly on lightly myelinated or unmyelinated neurons with narrow axons (Braak et al., 2004).
A recent neuropathological study was focused on the presence of \( \alpha \)-synuclein (\( \alpha \text{Syn} \)), tau, and amyloid \( \beta \) (A\( \beta \)) peptide in the brains of PD patients with and without dementia. All PD brains showed \( \alpha \text{Syn} \) and A\( \beta \) in the entorhinal cortex as well as a number of other brain regions; these concentrations of pathologic proteins increased in those who had dementia but were significant in non-demented PD. These results indicate that even in cognitively intact PD patients there is widespread cortical pathology in addition to the prevalent brainstem and subcortical changes (Kalaitzakis et al., 2009).

Micrograph investigations of pathological changes in the brains of PD patients have found extensive Lewy neurites and Lewy bodies in the transentorhinal region, which is the primary immediate entry into the main body of the entorhinal cortex. This disruption to the entorhinal cortex is greater than that seen in the anterior cingulate cortex, which also shows significant changes in PD patients. If pathology is related with cognitive and behavioral functioning, this pattern of pathology seems to indicate that memory disturbances might be at least as common as the well-recognized affective (e.g., apathy) disturbances. Additionally, there are Lewy neurites prevalent in the cornu ammonis (CA) of the hippocampus in PD patients (Braak & Braak, 2000). These neurites are clusters of proteins (primarily \( \alpha \)-synuclein) that are common in other neurodegenerative disorders, including Alzheimer’s disease (Marui et al., 2004). In Alzheimer’s disease, like in PD, Lewy neurites are common in the cornu ammonis of the hippocampus. This overlap in pathology between PD and AD might result in somewhat similar cognitive deficits.

These results demonstrate considerable progressive limbic system changes that occur in PD that could disrupt both cognitive and emotional functions. Specifically, the
entorhinal cortex is a sensitive predictor of early memory changes (Stoub, Rogalski, Leurgans, Bennett, & deToledo-Morrell, 2010; Braak & Braak, 1991). In a recent fMRI study, Brickman, Stern, and Small (2010) sought to associate distinct aspects of memory with blood flow (i.e., cerebral blood volume) in different components of the MTL. The researchers found a dissociation between the entorhinal cortex and the dentate gyrus for delayed recall and delayed recognition. Specifically, on a verbal list learning test, the authors found that cerebral blood volume in the entorhinal cortex was related to delayed free recall and retention performance.

There is additional evidence that memory tasks utilize the hippocampal region of the brain. Performance on a visual recognition task (part of the Benton Visual Memory Test) was correlated with blood flow in the dentate gyrus. The authors suggest that their results contribute to evidence that the entorhinal cortex is involved in maintaining representations in memory over a delay. This means that disruptions to the entorhinal cortex should result in faster decay of learned information. The entorhinal cortex is also involved in encoding during memory tasks as well as delayed cued recall of information (Fernandez, Brewer, Zhao, Glover & Gabrieli, 1999). Other research demonstrates a similar involvement of the entorhinal cortex in memory processes (Coutureau & Di Scala, 2009; Martin et al., 2010) and that the entorhinal cortex might be the primary site of hippocampal region dysfunction in Alzheimer’s disease (Reitz et al., 2009; Insausti, 1993).

The Cingulate in PD

The hippocampus and associated medial temporal lobe structures (entorhinal, perirhinal, and parahippocampal cortices) are merely one group and part of a distributed network. Another part of this network is the cingulum, a bundle of white matter fibers
that travels anterior and posterior in the brain just dorsal to the corpus callosum and just beneath the cingulate cortex (view Object 1-1 for a video introduction to the cingulum).

Object 1-1. Supplemental video created and narrated by Jared Tanner giving an introduction to the cingulum; work supported by NINDS K23-060660 (YouTube link: http://www.youtube.com/watch?v=8TAmyOAkCz8)

The cingulum travels from the basal forebrain above the cribiform plate of the skull to curve around and travel to the pole of the temporal lobe. The cingulum roughly parallels the path of the fornix – another pathway important in memory processes – and in fact, a portion of the cingulum and the crus of the fornix meet near the splenium of the corpus callosum where together they travel to and along the inferior hippocampus – the pes hippocampi (Schmahmann & Pandya, 2006). Further, the cingulum is interconnected with the uncinate fasciculus in both the frontal and temporal lobes, making what researchers have called a “limbic ring” travelling the circumference of the entire limbic system (Yakovlev & Locke, 1961). This limbic ring allows information from distributed brain regions to travel to and from the MTL in order to affect the creation and utilization of stored information, among other cognitive functions. While there are other pathways involved in memory, this limbic ring and associated pathways and structures is vital for normal memory functioning.

**Cingulate anatomy.** The cingulate (cingulate cortex and cingulum) is involved in multiple functions, including motivation, emotion, and memory; the cingulate is the major functional area of the limbic system. One function of the cingulum is to connect the cingulate cortex and septal nuclei with the parahippocampal gyri (Stadlbauer et al., 2008; Yasmin et al., 2009), of which the entorhinal cortex is a part, as well as to connect various brain regions to the MTL in general (Choo et al., 2010; Stadlbauer et al., 2008; Yasmin et al., 2009). Many of the fibers in the cingulum are bidirectional, creating loops
in connectivity; this means that the cingulum is not just carrying information to the MTL but also from it to other brain regions. The cingulate is part of network that James Papez initially proposed as an emotion circuit (Papez, 1937) but later research has shown that it is necessary for intact episodic memory (Zola-Morgan & Squire, 1993). Damage anywhere along the circuit can disrupt normal memory performance (Budson & Price, 2005). The Papez circuit (Figure 1-4) is roughly the following: hippocampus – fornix – mamillary bodies – mamillothalamic tract – anterior nucleus of the thalamus – cingulate cortex – cingulum (Papez, 1937).

**Retrospenial cortex.** The cingulate cortex also receives input from diverse association cortices, including the prefrontal cortex and the caudate nucleus. One area of the cingulate implicated in memory is the retrosplenial cortex (and adjacent posterior cingulate cortex). The retrosplenial cortex is one of the main areas of cortex providing and receiving connections to and from the entorhinal cortex (Kobayashi & Amaral, 2003). Up to 20% of the connections to the entorhinal cortex in a monkey are from the retrosplenial cortex (Insausti, Amaral, & Cowan, 1987). In the entorhinal cortex, the retrosplenial cortex connects via the cingulum (see Figure 1-5) mainly to the caudal portion in an overall topographical arrangement (e.g., lateral retrosplenial cortex connecting more laterally in the entorhinal cortex and the caudomedial aspects of retrosplenial cortex connecting more medially in the entorhinal cortex; Kobayashi & Amaral, 2003). It is believed that these areas are similarly connected in humans. Additionally, the retrosplenial cortex merges with the parahippocampal gyrus ventral to the corpus callosum. These close integrations with MTL structures imply a close functional relationship with areas pertinent to memory functioning.
Damage to the retrosplenial cortex can result in severe anterograde and retrograde amnesia (Valenstein et al., 1987). In the case study by Valenstein et al. (1987), the authors reported on a 39-year-old male who experienced an intracerebral hemorrhage just lateral to the left splenium. He additionally had an arteriovenous malformation surrounding the splenium in the pericollosal cistern. This hemorrhage resulted in the destruction of the retrosplenial cortex as well and the underlying cingulum. He experienced retrograde amnesia with impairments in episodic events of up to 4 years prior to his hemorrhage. He also had severely affected anterograde amnesia, especially for verbal information; nonverbal memory was relatively spared.

There is further evidence of the importance of the retrosplenial region in the formation and retrieval of memories. The retrosplenial cortex is heavily connected with the anterior and anterodorsal nuclei of the thalamus, which are key structures for memory processes (Vogt et al., 1987; Papez, 1937). Additionally, the retrosplenial cortex is a major termination site for the outflow of acetylcholine from the basal forebrain via the cingulum (Selden et al., 1998). The basal forebrain is affected by PD pathology, relatively early in the disease process (Braak et al., 2004), suggesting a potential disruption of acetylcholine input into the retrosplenial area in individuals with PD. The ties between acetylcholine, memory, and cognition are well-documented if not always straightforward for clinical treatment (Mesulam, 2004; Levin & Simon, 1998; Calabresi, Picconi, Terry & Buccafusco, 2003; Parnetti, & Di Filippo, 2006; Trinh, Hoblyn, Mohanty, & Yaffe, 2003).

There is evidence that some of the earliest signs of metabolic decline in Alzheimer’s disease occur in the retrosplenial cortex, even prior to metabolic changes in
the parahippocampal region (Minoshima et al., 1997; Villain et al., 2008; Vann, Aggleton, & Maguire, 2009). These metabolic changes are separate from the gray matter atrophy that early on and primarily affect the MTL in individuals who later develop amnestic memory disorders, such as Alzheimer’s disease (Chételat et al., 2003). It is believed that local structural and biochemical as well as distal changes result in the early retrosplenial and posterior cingulate hypometabolism. It is clear that the retrosplenic cortex, underlying cingulum, and hippocampal region all play important supportive roles in memory processes in the normally functioning brain as well as in dysfunction.

**Cingulum.** The broader cingulate area is involved in multiple functions as it spans much of the anterior-posterior length of the human brain. The cingulum carries the connections to and from areas of the cingulate cortex. As a result of its diverse functions and connections, it has fibers entering from and exiting to various areas of association cortices along its course (Schmahmann & Pandya, 2006). Thus, damage to the broader cingulate and underlying cingulum might indirectly as well as directly affect memory, especially if damage is in the posterior portion of the cingulate (Valenstein et al., 1987).

The cingulum is further important in this memory circuit because, as mentioned earlier, it serves as one of the primary afferent pathways into the entorhinal cortex and associated MTL structures. Papez (1937) reported that in a monkey brain, the posterior cingulum fibers are the prominent bundle that enters the hippocampus. While there are fibers that connect directly to the hippocampal formation via the cingulum, fibers connect to the pre-subiculum, subiculum, and, more importantly, to the entorhinal cortex; these fibers then enter the hippocampus via the perforant path. The entorhinal
and perirhinal cortices are immediately connected to the dentate gyrus of the hippocampus and thus serve as the primary input into the hippocampus. Thus, damage to the entorhinal cortex disconnects the hippocampus from limbic structures, such as the cingulate, as well as other association cortices (Salat et al., 2010).

**Cingulate changes in neurodegenerative disorders.** Choo and colleagues (2010) demonstrated posterior cingulate changes seen on diffusion MRI in MCI and AD patients. Karagulle Kendi et al. (2008) revealed decreased fractional anisotropy (FA) in the anterior cingulum of PD patients relative to controls. However, Gattellaro et al. (2009) found only altered mean diffusivity (MD) and not decreased FA in the cingulum of PD patients relative to controls. Thus, there is tentative evidence for altered integrity of the cingulum in PD patients. In addition to gross white matter changes there are changes to the gray matter of the cingulate.

**Cingulate cortex changes in PD.** There are clearly widespread neurobiological changes in PD patients even without dementia. However, research focused on structural brain changes in PD participants is sparse. There is evidence of gross cingulate change in participants with mild cognitive impairment; such impairment might be seen in Parkinson’s disease. Structural MRI studies of participants with amnestic MCI as well as those in the early stages of AD have shown reductions in both PCC and ACC volumes. Reduced cingulate volumes are useful in discriminating between MCI patients who do and do not go on to develop AD (Salmon & Laureys, 2009). While changes to the white matter can occur prior to gray matter changes, loss of white matter will cause changes to the connected gray matter and loss of gray matter will result in loss of connected white matter (Agosta et al., 2011). Thus, with loss of cortex, there
likely is also a concordant white matter loss, although the relationship is not necessarily direct or strong. It can then be assumed that with cingulate cortex atrophy, there will be a partial reduction in the integrity of the underlying cingulum bundle. Whether or not a similar pattern of atrophy and changes in non-demented idiopathic Parkinson’s disease patients can be seen is one of the goals of this present investigation. So far there appear to be neuroanatomic changes to the cingulate in PD but adding to this is evidence of neurochemical changes.

**Dopamine and the cingulate.** The cingulate cortex receives considerable dopaminergic input from the substantia nigra and ventral tegmentum. Reductions in dopamine (DA) in Parkinson’s disease directly and indirectly affect the functioning and structure of the cingulate; however, much of the DA input to the cingulate flows to the rostral cingulate premotor area, so the DA reductions might lead to DA-related motor symptoms more than DA-related cognitive symptoms (Vogt, Vogt, Purohit, & Hof, 2009). Dopamine depletion is only one of a number of neurobiological changes to the cingulate in Parkinson’s disease and other neurologic diseases. Like the hippocampus, the cingulate is also affected by Lewy bodies in idiopathic Parkinson’s disease, Alzheimer’s disease, Parkinson’s disease dementia (PDD), dementia with Lewy bodies, and even ‘normal’ aging (Mattila et al., 2000; Vogt et al., 2009). In fact, the cingulate gyrus seems to be particularly vulnerable to Lewy body aggregation, especially in patients who are progressing towards or have PDD or dementia with Lewy bodies (Braak et al., 2004). In PD patients, there is evidence that the number of Lewy bodies in the cingulate gyrus correlates with cognitive impairment as measured by criteria set by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) criteria (Mattila et al., 2000). One
caveat is that this relationship was based on a non-specific global scale of cognitive impairment and thus might have poor specificity for memory, although memory generally declines with global cognitive decline. Another caveat about applying those findings to the present study is that DA and Lewy body changes are not directly measurable with current structural MRI technology and thus might not result in gross structural changes. However, what is important about Mattila and colleagues’ (2000) findings is that they provide additional evidence for a link between cingulate changes and cognitive impairments.

**Acetylcholine in PD**

A group of neurons in the basal forebrain called the nucleus basalis of Meynert (nbM) contains an aggregation of cholinergic cells that project widely to the neocortex. The basal forebrain also projects directly to the hippocampus through the fornix (Selden et al., 1998). Because of this, acetylcholine is thought to be involved in memory processes. Additionally, patients with dementias, including Alzheimer’s disease and Lewy body dementia, are given acetylcholinesterase inhibitors, which have been shown to be modestly effective in temporarily reversing some of the memory deficits (Pepeu & Giovannini, 2010). Patients with Alzheimer’s disease show reduced activity of choline acetyltransferase (ChAT) throughout the brain, including the cortex, striatum, and hippocampus (Bartus et al., 1982; Zola-Morgan & Squire, 1993). In addition to Alzheimer’s disease patients, choline acetyltransferase activity is also reduced in patients with PD both without and with dementia (Mattila et al., 2001; Dubois et al., 1983; Whitehouse et al., 1988) and even in the absence of AD pathology (Perry et al., 1985). Parkinson’s disease patients without dementia had reductions in choline acetyltransferase in parietal and occipital cortices. Parkinson’s disease patients with
cognitive impairments had greater loss of ChAT activity throughout the cortex except occipital cortex compared to non-cognitively impaired PD patients. Parkinson’s disease patients with concurrent pathologically-confirmed Alzheimer’s disease had more ChAT loss only in the entorhinal cortex compared to cognitively impaired PD patients even though their degree of cognitive impairment was greater than cognitively impaired PD patients without AD. Demented (not AD) and non-demented PD patients also had reductions of acetylcholinesterase throughout the cortex with greater reductions seen in PD patients with dementia than those without dementia (Perry et al., 1985).

Using positron emission tomography (PET) and single photon emission computed tomography (SPECT), clinicians and researchers are able to study neurochemical changes in vivo. In non-demented idiopathic PD patients, there were reductions in the SPECT vesicular acetylcholine transporter (VAChT) ligand [I-123]-IBVM in the parietal and occipital cortices; however, in demented PD patients, there were greater and more widespread deficits. Additionally, acetylcholine esterase (AChE) activity and levels are significantly reduced in PD patients without dementia with further reductions in demented PD patients (Bohnen & Albin, 2010). Loss of cholinergic neurons in the basal forebrain as well as reduced ACh activity in the cortex can serve as markers for the severity of cognitive disturbances in PD.

With much of the production of ACh in the basal forebrain, neuronal degeneration of the basal forebrain will reduce ACh levels and affect related proteins. In Parkinson’s disease there is evidence of degeneration of the nucleus basalis of Meynert (particularly marked by an accumulation of α-synuclein in the basal forebrain) early in the disease process and even in the absence of dementia (Bohnen & Albin, 2010; Braak et al.,
Kalaitzakis and colleagues (2009) found high concentrations of αSyn pathology in the nucleus basalis of Meynert in both demented and non-demented PD participants. The authors believe these findings point to a universal cholinergic deficit in PD. Thus, it is possible that some cognitive deficits – especially memory dysfunction – in PD are associated more closely with basal forebrain degeneration (and concurrent depletion of acetylcholine) than with substantia nigra deterioration and dopamine deficits. The implication from this is that memory difficulties in PD appear to be at least partially ‘cortical’ rather than completely ‘subcortical’.

One area of the brain ACh deficits affect is the cingulate gyrus. The medial cholinergic pathway travels out from the nbM primarily through the cingulum with terminations throughout cerebral cortex, including the cingulate gyrus and retrosplenial cortex (Selden et al., 1998). Thus, degeneration of the nbM might lead to reductions in the integrity of the cingulum. Whether or not these changes can be visualized using imaging methods such as those produced from diffusion-weighted scans remains to be determined. Also, it is possible to disrupt the cholinergic pathways without damaging the basal forebrain directly (Selden et al., 1998); disruption of the cingulum, whether by lesion or loss of axonal integrity, could result in cholinergic denervation ‘downstream’ from the site of disruption. This basal forebrain-retrosplenial ACh pathway through the cingulum is also important in light of research demonstrating profound anterograde amnesia with damage to the retrosplenial cortex (Valenstein et al., 1987).
Figure 1-1. Schematic of the long-term memory system.
Figure 1-2. Rendering of the anatomy of the medial temporal lobe. The entorhinal cortex is not labeled in this image but is part of what is labeled 'Parahippocampal gyrus'.

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Figure 1-3. Schematic representation of the structure and connections of the medial temporal lobe.
Figure 1-4. Simplified schematic representation of the Papez circuit.
Figure 1-5. Fiber tracking image showing the ventroposterior cingulum connecting between the retrosplenial cortex and the entorhinal cortex. Image visualization using TrackVis (Wang, Benner, Sorensen, & Wedeen, 2007)
CHAPTER 2
AIMS, HYPOTHESES, AND METHODS

Study Rationale

It is not well understood what extent of verbal memory deficits in PD patients can be explained by damage to the medial temporal lobes, closely connected cortical regions, and associated white matter areas, such as the posterior cingulum. What is clear is that many PD patients experience verbal memory difficulties, even early in the disease process. There is also evidence that, for some PD patients, a portion of their memory difficulties is amnestic in nature (Filoteo et al., 1997) but the few studies assessing verbal memory heterogeneity in PD were heterogeneous in results with reports of 7% to 23% of non-demented individuals with PD experiencing amnestic memory deficits. The current study will help clarify the proportion with amnestic memory deficits in early PD.

Memory for verbal information is heavily dependent on the MTL, which experiences pathological changes early in the course of idiopathic PD. There are also other changes that occur in related brain areas, such as the cingulum; the posterior section of the cingulum carries the bulk of the connections between entorhinal and retrosplenial areas, both of which are involved in memory processes. The purpose of this study is thus to elucidate the relationship between verbal memory and the MTL and posterior cingulum in non-demented individuals with PD. This is not ignoring or minimizing the contributions of changes in subcortical structures, such as the basal ganglia that are heavily dependent on dopamine for functioning; rather, the purpose of this study is to investigate the relative contributions of the MTL and a related white matter pathway to the verbal memory performance of individuals with PD.
Specific Aims and Hypotheses

**Aim 1: Is there a Verbal Memory Deficit in PD?**

To examine verbal memory abilities using clinical tools (list learning, story memory) in non-demented individuals diagnosed with PD (n=40) relative to age and education matched non-PD peers (i.e., Controls, n=40).

**Sub-aim.** Semantic knowledge of the same individuals will also be assessed in order to serve as a dissociation with verbal memory.

**Hypothesis.** Due to potential disruption of the medial temporal lobe and associated fiber pathways in PD patients, it is hypothesized that individuals with PD will score lower than non-PD peers on a combined set of memory indices assessing savings, retention, and discrimination between true and false positives on recognition testing (i.e., learned information versus foils). This will be assessed with a multivariate analysis of variance (MANOVA). Follow-up univariate analyses will seek to confirm hypotheses that individuals with PD perform more poorly than controls on individual indices of savings, delayed recall, and recognition discriminability from the PrVLT as well as Story memory savings index (percent retained), delayed recall, and recognition discriminability scores. These relationships between group and verbal memory will be partially explained by processing speed but variance in scores between groups will not be fully explained by processing speed.

**Between group sub-aim.** Conversely, it is predicted that there will be no group difference in scores on the Boston Naming Test or Association Index (AI) – a scale derived from a test of semantic fluency – because the semantic knowledge system is thought to be largely intact in PD. This will serve as a dissociation with verbal memory because memory should be impaired but language should not be impaired.
Within group memory sub-aim. Although it is predicted that verbal memory performance will be worse in individuals with PD compared to non-PD peers, it is further predicted that there will be heterogeneity in verbal memory profiles for individuals with PD when using control data as normative values. Additionally, because of prominent and general executive and processing speed deficits in PD patients, for the PrVLT the delay memory and recognition discriminability indices will be more compromised relative to the savings index, which is less affected by executive and processing functions. However, processing speed deficits will not fully explain memory deficits.

As part of this analysis, I will seek to relate other cognitive measures with the components of list-learning and story memory indices. Measures of processing speed (the processing speed index) will have a positive relationship with PrVLT delayed recall and Story recall but a weaker relationship with PrVLT recognition discriminability or Story recognition. This relationship is expected because while processing speed is an important substrate of working memory (Dujardin et al., 2007) and thus encoding of information, the effects of processing speed are minimized on a recognition task. In other words, recognition is not as dependent on effortful retrieval as free recall is (Filoteo et al., 2009). It is also predicted that within the PD group, there will be an inverse relationship between disease severity and verbal memory performance.

Aim 2: Are there Differences in Verbal Memory Brain Structures for PD?

To investigate differences in verbal memory neuroanatomical structures (entorhinal cortex and entorhinal to retrosplenial connections) for individuals with PD and healthy non-PD peers. As a sub-aim, group differences in the integrity of semantic knowledge white matter pathways (specifically, part of the left superior longitudinal/arcuate fasciculus) will also be assessed.
Hypothesis. It is predicted that individuals with idiopathic non-demented PD (n=40) will have smaller entorhinal cortex volumes and decreased integrity of the connection between the entorhinal and retrosplenial cortices (which travels through the cingulum), relative to non-PD age and education-matched peers (n=40). This prediction is based on evidence of both hippocampal and entorhinal atrophy in non-demented individuals with PD (Laakso et al., 1996; Jokinen et al., 2009) as well as evidence of cingulate changes, particularly in the posterior region of the cingulate, in individuals with PD (Braak & Braak, 2000). Additionally, with entorhinal changes, verbal memory changes, reductions in acetylcholine, concentrations of Lewy bodies, and the number of connections between the entorhinal cortex and the retrosplenial cortex, it is expected that there will be connectivity changes between the retrosplenial and entorhinal cortices.

Between-group Sub-aim. Conversely, it is predicted that there will not be a difference in the integrity of the arcuate fasciculus (AF), specifically, connections between the left middle temporal gyrus (MTG) and ventrolateral frontal regions (i.e., pars opercularis). This area of the left frontal lobe has been implicated in producing spoken words and broader language functioning (Indefrey & Levelt, 2004). Object-related semantic knowledge is particularly dependent on the posterior temporal lobe (Damasio & Tranel, 1993). In older adults, when producing word sounds and words, the middle temporal gyrus seems to be more involved than in younger adults (Sörös et al., 2009), making connections to this region potentially important for understanding language. Language, of which semantic knowledge is a subset, is dependent upon a wide network of brain areas including the frontal, parietal, and temporal lobes, particularly in the left hemisphere (Broca, 1861; Wernicke, 1874; Catani, Jones, &
ffytche, 2005). Given that these regions are considered rather unaffected early in the disease process, it is not anticipated these regions would be differentially compromised in PD relative to non-PD age matched peers.

**Aim 3: Are there Specific Structural-Cognitive Patterns?**

To investigate the relative contribution of retrosplenial to entorhinal connectivity and the entorhinal cortex volume to verbal memory performance in PD and Control participants. Also to investigate the contribution of AF connectivity to semantic knowledge.

**Hypothesis.** It is predicted that there will be a positive correlation between left entorhinal cortex volume and recall and recognition performances on verbal memory measures across both groups. That is, regardless of group (PD, Control), participants with smaller left entorhinal cortices will have lower scores for both recall and recognition components of verbal memory tests. A similar pattern will exist for the relationship between left entorhinal to retrosplenial (ERC – RSC) connectivity and verbal memory. It is specifically predicted that lower integrity of the left ERC – RSC connections will relate with worse delayed recall and recognition verbal memory performance. Analyses will also be run assessing the associations of disease severity with brain and verbal measures. It is predicted that verbal memory measures will associate with disease severity.

**Sub-aim.** To investigate the relationships between arcuate fasciculus (AF) connectivity and measures of language across both groups. It is predicted that there will be a positive correlation between language (BNT and the AI scale from semantic fluency) and AF connectivity.
**Sub-aim.** To investigate the relationships between 1) ERC – RSC connectivity and semantic knowledge and 2) AF connectivity and verbal memory. It is predicted that there will not be a significant relationship between the cingulum (ERC – RSC) and semantic knowledge neither will there be a significant relationship between the arcuate fasciculus and verbal memory, providing evidence of dissociation between functions of the tracts.

**Within-group sub-aim.** For both PD and Control groups, the associations between brain structure and verbal memory will be calculated in order to assess the hypothesis that worse memory performance is related with smaller left entorhinal volumes and lower ERC – RSC connectivity. These relationships will additionally be controlled for disease severity; it is predicted that within each group, controlling for disease severity measures will not change the associations between brain structure and memory performance.

**Methods**

**Study Design**

This was a prospective use of structural MRI and neuropsychological assessment data from a recently ended NINDS funded investigation (NINDS: K23NS060660; Price).

**Participants**

Two age-matched participant groups were used to address Aims 1 and 2. The groups were combined in order to address Aim 3.

- Idiopathic Non-demented Parkinson’s Disease
- Age and education matched non-PD peers
The final participant pool included 80 participants (40 per group). Inclusion and exclusion criteria were based on the criteria for the NINDS funded study from which these data were acquired (see APPENDIX A).

**Recruitment.** The current study acquired participants recruited as part of a National Institute of Neurological Disorders and Stroke funded study that examined white matter in Parkinson’s disease (NINDS; Primary Investigator = Catherine Price, Ph.D.). Male and female PD participants over the age of 60 were recruited from the community through referrals from the University of Florida Center for Movement Disorders and Neurorestoration as well as through community flyers. Parkinson’s disease participants had consensus-confirmed diagnosis of Parkinson’s disease based on the United Kingdom PD Society Brain Research Center criteria (Gibb & Lees, 1988). All individuals with PD were non-demented and with Hoehn and Yahr scale range of 1-3 (Hoehn & Yahr, 1967). Individuals with other neurodegenerative disorders, significant medical disease that could limit lifespan, or major psychiatric disorders were excluded from participation. Included PD participants were thus representative of healthy community-dwelling older adults with Parkinson’s disease. Some members of the Control group were family of PD participants but most were recruited from flyers and direct mailings to the community. Control group participants had similar exclusionary criteria and closely matched PD participants other than not having symptoms of PD. While participants were recruited from the general community and recruitment was as inclusive as possible, the final participant pool did not include members of ethnic minority groups.
Neuropsychological Variables

To rule out dementia, participants were administered a comprehensive testing protocol covering major domains of cognition and memory: attention, processing speed, language, visuoperceptual abilities, intelligence, verbal and visual memory, and executive function.

Primary dependent measures for the present investigation include: the Philadelphia (repeatable) List Learning Test (PrVLT) and the Logical Memory (Story) test from the Wechsler Memory Scale 3rd Revision (WMS-III) are of primary interest. Secondary dependent measures for the present investigation include: Association Index from Animal Fluency and Boston Naming Test.

Philadelphia Repeatable Verbal Learning Test

Even though the Philadelphia (repeatable) Verbal Learning Test was previously briefly described, it will be described again for the methodology of this study. The PrVLT is a list learning and memory test designed for use with older research participants that has been shown to be sensitive to different patterns (e.g., cortical or subcortical) of verbal memory impairment (Price et al., 2009; Libon et al., 2010; Tanner et al., 2011). It has a similar design to the California Verbal Learning Test (CVLT) but with lists of either 9 or 12 words. One other notable difference from the CVLT is that the PrVLT includes words pulled specifically from a corpus of words produced by healthy older adults. There are 5 learning trials (list A), one interference trial of a novel list of 12 words (list B), short and long delay cued and free recall, and a recognition trial. The recognition trial includes all 12 words from list A, all 12 from list B, 12 unrelated foils, and 12 semantically related foils. The PrVLT allows for fine-tuned analyses of learning and
memory, especially for distinguishing between memory impairment profiles (Price et al., 2009).

PrVLT scores considered sensitive to MTL changes were created for targeted analysis for Aim 1. The following scores from the PrVLT were used as dependent variables in analyses: long delayed free recall, a savings index (Lamberty, Kennedy, & Flashman, 1995; Welsh et al., 1994), and recognition discriminability.

**Long delayed free recall.** The total number of words correctly and freely recalled (i.e., without cuing) after a 25 minute filled delay were recorded as the long delayed free recall score.

**Savings index.** The savings index is a measure of information retained from the immediate learning to the delayed time period. It was calculated as free delayed recall / learning trial 5 (Filoteo et al., 2009; see also for comparison, Lamberty et al., 1995). This savings score has been shown to be sensitive to early memory changes in dementia (Welsh et al., 1994).

**Recognition discriminability.** Recognition discriminability is the number of words correctly endorsed on recognition testing is corrected for the ‘noise’ of foils endorsed. This was calculated using d’ from signal detection theory.¹

**Story Memory**

Logical Memory from the WMS-III is a commonly used clinical and research story memory test. For this test a brief, paragraph passage of prose was read. The individual was then asked to recall as much of the story using the same words and in the same

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¹ Calculated in Excel using the formula NORMSINV(prob), where prob is P(h) or P(fa). This gives the area under the curve of the normal distribution: d’ = NORMSINV( P(h) ) - NORMSINV( P(fa) )
order as was presented, if possible. After this a different story was presented and the individual asked to recall the second story. Then this process was repeated for the second story (i.e., the second story was presented and recalled twice). After a 20-30 minute delay, the individual was asked to recall each of the two stories. Lastly, a recognition component was presented where a series of yes/no questions were asked about the two stories.

The story memory index scores of interest for use as dependent variables were delayed recall (total number of story elements freely recalled after a filled 25 minute delay), savings (retention percent – ratio of delayed recall to immediate [learning] recall), and the recognition score.

**Boston Naming Test**

The Boston Naming Test (BNT) is a 60 item test of receptive language (Kaplan, Goodglass, & Weintraub, 1983). Participants were shown simple line drawings of objects and asked to produce the names of the objects. The total items correctly named without cuing was the score of interest for analysis.

**Association Index**

Category (semantic) fluency tests are sensitive to cortical disruption, primarily of the temporal lobe (Rodriguez-Ferreiro et al., 2011). Using characteristics of words, it is possible to classify the cohesion between responses on semantic fluency tests. Animal fluency responses can be classified using various taxonomic and zoological categories: size, geographic location, habitat, zoological class, zoological orders and families, and diet (Carew et al., 1997). Using these categories, the shared attributes between successive words can be classified and scored as the sum of shared attributes across dyads of words for all responses, divided by the total number of responses minus one.
For example, if an individual gave 16 responses, starting with horse and cow, the association between that particular dyad would be 5 because those animals match on 5 of 6 categories: big, local, herbivore, mammal, and farm. Doing this for each successive dyad results in a total association score. For 16 responses, if the total of association scores was 58, the association index (AI) score would be $\frac{58}{16 - 1} = 3.87$.

It has been shown that individuals with ischemic vascular dementia have relative preservation of semantic networks compared to individuals with Alzheimer's disease, even though the number of generated words is similar to that by individuals with AD (Carew et al., 1997). This is interpreted to mean that even though those with subcortical dementias have reduced output, there is still an understanding of the subordinate connections between words (animals). This means that those with subcortical disorders are still able to cluster words semantically and thus any deficits are not likely due to semantic problems but rather to processing speed deficits or executive dysfunction. Even though non-demented individuals with PD should have considerable and growing temporal lobe PD pathology (Braak et al., 2004) that could potentially affect performance on the Association Index, due to their lack of general cognitive deficits, it is not likely that individuals in early stage PD would experience deficits in AI scores. The primary variable of interest for this analysis was total AI score.

**Imaging Protocols**

**Magnetic resonance imaging and Parkinson’s disease.** Magnetic resonance imaging (MRI) is a type of imaging that allows researchers and clinicians to acquire high resolution in vivo images of the human brain. Magnetic resonance imaging is based on the fact that various types of tissues or chemicals have different physical (cellular, molecular, and atomic) properties that react differently to manipulations within a strong
magnetic field. Basically, protons, when exposed to the strong magnetic field in an MRI machine, tend to align with the magnetic field. Using pulsed gradients of radio waves, the MRI machine shifts protons out of alignment, and in the process, measures changes in the radio frequency signal as the protons return to their aligned resting states. By varying signal gradients and measurements, different components of a brain, for example, can be visualized with some clarity. For the present study there were two types of MRI scans that were pertinent – T1 weighted structural scans and diffusion weighted structural scans.

**T1 imaging.** T1 MR images are commonly produced clinically and for research to provide clear images of the structure of the brain. At magnetic field strengths of 3 Tesla (3T), it is possible to obtain high resolution (1x1x1mm voxels) 3D images within a relatively brief period of time (5-10 minutes). T1 scans offer good contrast between gray and white matter and cerebrospinal fluid (CSF). In T1 scans, gray matter (cell bodies) appears darker than white matter (myelinated axons), and CSF appears even darker than gray matter. Using T1 scans, researchers can differentiate between various cortical and subcortical areas of the brain. Consequently, it is possible to obtain reliable estimates of the volumes of brain regions; these volume estimates allow for statistical analyses to be performed with and clinical judgments made about various brain structures.

**Diffusion weighted imaging.** Diffusion weighted MRI (DWI) measures the displacement of water molecules over time. In cell bodies and CSF, the displacement is relatively quick and isotropic but in the white matter of the brain, the displacement is more anisotropic, that is, it tends to move in a restricted, directional manner rather than
equally in all directions. Because water molecule displacement is directional in white matter, diffusion weighted imaging is particularly useful for investigating the structure and integrity of the white matter. DWI thus can be considered as providing a measure of the microstructural integrity of brain cells (Le Bihan, 1995) and is useful for investigating altered white matter microstructure (Rosas et al., 2010). Investigations of microstructural alterations can be done between groups or within groups of individuals. For example, researchers found changes in the white matter of the corpus callosum in Huntington’s disease (Rosas et al., 2010), altered diffusivity in the frontal lobes of Parkinson’s patients (Karagulle Kendi et al., 2008), and changes in the white matter near the substantia nigra in Parkinson’s patients (Yoshikawa et al., 2004). Diffusion weighted imaging thus is a tool that can be used to see disruption of circuits in the brain.

In order to perform these analyses, MRI requires time spent with automated and manual processing of the images.

Image Processing

Figure 2-1 provides an overview of the workflow that was utilized for the fiber tracking analysis of the diffusion weighted images. The major components of the pipeline will be briefly described.

Data acquisition. Data were acquired with a Siemens 3T Verio scanner. Single-shot EPI diffusion weighted images were acquired with diffusion gradients applied along 6 directions \((b = 100 \text{ s/mm2})\) and 64 directions \((b = 1000 \text{ s/mm2})\). These diffusion scans were then combined and motion corrected in order to increase the signal to noise ratio. Imaging parameters were 73 contiguous axial slices with a slice thickness of 2mm, and \(TR/TE = 17300/81\text{ms}\). Two T1-weighted sequences were acquired with the following parameters: 176 contiguous slices, \(1\text{mm}^3\) voxels, \(TR/TE = 2500/3.77\text{ms}\). Multiple T1-
weighted volumetric sequences were acquired in order to average the T1 scans to optimize the signal-to-noise ratio by reducing the effects of motion as well as by increasing gray-white contrast.

**Diffusion image processing.** Diffusion weighted MRI data from all participants were processed using in-house software based on an advanced fiber tracking analysis called mixture of Wishart (MOW) that allows for the visualization and quantification of white matter. This method is an improvement over diffusion tensor analysis (DTI) by enhancing the parameterization of complex fibers within voxels (Jian et al., 2007). See Figure 2-2 for examples of the modeling improvements of MOW over DTI for fiber tracking.

In less complex areas without 'kissing' or 'crossing' fibers, such as medial portions of the corpus callosum or core regions of the cingulum, the difference between DTI and MOW might be marginal; however, given that the MOW modeling includes DTI as a subset, there is no detriment to using MOW instead of DTI. See Figure 2-3 for examples of glyphs from the cingulum. This area was chosen for visual comparison between DTI and MOW methods because it is highly directional and thus, relatively simple structurally. Other areas of the cingulum are more complex but this area was chosen to provide contrast with the frontal area in Figure 2-2.

**Diffusion variables of interest.** A measure of connectivity strength was used to quantify the cingulum between the entorhinal cortex and retrosplenial cortex. This connection between regions of interest (nodes) was quantified in the following manner. Any two nodes \((N_{a,b})\) are connected with an edge \((E_{a,b})\) if there is at least one fiber \((f)\) that starts and stops in the two nodes \((N_{a,b})\). Each edge \((E)\) has both a length \((l_{E})\) and
weight ($w_E$). Weight ($w_E$) was defined as: $w_E = \sum_{f \in F_E} \frac{1}{l_f}$. This mathematical model corrected for the bias that the lengths of fibers have on the weight $w_E$ (Hagmann et al., 2007). Next $w_E$ was corrected for voxel volume ($V$) and fiber seed density (SD):

$$w_E \times \frac{V}{SD}.$$ In the present study, $V = 8$ and $SD = 64$. Then, to account for differences in ROI surface areas, the corrected edge weight ($w_{Ec}$) was multiplied by two and divided by the sums of the surface areas $SA_{a,b}$: $EW_C = \frac{2 \times w_{Ec}}{SA_a + SA_b}$. In order to control for potential connectivity differences caused by differences in head size (see Yan et al., 2011), $EW_C$ was then divided by intracranial volume (ICV) in mm$^3$, giving a final $EW_C / ICV$ variable of interest. Some variables were scaled linearly in order to increase apparent value for ease of interpretation.

**Entorhinal volumetrics.** Structural T1 scans were processed using FreeSurfer, which is a set of MRI analysis tools. These tools allow for automated processing of T1 MRI data (Segonne et al., 2004; Fischl et al., 2002), ideally with little initial input from the user; however, quality checking was performed in order to assess reliability of results. From the FreeSurfer processing, an averaged brain (across both acquired T1 images) with enhanced gray-white contrast and increased signal-to-noise was aligned to the MNI152 template brain (Fonov et al., 2011; Mazziotta et al., 2001) using a linear, non-destructive registration technique with 6 degrees of freedom (FLIRT; Jenkinson et al., 2002; Jenkinson et al., 2001; Greve et al., 2009). This was done in order to correct for head tilt and to align participants’ brains along the anterior commissure – posterior commissure axis. Entorhinal cortices were then manually traced by an expert rater.
according to published methods of identifying the entorhinal cortex on MR scans (refer to Insausti et al., 1998 for an in-depth presentation of this process).

Briefly, starting 2mm posterior to the appearance of the temporal stem, the lateral wall of the parahippocampal gyrus was traced between the sulcus semiannularis and the collateral sulcus, descending into the collateral sulcus at varying depths depending on the overall depth of the collateral sulcus. This method closely matches the cytoarchitecture of the entorhinal cortex and allows for localization on T1 MRI (Insausti et al., 1998).

This method is reliable (intra-rater DSC > 0.8; inter-rater reliability DSC > 0.8) and has been shown to relate with verbal memory performance in older adults (Price et al., 2010).

**Retrosplenial region of interest.** Structural T1 scans were processed through the FreeSurfer pipeline. From the cortical parcellation (labeling of different areas of the cortex based on template atlases while accounting for individual sulcal and gyral variability), the isthmus of the cingulate was exported, inflated by 1mm in 3 dimensions, and imported into ITK-SNAP for manual cleaning (e.g., to remove overlap with corpus callosum) to localize the ROI to the perisplenial region (retropsplenial cortex plus underlying white matter in order to improve tracking results).

**Final imaging variables of interest.** Entorhinal cortex - the volumes of the left entorhinal cortices (as calculated above) were entered into statistical analyses. These volumes were adjusted for intracranial volume. Entorhinal cortex to retrosplenial cortex connectivity strengths (ERC – RSC EW_c; as calculated above) was entered into statistical analyses. These values (EW_c) were also corrected for intracranial volume as
described above. This value is hereafter abbreviated to ‘ERC – RSC EWc’. Connectivity between the left MTG and frontal regions (AF EWc) was also entered into the analyses.

Statistical Analyses

Data that were not normally distributed were normalized using the Box-Cox procedure (Osborne, 2010), which allows for more robust normalization of value distributions than more traditional normalization methods; these traditional methods (e.g., square root, log, square root) are variations of power transformations. The Box-Cox procedure normalizes by allowing for an optimal transformation to be chosen from a range of power transformations. The Box-Cox procedure incorporates other traditional power transformations but is more robust than any of them individually.

Analyses were Bonferroni corrected where appropriate to control for multiple comparisons.

Aim 1. Index scores from the PrVLT and Story memory were used in a between-group (PD and Control) MANOVA model to assess if PD participants overall across all included index scores have lower verbal memory scores than Control participants. Additionally, the Processing Speed Index (PSI) was used as a covariate in a one-way MANCOVA analysis in order to control for the effects of speed of processing on memory. All multivariate analyses were followed up by univariate analyses in order to assess individual index score group differences.

Sub-aim. The total score on the Boston Naming Test and the Association Index (AI) from animal fluency were used in a between-group one-way MANOVA model to assess if PD and Control participants had similar semantic abilities.

Within PD group analysis. Scores on the PrVLT and Story memory indices were compared with the score on the recognition discriminability index in order to investigate
the heterogeneity of levels impairment. Z scores established using data from Controls were used to create frequency counts of impairment in each verbal memory index score (scores above $z = -1.0$ were classified as ‘Not Impaired’; scores between $z < -1.0$ and $>-1.5$ were classified as ‘Mild Impairment’, scores between $z < -1.5$ and $>-2.0$ were classified as ‘Moderate Impairment’, and scores below $z = -2.0$ were classified as ‘Severe Impairment’). Given how closely matched the PD and Control groups were, this classification system was an appropriate compromise between minimizing Type I and Type II errors.

Further, to assess the level of and variability in overall memory impairment for each PD participant, a cumulative sum of ‘z score impairment’ was used to assess individual memory performance variability. Z scores < 0 were added together to create this summed impairment for each individual.

Additionally, for the PD and Control groups separately the PrVLT scores were correlated with cognitive measures of processing speed (Processing Speed Index) to assess the role processing speed plays within groups.

**Aim 2.** Left entorhinal cortex volumes were quantified, as was ERC – RSC $E_{WC}$. These values were used as the variables of interest. All volumetric analyses were then controlled for total intracranial volume to reduce structure volume variability that results from head size differences. These quantifications of the entorhinal cortices and ERC – RSC $E_{WC}$ were then entered into Student’s t-test analyses to determine group differences between PD and Control participants.

**Within group correlations.** Bivariate correlations between measures of disease severity (total l-Dopa intake and UPDRS total score) and neuroanatomical variables
were run in order to assess the relationship between disease severity and neuroanatomy.

**Sub-aim.** Arcuate fasciculus EW<sub>c</sub> was entered into an independent samples Mann-Whitney U Test to assess the hypothesis that there are no group differences in the structural integrity of this white matter pathway.

**Aim 3.** Using bivariate correlations relationships between verbal memory performance on the index scores from Aim 1 and neuroanatomical variables (left entorhinal to retrosplenial cortex connectivity and left entorhinal volume variables) were calculated. This allowed for the investigation of the relationships of specific neuroanatomical regions with list learning and story memory.

In order to simplify comparisons, a verbal memory composite score was calculated to assess the relationships between overall memory performance and brain structure. Additionally, bivariate correlations were calculated between verbal memory index scores and disease severity as well as neuroanatomy and disease severity. Further, within group comparisons were run in order to assess relationships between neuroanatomy and verbal memory with and without controlling for disease severity.

To assess dissociations in the relationships between neuroanatomy and cognition, bivariate correlations were also calculated between left AF EW<sub>c</sub>, the left ERC – RSC EW<sub>c</sub>, left ERC volume, measures of language (BNT and the AI scale from semantic fluency), and verbal memory index scores.
Figure 2-1. Schematic showing the image processing pipeline from scanner to fiber tracking and volumetric output. A full-size image is attached in Appendix B.
Figure 2-2. Series of images demonstrating the modeling of diffusion within a single voxel. A) color fractional anisotropy image with crosshairs centered on a voxel in the frontal forceps, which is an area with many crossing axonal fibers, B) DTI glyph showing a single voxel with complex (crossing) fibers, in this instance an area close to the frontal forceps in the white matter of the frontal lobe, C) MOW glyph showing the same voxel as in B. Note the ability to resolve the complexity of the fibers better than DTI.
Figure 2-3. Series of images demonstrating the modeling of diffusion within a single voxel. A) color fractional anisotropy image with crosshairs centered on a voxel in the cingulum, which is an area with few crossing axonal fibers, B) DTI glyph showing a single voxel with relatively simple (directional) fibers, in this instance an area in the core of the cingulum, C) MOW glyph showing the same voxel as in B. The differences between MOW and DTI in this instance are likely marginal.
CHAPTER 3
RESULTS

Participant Characteristics

A set of 40 PD participants and 40 Controls matched on demographic variables, intelligence estimates, and general cognition (all $p > 0.05$; see Table 3-1). Groups differed significantly on measures assessing PD symptom severity, disease duration, and processing speed (see Table 3-1).

Aim 1: Is there a Verbal Memory Deficit in PD?

Multivariate Analyses: Group by Verbal Memory

As hypothesized, PD participants obtained significantly lower scores than Control participants when combining the six index scores in a one-way MANOVA (see Table 3-2). The multivariate analysis revealed a significant effect for group (Wilks' lambda $F = 3.83$, $p < 0.01$, partial eta squared $= 0.24$; power to detect the effect was 0.95).

When covarying for processing speed (PSI), there was no longer a significant multivariate group difference across all six verbal memory index scores (MANCOVA; Wilk’s lambda $F = 1.84$, $p = 0.10$).

Sub-aim: Language Group Differences

As hypothesized, the one-way MANOVA with language measures was not significant (Wilks' lambda $F = 0.91$, $p = 0.50$; partial eta squared 0.02; see Table 3-3). Neither individual measure significantly differed between groups.

PD Verbal Memory Performance by Index

Univariate analyses showed that PrVLT recognition discriminability and Story recognition discriminability scores had the strongest between group effect sizes.
Savings scores from both the PrVLT and the Story memory task did not differ between groups.

**PrVLT long delay free recall.** See Figure 3-1. PD < Controls. Parkinson’s disease participants recalled an average of 8.13 words; Control participants recalled an average of 9.65 words (F = 9.69, p < 0.01, eta² = 0.11). In a follow-up analysis, when controlling for PSI, PD < Controls (F = 4.09, p < 0.05).

**PrVLT savings.** Parkinson’s disease participants were not significantly reduced compared to Controls. Parkinson’s disease mean = 84.18%; Control mean = 88.67% (F = 1.66, p = 0.20, eta² = 0.02). In a follow-up analysis, there was not a significant group difference when controlling for PSI (F = 1.33, p = 0.25).

**PrVLT recognition discriminability.** See Figure 3-1. PD < Controls. PD mean = 3.01; Control mean = 3.49. F = 12.58, p < 0.01, eta² = 0.14. Follow-up analyses revealed that PD participants endorsed more false negatives (PrVLT recognition hits; PD mean = 11.13, Control mean = 11.48, p = 0.05) and false positives (PrVLT recognition errors; PD mean = 2.78, Control mean = 1.69, Mann-Whitney U p < 0.01) than Controls. In a follow-up analysis, there was a significant group difference (PD < Controls) when controlling for PSI (F = 9.55, p < 0.01).

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1 A follow-up analysis of intrusions on delayed recall revealed that PD did not differ from Controls in the number of long delay free recall intrusions produced but PD > Controls in the number of long delay cued recall intrusions. **Long delay free recall intrusions:** PD free recall intrusions (mean = 1.08) > Control free recall intrusions (mean = 0.63); Mann-Whitney U p = 0.08. **Long delay cued recall intrusions:** PD recall intrusions (mean = 3.00) > control participants (mean = 1.83); (Mann-Whitney U p = 0.03).

2 A sub-analysis of the false positive errors on recognition testing revealed that the group differences were driven by semantically-related novel distracter words (PD mean = 1.90, Control mean = 0.88; Mann-Whitney U p < 0.01) but not distracter words from the interference trial (List B; PD mean = 0.30, Control mean = 0.18, Mann-Whitney U p = 0.67) or unrelated novel distracters (PD mean = 0.08, Control mean = 0.05, Mann-Whitney U p = 0.55).
**Story delayed recall.** PD < Controls. Parkinson’s disease participants recalled an average of 24.80 story elements; Control participants recalled an average of 28.60 story elements (F = 6.22, p = 0.02, eta² = 0.07). See Figure 3-1. In a follow-up analysis, after controlling for PSI, there were no group differences in Story delayed recall (F = 2.90, p = 0.09).

**Story savings.** Parkinson’s disease participants’ scores were not significantly reduced compared to Controls. PD = 81.72%, Controls = 87.90% (F = 3.46, p = 0.07, eta² = 0.04). In a follow-up analysis, there was not a significant group difference when controlling for PSI (F = 1.48, p = 0.23).

**Story recognition discriminability.** See Figure 3-1. PD < Controls. PD mean = 84.08, Control = 90.74 (F = 11.92, p < 0.01, eta² = 0.14). In a follow-up analysis, after controlling for PSI, there were no group differences in story recognition discriminability (F = 3.59, p = 0.06).

**Within Group Heterogeneity of Memory Impairment**

Within the PD group there was variability in memory performance. Using scores from the matched Controls, norms were created for the PD participants. Four levels of impairment were created based on z scores: Not Impaired (z score > -1.0); Mild Impairment (z score > -1.5 & < -1.0); Moderate Impairment (z score > -2.0 & < -1.5); and Severe Impairment (z score < -2.0). Using these classifications for the six verbal memory index scores, as many as 66% of PD participants exhibited impairment (see Table 3-4 and Figure 3-2).

PD participants demonstrated greater compromise of recognition discriminability scores for both verbal memory measures than for both delayed recall and savings.
Verbal memory associations with processing speed and disease severity.

The Processing Speed Index had a positive relationship with PrVLT LDFR ($r = 0.33$, $p < 0.05$) but did not relate with any other verbal memory index score (all $r$ values $< 0.15$, all $p$ values $> 0.35$). Within the PD group, there are no correlations between disease severity (UPDRS total score), levodopa intake (LED: levodopa equivalence dosage), and verbal memory index scores (all $p$ values $> 0.06$).

Individual verbal memory variability. When cumulative z impairment scores (any z score $< 0$) were summed for PD participants, individual heterogeneity in verbal memory performance was seen (see Figures 3-3, 3-4, and 3-5).

Of 39 PD participants (one PD individual was excluded for missing PrVLT data): 14/39 (35.90%) averaged at least 1 z score below the Control mean across 3 PrVLT index scores; 5/39 (12.82%) averaged at least 2 z scores below the mean compared to Controls across 3 index scores; and 7/39 (17.95%) individuals scored at or above the mean for all 3 index scores of the PrVLT compared to Controls (see Figure 3-3).

For Story memory, 17/40 (42.5%) PD participants averaged at least 1 z score below the Control means across the 3 index scores while 5/40 (12.5%) averaged at least 2 standard deviations below the Control means. 6/40 (15%) PD participants scored at or above the mean of Controls across all 3 story index scores (see Figure 3-4).

When combining both verbal memory measures and all 6 index scores: 18/39 (46.15%) individuals averaged at least 1 standard deviation below the mean of Control participants; 2/39 (5.13%) averaged 2 standard deviations below the mean; and 2/39
(5.13%) individuals performed at or above the mean for all 6 index scores (3 PrVLT, 3 Story) compared to Controls (see Figure 3-5).

**Aim 2: Is there a Difference in Verbal Memory Brain Structures for PD?**

**Medial Temporal Lobe Structure Group Differences**

The manual segmentation method used to acquire entorhinal volumes is reliable (intra-rater DSC > 0.8; inter-rater reliability DSC > 0.8). Left entorhinal volumes were normally distributed. Left ERC – RSC EWs were not normally distributed, thus Box-Cox normalization was run to fit the data to a Gaussian distribution. See Figure 3-6 for representative images of entorhinal volumetric and ERC – RSC tracking results.

As hypothesized, using an independent samples t-test analysis, PD participants showed reduced left entorhinal volumes when corrected for TICV compared to Control participants (t = 2.71, p < 0.01; see Table 3-5 and Figure 3-7). Left entorhinal volumes were 11% smaller in PD participants than in Controls (Cohen’s d = 3.82, observed power = 0.93). Contrary to what was predicted, however, PD participants did not significantly differ from Controls in entorhinal to retrosplenial edge connectivity (t = 0.88, p = 0.38; Cohen’s d = 0.21; see Table 3-5 and Figure 3-7). An independent samples Mann-Whitney U test was also performed on the original, uncorrected left ERC-RSC EW data; as with the t-test, there were no significant differences in the distribution of the EW values between groups (p = 0.24).

**Within Group Correlations With Disease Severity**

Within the Control group, there were no significant relationships between l-Dopa intake\(^3\), PD symptom severity, and neuroanatomical variables (all p values > 0.12).

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\(^3\) One Control participant was on a dopamine agonist medication for restless leg syndrome.
Within the PD group, there were no significant relationships between L-Dopa intake, PD symptom severity, and neuroanatomical variables (all p values > 0.51).

Sub-aim: Language Track Group Differences

Non-normality resulted in an independent samples Mann-Whitney U Test being performed with the data. As hypothesized, there were no group differences in the distributions of edge weight of the white matter of the arcuate fasciculus (AF) connecting the middle temporal gyrus with the pars opercularis (Mann-Whitney U p = 0.47; refer to Table 3-6 for group means; see Figure 3-9 for an example of the AF fiber tracking output). See Figure 3-8 for a scatterplot of AF Edge Weight values by group.

Aim 3: Are there Specific Structural-Cognitive Patterns?

Brain Variables and Verbal Memory Performances Regardless of Group Type

As expected, there were relationships between neuroanatomical regions of interest and verbal memory. For all individuals (PrVLT: n = 79; Story: n = 80), one-way bivariate correlations yielded positive associations between ERC variables and verbal memory index scores (see Table 3-7, Figure 3-10, and Figure 3-11), but the strength of the associations varied by test index. The strongest associations were identified for PrVLT recognition discriminability, story recognition discriminability, and story savings. While the left ERC volume had a positive association with Story recognition discriminability and Story savings, contrary to what was predicted it did not relate to PrVLT index scores or Story delayed recall. While the left ERC-RSC EW was positively associated with PrVLT recognition discriminability, it did not relate with other verbal ________________

4 Supplemental within-group analyses were performed to assess if there was a relationship between PD side of onset and brain structure. Results are shown in Appendix C.
memory index scores. Additionally, a positive relationship was found between the edge weight of the left AF between the pars opercularis and the middle temporal gyrus and PrVLT savings scores (see Table 3-7).

**Brain Variables and Semantic Performances Regardless of Group Type**

Table 3-7 displays correlations between semantic measures and brain variables. The left arcuate fasciculus did not relate with either semantic measure. The left ERC and the left ERC-RSC EW also did not relate with either semantic measure.

**Verbal Memory Composite and Structure Relationships**

A composite score was calculated to pool verbal memory test variance and control effects of multiple comparisons. Using the composite of the six verbal memory scores, a mild but significant association was found between left ERC volume, corrected for ICV, and verbal memory across all subjects ($r = 0.22$, $p < 0.05$; see Figure 3-12). There were no significant associations between the verbal memory composite and left ERC – RSC EW or left AF EW ($p$ values > 0.39).

**Associations with Disease Severity**

**Disease severity and verbal memory.** When combining all participants, there are significant negative associations between UPDRS total score and verbal memory index scores. Total levodopa dose did not relate with verbal memory except for Story recognition discriminability (see Table 3-8).

**Disease severity and neuroanatomy.** When combining PD and Control participants there were no relationships between L-Dopa intake, UPDRS score, and neuroanatomical variables except for a mild negative association between UPDRS total score and left entorhinal volume ($r = -0.30$, $p < 0.01$; all other $p$ values > 0.09).
Within Group Comparisons

**PD.** Within the PD group there were significant correlations between verbal memory performance and brain structure: Story savings and left ERC volume ($r = 0.29$, $p = 0.04$); PrVLT recognition discriminability and left ERC – RSC EW ($r = 0.33$, $p = 0.02$). All other relationships are non-significant. There was a trend for a relationship between left AF and PrVLT savings ($r = 0.24$, $p = 0.07$).

**Controlling for disease severity.** When removing the effects of total UPDRS score, significant correlations were found between left ERC volume and Story savings ($r = 0.28$, $p < 0.05$) and left ERC – RSC EW and PrVLT recognition discriminability ($r = 0.32$, $p = 0.02$).

When removing the effects of levodopa intake, significant correlations were found between left ERC – RSC EW and PrVLT long delay free recall ($r = 0.29$, $p = 0.04$) and left ERC – RSC EW and PrVLT recognition discrimination ($r = 0.42$, $p < 0.01$). There was a significant correlation between left AF EW and PrVLT savings ($r = 0.29$, $p = 0.04$). There was also a trend for left ERC volume and Story savings ($r = 0.27$, $p = 0.06$).

After for covarying for processing speed, significant correlations were found between left ERC – RSC EW and PrVLT recognition discriminability ($r = 0.33$, $p = 0.02$) as well as left ERC volume and Story savings ($r = 0.23$, $p = 0.04$).

**Controls.** Within the Control group there also were significant correlations between brain structure and verbal memory performance: Story savings and left ERC volume ($r = 0.41$, $p < 0.01$).

**Controlling for disease severity.** When controlling for the effects of processing speed, the relationship between Story savings and left ERC volume remained ($r = 0.41$, $p < 0.01$).
Dissociation Between PrVLT Performance, Left ERC-RSC EW, and Left AF EW

Left ERC – RSC EW_C was moderately and positively associated with PrVLT recognition discriminability (Spearman’s rho = 0.29, p = 0.01). No relationship was identified for the left AF EW_C to the PrVLT recognition discriminability score (Spearman’s rho = 0.03, p = 0.82). However, conversely, left AF EW_C correlated with Story savings but left ERC – RSC EW_C did not; this dissociation was not predicted.
<table>
<thead>
<tr>
<th>Measure</th>
<th>PD (n=40)</th>
<th>Control (n=40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.85 (5.47)</td>
<td>67.95 (4.65)</td>
<td>0.93</td>
</tr>
<tr>
<td>Education</td>
<td>16.23 (2.94)</td>
<td>16.55 (2.49)</td>
<td>0.60</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.93 (1.25)</td>
<td>29.25 (0.93)</td>
<td>0.19</td>
</tr>
<tr>
<td>DRS-2 Total</td>
<td>139.45 (3.22)</td>
<td>140.23 (2.54)</td>
<td>0.24</td>
</tr>
<tr>
<td>WTAR</td>
<td>107.55 (7.47)</td>
<td>108.80 (8.76)</td>
<td>0.49</td>
</tr>
<tr>
<td>UPDRS Total</td>
<td>30.78 (15.86)</td>
<td>3.63 (3.67)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>7.58 (5.09)</td>
<td>N.A.</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>L-Dopa Equiv. Score</td>
<td>694.34 (364.88)</td>
<td>1.00 (6.33)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Processing Speed Index</td>
<td>99.44 (10.50)</td>
<td>112.45 (11.14)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination; DRS-2 = Dementia Rating Scale – 2nd Version; WTAR = Wechsler Test of Adult Reading; UPDRS Total = United Parkinson’s Disease Rating Scale Total score; L-Dopa Equiv. Score = Levodopa Equivalent Score = Total Daily levodopa dosage intake in milligrams. One control was on levodopa for restless leg syndrome. Processing Speed Index = Composite index score from the Wechsler Adult Scale of Intelligence – III.
Table 3-2. Verbal memory MANOVA group contrast

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD (n=39)</th>
<th>Control (n=40)</th>
<th>P Value</th>
<th>Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrVLT LDFR</td>
<td>8.13 (0.35)</td>
<td>9.65 (0.34)</td>
<td>0.003</td>
<td>0.11**</td>
</tr>
<tr>
<td>PrVLT Savings</td>
<td>84.18 (2.49)</td>
<td>88.67 (2.45)</td>
<td>0.202</td>
<td>0.02*</td>
</tr>
<tr>
<td>PrVLT R. Discr.</td>
<td>3.01 (0.10)</td>
<td>3.49 (0.09)</td>
<td>0.001</td>
<td>0.14***</td>
</tr>
<tr>
<td>Story Delay Free</td>
<td>24.80 (1.09)</td>
<td>28.60 (1.07)</td>
<td>0.015</td>
<td>0.07**</td>
</tr>
<tr>
<td>Story Savings</td>
<td>81.72 (2.37)</td>
<td>87.90 (2.34)</td>
<td>0.067</td>
<td>0.04*</td>
</tr>
<tr>
<td>Story R. Discr.</td>
<td>84.08 (1.37)</td>
<td>90.74 (1.35)</td>
<td>0.001</td>
<td>0.14***</td>
</tr>
</tbody>
</table>

* Small effect size, ** Medium effect size, ***Large effect size. LDFR = long delay free recall; R. Discr. = recognition discriminability. Note: one PD participant was excluded because of missing PrVLT data as a result of administration error. An additional analysis was conducted assessing side of onset of PD symptoms and relationships with verbal memory; all relationships were non-significant (p > 0.05).
Table 3-3. Semantic knowledge MANOVA group contrast

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD (n=40)</th>
<th>Control (n=40)</th>
<th>P Value</th>
<th>Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>56.78 (3.32)</td>
<td>57.58 (2.19)</td>
<td>0.282</td>
<td>0.01**</td>
</tr>
<tr>
<td>AI Total</td>
<td>3.30 (0.48)</td>
<td>3.24 (0.53)</td>
<td>0.583</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

* Small effect size; ** Small effect size. Note: BNT = Boston Naming Test; AI = Association Index (Carew et al., 1997), which assesses consistency of semantic features for word exemplars. BNT and AI scores were normalized using the Box-Cox procedure (Osborne, 2010) due to significant skew and kurtosis. Mean raw scores are presented in the table for ease of interpretation.
<table>
<thead>
<tr>
<th>Measure</th>
<th>N.I.</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrVLT LDFR</td>
<td>61.53%</td>
<td>15.38%</td>
<td>12.82%</td>
<td>10.26%</td>
</tr>
<tr>
<td>PrVLT Savings</td>
<td>71.79%</td>
<td>7.69%</td>
<td>15.38%</td>
<td>5.13%</td>
</tr>
<tr>
<td>PrVLT R. Discr.</td>
<td>43.59%</td>
<td>25.64%</td>
<td>7.69%</td>
<td>23.08%</td>
</tr>
<tr>
<td>Story Delay Free</td>
<td>60.00%</td>
<td>2.50%</td>
<td>20.00%</td>
<td>17.50%</td>
</tr>
<tr>
<td>Story Savings</td>
<td>72.50%</td>
<td>7.50%</td>
<td>12.50%</td>
<td>7.50%</td>
</tr>
<tr>
<td>Story R. Discr.</td>
<td>57.50%</td>
<td>7.50%</td>
<td>12.50%</td>
<td>22.50%</td>
</tr>
</tbody>
</table>

Note: LDFR = long delay free recall; R. Discr. = recognition discriminability. N.I. = Not impaired: z score > -1.0; Mild = z score > -1.5 & < -1.0; Moderate = z score > -2.0 & < -1.5; Severe = z score < -2.0.
Table 3-5. Medial temporal lobe structures group contrast

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD (n=40)</th>
<th>Control (n=40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L ERC/ICV</td>
<td>7.04 (0.22)</td>
<td>7.88 (0.22)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>L E-R/ICV EW</td>
<td>4.7 x 10^{-3} (2.8 x 10^{-3})</td>
<td>5.3 x 10^{-3} (2.9 x 10^{-3})</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Note: ERC/ICV = Entorhinal cortex volume corrected for intracranial volume X 10000; E-R/ICV EW = Entorhinal cortex to retrosplenial cortex edge weight normalized and adjusted for intracranial volume (values also normalized using Box-Cox procedure).
Table 3-6. Left arcuate fasciculus group contrast

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD (n=40)</th>
<th>Control (n=40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left AF/ICV EW</td>
<td>9.00 (9.12)</td>
<td>10.56 (9.14)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Note: AF/ICV EW = Arcuate Fasciculus edge weight normalized and adjusted for intracranial volume.
Table 3-7. Brain – verbal memory and language bivariate correlations

<table>
<thead>
<tr>
<th>Measure</th>
<th>Left ERC/ICV</th>
<th>Left E-R/ICV EW</th>
<th>Left AF/ICV EW</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrVLT LDFR</td>
<td>0.12</td>
<td>0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>PrVLT Savings</td>
<td>0.08</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>PrVLT R. Discr.</td>
<td>0.15</td>
<td>0.24*</td>
<td>0.13</td>
</tr>
<tr>
<td>Story Delay Free</td>
<td>0.06</td>
<td>0.08</td>
<td>-0.03</td>
</tr>
<tr>
<td>Story Savings</td>
<td>0.39**</td>
<td>0.05</td>
<td>-0.01</td>
</tr>
<tr>
<td>Story R. Discr.</td>
<td>0.22*</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>BNT</td>
<td>0.09</td>
<td>0.05</td>
<td>-0.07</td>
</tr>
<tr>
<td>AI</td>
<td>-0.05</td>
<td>-0.05</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Note: *p<0.05, **p<0.01; ERC/ICV = Entorhinal cortex volume corrected for intracranial volume X 10000; E-R/ICV EW = Entorhinal cortex to retrosplenial cortex edge weight normalized and adjusted for intracranial volume; AF/ICV EW = arcuate fasciculus edge weight normalized and adjusted for intracranial volume; LDFR = long delay free recall; Recog. Discr. = Recognition discriminability. BNT = Boston Naming Test; AI = Association Index from semantic fluency. Note: Running two-way bivariate correlations did not change the significance of the results.
<table>
<thead>
<tr>
<th>Measure</th>
<th>UPDRS Total</th>
<th>L.E.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrVLT LDFR</td>
<td>-0.30**</td>
<td>-0.22</td>
</tr>
<tr>
<td>PrVLT Savings</td>
<td>-0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>PrVLT R. Discr.</td>
<td>-0.39**</td>
<td>-0.22</td>
</tr>
<tr>
<td>Story Delay Free</td>
<td>-0.31**</td>
<td>-0.17</td>
</tr>
<tr>
<td>Story Savings</td>
<td>-0.27*</td>
<td>-0.14</td>
</tr>
<tr>
<td>Story R. Discr.</td>
<td>-0.36**</td>
<td>-0.25*</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01. LDFR = long delay free recall; R. Discr. = recognition discriminability; UPDRS Total = total score on the United Parkinson’s disease Rating Scale; L.E.D. = Levodopa Equivalence Dosage score.
Figure 3-1. Verbal memory index scores showing significant group difference (PD < Controls). A) Mean PrVLT Long Delay Free Recall (PD = 8.13 [0.35]; Control = 9.65 [0.34]), B) Mean PrVLT Recognition Discriminability (PD = 3.01 [0.10]; Control = 3.49 [0.09]), C) Mean Story Delayed Free Recall (PD = 24.80 [1.09]; Control = 28.60 [1.07]), and D) Mean Story Recognition Discriminability (PD = 84.08 [1.37]; Control = 90.74 [1.35]).
Figure 3-2. Image showing cumulative frequency percents for PD participants across six verbal memory index scores. Blue = frequency of Not Impaired, Green = Mild Impairment, Orange = Moderate Impairment, and Red = Severe Impairment.
Figure 3-3. Chart showing all PD participants' (n = 40) cumulative z score impairment on 3 PrVLT index scores. Higher bars indicate more impairment. Z scores were only included if they were < 0. The absolute values of negative z scores were taken and z scores summed across 3 PrVLT indices. *cepk005 was missing PrVLT data.
Figure 3-4. Chart showing all PD participants’ (n = 40) cumulative z score impairment on 3 Story index scores. Higher bars indicate more impairment. Z scores were only included if they were < 0. The absolute values of negative z scores were taken and z scores summed across 3 Story indices.
Figure 3-5. Chart showing all PD participants’ (n = 40; *cepk005 was missing PrVLT data but is displayed above) cumulative z score impairment on 2 verbal memory measures (across 6 total index scores). Higher bars indicate more impairment. Z scores were only included if they were < 0. The absolute values of negative z scores were taken and z scores summed across both tests.
Figure 3-6. Images representative of MTL volumetric and fiber tracking results. A) A representative image of the left entorhinal cortex, B) Image showing cingulum fibers between the entorhinal cortex and retrosplenial cortex; C) Alternate image showing fibers between entorhinal cortex and retrosplenial cortex.
Figure 3-7. Images showing group X brain structure scatter plots. A) Group difference in left entorhinal cortex volumes, B) Group difference in left ERC – RSC EW values. Note: The highest neuroanatomic variable values in A and B are not the same individual.
Figure 3-8. Image showing group X left AF normalized edge weight. Edge weight values were scaled by a factor of $1 \times 10^6$. 
Figure 3-9. A representative image showing the AF fiber tracking.
Figure 3-10. Scatter plot showing relationship between left ERC – RSC EW and PrVLT recognition discriminability index scores. Trend line and 95% confidence interval depicted.
Figure 3-11. Images showing scatter plots with trend line and 95% confidence intervals relating left ERC volume and Story memory index scores. A) Left ERC / ICV and Story savings, B) Left ERC / ICV and Story recognition discriminability.
Figure 3-12. Image showing scatter plot with trend line and 95% confidence intervals relating left ERC volume and verbal memory composite score.
Aim 1: Is there a Verbal Memory Deficit in PD?

The current study involving a group of non-demented individuals with idiopathic Parkinson’s disease indicates that there is reason for the concern many individuals with PD have about memory; memory complaints in PD are not solely subjective. Participants with Parkinson’s disease, on average, recalled fewer words from a learned list after a 25-minute delay compared to matched Control participants. They also endorsed fewer words and made more false positives than matched peers during a delayed recognition trial. On a separate verbal memory task, PD participants also recalled fewer elements from short stories after a delay than matched Controls and had greater difficulty correctly recognizing what they previously heard.

Processing speed was a contributor to the memory differences and accounted for significant variance in the overall multivariate model but univariate results demonstrate that slowed processing speed cannot fully account for the changes in memory. These findings of verbal memory deficits match with previous work focused on memory in PD (e.g., Filoteo et al., 1997) but extend past research by demonstrating deficits on multiple verbal memory measures, which provides stronger evidence of significant memory deficits (Zahodne et al., 2011). In contrast to verbal memory deficits, there were no differences in semantic abilities between PD and Control participants. Thus, mild to moderate verbal memory deficits occur relatively early in the PD disease process and in the absence of deficits in language or global cognition; these memory deficits cannot be fully explained by processing speed declines.
**Verbal memory differences.** Individuals with PD recalled fewer words (average of 1.5) after a delay. Disruptions at different stages along the learning and memory process can each affect performance. It is possible that the group difference in remembering a list of words could be explained in part by PD participants’ greater difficulty in learning words compared to Controls.\(^1\) If PD participants struggle more when learning information, these difficulties might be due to either amnestic or dysexecutive memory deficits or a combination of both. Individuals with amnestic memory deficits display less learning, worse recall, and poor recognition of previously seen items. In the present study, individuals with PD recalled fewer words after a delay and had poorer recognition of words relative to their peers.

Individuals with amnestic memory deficits also experience rapid forgetting of learned words. However, in the present study there was no evidence of differences in the ability to retain learned words between groups. Even though there were no statistically significant group differences, a significant subset of PD participants (see Figure 3-2) had difficulty retaining learned information on both list-learning and story measures.\(^2\) Therefore, at least a sub-group of PD patients appears to have difficulty retaining learned information over a delay. This idea of subgroups of PD participants with amnestic difficulties will be explored later in this discussion.\(^3\)

\(^1\) PD participants learned an average of 1 fewer words per trial; e.g., Trial 5 Control mean: 10.78, Trial 5 PD mean: 9.70, p < 0.01

\(^2\) Using a typical clinical cut-off score of z = -1.5 (calculated using the matched controls as norms) 20.51% and 20% of individuals with PD had increased rates of forgetting of learned words and stories, respectively.

\(^3\) It should be noted that the level of impairment and rates of impairment on Story Savings are higher than what is seen using traditional norms such as from the Wechsler Memory Scale. Using norms from the Wechsler Memory Scale – III, no PD participants scored more than 1.5 standard deviations below the mean and only 5% (2/40) had Story Savings greater than 1 standard deviation below the mean. Thus,
Even though there might be amnestic memory deficits among the PD patients, the results so far could be explained largely by dysexecutive/frontal difficulties in PD. There is, however, further evidence that the memory deficits in PD are not entirely explained by dysexecutive difficulties. Individuals with PD have significant reductions in processing speed compared to controls, yet when controlling for processing speed, group differences in individual verbal memory index scores remain. Processing speed and executive function are closely related and affected similarly by pathology (see for example, Prins et al., 2005). Processing speed is a major component of executive function and is thought to be dependent upon the frontostriatal system and dopamine, which are disrupted in Parkinson’s disease (Gabrieli, Singh, Stebbins, & Goetz, 1996). However, controlling for deficits in processing speed does not explain all reductions seen in verbal memory in PD.

Individuals with amnestic memory deficits also typically produce extra, unlearned words after a delay (Canolle et al., 2008, Delis et al., 1991). While not part of the main analyses for this study, a follow-up analysis (see Chapter 3 Footnote 1) demonstrated that PD participants produce extra unlearned words on list recall and endorse more semantically-related false positives during recognition testing than their matched peers make and endorse, which is suggestive of amnestic-type difficulties in PD.

Adding to the case for amnestic difficulties in PD is the finding that individuals with PD had more difficulty than Controls on a story memory task, a test that is believed to

without using carefully matched Controls, deficits are underestimated (Type II error). These findings seem to demonstrate the benefit of using normative data based on a closely matched control group rather than using population-based norms, particularly in a sample such as the one for the present study that includes individuals who are on the whole more educated than the general population. Using population-based norms can result in severe underestimates of impairment.
be relatively resistant to executive deficits (Lezak, Howieson, & Loring, 2004; Price et al., in revision). Parkinson’s disease participants were impaired recalling the stories after a delay as well as correctly answering yes/no questions about the stories. As previously mentioned, 20% of PD participants had rapid forgetting of the stories relative to Control participants. While not statistically significant, a subset of individuals with PD did not retain as much story information. This reduction could have significant clinical, ecological, and subjective implications (e.g., tracking conversations and remembering them afterward might be more difficult for individuals with PD). Not retaining information is common in amnestic memory deficits (Delis et al., 1991).

The results from the present study and from past research provide evidence of amnestic difficulties affecting individuals with PD. One recent study found that while there appear to be deficits in both familiarity and recollection in PD that are linked with executive aspects of memory, the researchers also found evidence of recollection and familiarity deficits that were MTL-linked and thus ‘pure’ memory difficulties (Cohn, Moscovitch, & Davidson, 2010). On the other hand, while not specific to PD, individuals with focal frontal lobe lesions have been shown to have poorer delayed recall, increased intrusion rates, and impaired recognition memory on a list-learning test (Baldo, Delis, Kramer, & Shimamura, 2002), which generally matches the memory profile expected following damage to the medial temporal lobe. While this potentially makes it difficult to classify memory difficulties as amnestic or dysexecutive, the findings of Baldo et al. point to the importance of demonstrating MTL changes when making conclusions about the nature or type of memory deficits.
The results from the present study and others demonstrate that there likely exist subtypes of PD-MCI where some individuals have primarily memory or a combination of memory and executive difficulties, others have mainly executive deficits, and still others are relatively intact cognitively. On a positive note, the findings indicate that at an average of 7 years after diagnosis, significant numbers of individuals with PD have relatively unaffected memory.

There are no apparent relationships between disease severity and verbal memory performance in individuals with PD so impairments in verbal memory cannot be entirely explained by disruptions to dopaminergic systems that are believed to be driving many of the motor and related symptoms of Parkinson’s disease. In the context of intact global cognition, PD participants have deficits on multiple verbal memory measures. This multi-measure impairment indicates that not only is memory an early concern in PD but also that memory difficulties might not be wholly attributable to executive deficits. Conversely, it might demonstrate that the Story memory task is more affected by processing speed and executive processes than popularly believed. Even if that is the case, the results of the present study contribute to the building evidence that a subgroup – around 20% – of individuals with PD appear to experience amnestic memory deficits (Cohn et al., 2010; Filoteo et al., 1997). Findings of smaller entorhinal volumes in PD support this conclusion.

**Aim 2: Are there Differences in Verbal Memory Brain Structures for PD?**

Left entorhinal volumes were 11% smaller in PD participants than in matched Controls when correcting for head size. A corresponding difference, however, in the strength of white matter connections between the entorhinal cortex and retrosplenial cortex area was not found. As expected, there were also no group differences in the
strength of the connection between the left middle temporal gyrus and the pars operculus. While reductions in entorhinal cortex volumes in non-demented PD have been found previously (see for example, Goldman et al., 2012), this study adds to the evidence of structural changes to the MTL in non-demented individuals with Parkinson’s disease. These medial temporal lobe changes can be interpreted as providing indirect evidence of PD Lewy body, Lewy neurite, amyloid-Beta pathology, and α-synuclein pathology. Reductions in entorhinal volume might even substitute as an in vivo pathological burden. However, without direct pathological confirmation, this is only speculative.

**Causes of Entorhinal Volume Loss**

According to the Braak staging hypothesis (Braak et al., 2004) the MTL is a region of the brain that is affected early by PD pathology. Some have proposed that PD pathology might have two originating regions – olfactory bulb and lower medulla oblongata. Hawkes, Del Tredici, and Braak (2007) formulated this into a dual-stage hypothesis for PD – namely that PD pathology starts at both olfactory and medullary regions, spreading to adjacent regions until the whole brain is affected. Researchers have shown that early clinical symptoms can be explained by these sites of pathological disruption. For example, olfactory deficits are common in early Parkinson’s disease as are sleep disorders, autonomic disorders, and gastrointestinal dysfunction (Hawkes et al., 2007). These early non-motor clinical symptoms, which pre-date motor symptoms, match the sites in PD most affected early by Braak stage pathology. Once clinical motor symptoms of PD occur (typically between Braak stages 3 and 4), the MTL is already affected by PD pathology, possibly even doubly so as a result of being a potential convergence site between the olfactory bulb and the medulla oblongata. Neurons in the
entorhinal cortex, Ammon’s horn of the hippocampus, and related components of the limbic system (e.g., amygdala) are particularly vulnerable to PD pathology (Braak & Braak, 2000; Braak et al., 2004). It is also possible that individuals with PD and cognitive and memory impairments have more limbic and neocortical pathology than individuals without clinically significant non-motor symptoms (Jellinger, 2009); this indicates that potential motor and cognitive subtypes of PD might have pathological causes.

With these pathological changes, it is possible that there are concomitant structural changes; however, pathology can result in severe functional impairment long before considerable neuronal death and atrophy occur (Braak et al., 2000). Even so, while the present study does not include direct pathological measurements, there is evidence of volume loss in the entorhinal cortex. Futher, Lewy body aggregation in the entorhinal cortex is predictive of cognitive functioning and dementia within Parkinson’s disease (Kovari et al., 2003). Individuals with PD who have smaller entorhinal volumes are also more likely to have dementia (Goldman et al., 2012). Thus, within the present sample it is possible that individuals with reductions in ERC volumes might be at greater risk for developing dementia in the future. Quantifying entorhinal and other MTL volumes early in the disease process could help inform clinical diagnosis and treatment and help increase accuracy of predicting future cognitive decline.

While there is considerable evidence to support the Braak stages of PD pathology, there is controversy over the clinical utility of the stages (for a review, see Jellinger, 2009). In short, Braak-proposed PD pathology stages do not relate to clinical manifestations of PD; in other words, severity of Braak stage PD pathology is not
predictive of severity of clinical symptoms (Jellinger, 2008; Jellinger, 2009; Beach et al., 2009). Additionally, 30-55% of older adults exhibit widespread Lewy body and Lewy neurite pathology without meaningful clinical phenotypical expression (Jellinger, 2009). What might be most helpful in predicting severity of clinical symptoms is a combination of Lewy body, Lewy neurite, α-synuclein, and neuronal cell loss analyses; in other words, quantifying structural and regional neuronal loss in addition to pathology should increase sensitivity and specificity to clinical stages of PD and cognitive impairments within PD. This seems to imply that when pathological studies are not possible (e.g., in living subjects), decreases in neuronal integrity and neuronal loss might be the most sensitive measure of clinical dysfunction. This gives further support to the idea of consistently quantifying structural brain changes for clinical use.

**Explanations of ERC-RSC Findings**

While it was expected that there would be reductions in PD, there were no significant group differences in the connectivity between the entorhinal cortex and the retrosplenial cortex. It might be the case that there are no gross disruptions in the temporal portion of the cingulum connecting entorhinal and retrosplenial cortices but there are a number of possible explanations and confounding factors that need to be addressed.

If there are no group differences in edge weight it might be that this particular white matter pathway is, in early stages of non-demented PD, not strongly affected by the PD disease process. While there is good rationale for the disruption of this pathway in PD (Mattila et al., 2001; Park & Stacy, 2009; Metzler-Baddeley et al., 2012; Lee et al., 2010; Kobayashi & Amaral, 2003), it is possible that such disruptions have not yet translated into gross structural changes of the white matter. In other words, PD
pathology, functional (neurotransmitter) changes, and loss of entorhinal cortex volume might not have disrupted the white matter connecting the entorhinal cortex and the retrosplenial cortex.

It is also possible that only a subgroup of individuals with PD has reduced ERC – RSC connectivity. There are, however, no individuals with PD who have ERC – RSC edge weights that are more than 1 standard deviation lower than the mean EW of Controls. This relatively tight distribution of values does not necessarily mean that edge weights are unimpaired – a small reduction in edge weight might be significant as a proxy for pathology and significant clinically. This issue will be addressed as part of Aim 3.

From a qualitative standpoint, tracking results match known anatomical connections. This method of fiber tracking is novel and involves a number of technical and complex steps for analysis. Steps were taken along each part of the processing of data to minimize error. However, because quantitative fiber tracking is a relatively new method and because it relies on a complex interplay between biology and technology, there are a number of technical difficulties in fiber tracking that potentially affected the results. Such potential difficulties will be discussed later.

In summary, left entorhinal volumes were 11% smaller in PD participants than in matched controls when correcting for head size. A difference, however, in the strength of white matter connections between the entorhinal cortex and retrosplenial cortex was not found. This provides evidence of MTL cortical loss in non-demented individuals with idiopathic PD but relatively intact white matter connecting to the entorhinal cortex.
Aim 3: Are there Specific Structural-Cognitive Patterns?

As expected, across all subjects there was a positive association between increasing left ERC volume and the ability to retain learned story information and correctly answer questions about the stories. These findings replicate previous research demonstrating associations between entorhinal volume and Story memory (Price et al., 2011). Generally, past research has shown a relationship between the volume of the entorhinal cortex (Killany et al., 2002; Rodrigue & Raz, 2004) or activity of the entorhinal cortex (Goto et al., 2011; Cabeza, Dolcos, Graham, & Nyberg, 2002) and performance on verbal memory measures (Price et al., 2010). MTL structures are necessary for the process of making information usable at a later time (Squire, Stark, & Clark, 2004). While the functions of the individual structures (e.g., entorhinal cortex, hippocampus, or perirhinal cortex) can be dissociated from each other to some extent, there are not always clear distinctions between what each structure does (Squire et al., 2004) so finding clear associations between structure and cognitive function is not always possible.

While the volume of the entorhinal cortex was important in remembering a passage of prose, the integrity of the white matter between the entorhinal and retroplenial cortices associated with the ability of older adults to correctly recognize previously heard words from a list. This suggests distinct differences in gray versus white matter function for verbal memory performance in the PD and Control samples.

When relationships between structure and memory were assessed for both groups separately, for both groups left ERC volume was a significant predictor of the ability to retain learned story information. When groups were analyzed separately, the positive association between the integrity of the white matter between the left entorhinal and
retrosplenial cortices and list recognition remained only for the PD group. The involvement of this temporal portion of the cingulum in recognition memory demonstrates the role of brain networks in memory processes.

The recognition score analyzed was taken from signal detection theory. In order to perform well, an individual has to not only correctly recognize target words (true positives) but also correctly reject distractor words (true negatives). There is evidence of reduced parietal glucose metabolism early in Alzheimer’s disease. Some have speculated that the interface between temporal and parietal lobes is important for normal memory functioning (Buckner, 2004). It has been hypothesized that the retrosplenia cortex serves as an interface between working memory, which is highly dependent on frontal and parietal regions and long-term memory; this is in turn, highly dependent on the medial temporal lobe (Kobayashi & Amaral, 2003; Buckner, 2004).

Given past research demonstrating frontal lobe lesions resulting in reduced memory performance, including increased intrusions (i.e., “false memories”; Baldo et al., 2002), and given the close connections the retrosplenia cortex (and cingulum) has with the frontal lobes, it is not surprising the long association pathway of the cingulum plays a role in recognition – being able to accurately choose target words and suppress distractions.

Whereas there was a significant relationship between the left ERC – RSC connectivity and performance on PrVLT recognition discriminability, there was no relationship between edge weight of the left arcuate fasciculus and PrVLT recognition discriminability. These results show a dissociation between fiber pathways and their relationship to a component of verbal memory.
In summary, individuals with larger entorhinal cortex volumes – relative to intracranial volume – retain and recognize more elements from a prose passage than do those who have smaller entorhinal cortex volumes. In short, the entorhinal cortex is involved in preventing decay of learned prose information. Further, individuals who have stronger white matter connections between the entorhinal cortex and retrosplenial cortex perform better on a verbal recognition memory task. The current project was designed as a start to better understand the role that structures and networks play in verbal memory processes in individuals with Parkinson’s disease.

Final Summary

The results from the present study provide conclusive evidence of both early memory disruptions and entorhinal volume loss in early stage, idiopathic, non-demented PD. The verbal memory changes are partially due to deficits in processing speed and executive functions but the results of the present study lend support to the idea that mild but pure amnestic deficits, at least for a subset of individuals with Parkinson’s disease, exist early in the Parkinson’s disease process. Further, these verbal memory deficits occur without concomitant semantic system degradation as measured by category fluency and naming tests in the context of intact global cognition. The present study has five major implications.

Study design and verbal memory. First, these memory deficits in PD were discovered in part due to the well-controlled nature of the study. In other words, the present study demonstrated the need for good comparison groups. It is likely that without a carefully matched control group, verbal memory impairment would be understated. An example of this is looking at rates of Story memory impairment using test norms rather than Control group norms. Using demographically-corrected test
norms, no individuals with PD scored less than 1.5 standard deviations below the mean for Story savings (percent retention), yet deriving normative data from the Control group yielded 20% of individuals with PD having Story savings scores 1.5 standard deviations or more below the Control mean. This means that without using carefully matched Control groups, Type II error rates are likely higher than desired.

Second is that memory impairment in non-demented PD is marked across two verbal memory measures – list-learning and Story memory. While both measures assess verbal memory, both are differentially affected by other cognitive processes. Having deficits on multiple verbal memory measures provides stronger evidence of real memory deficits (Janecek et al., 2011; Zahodne et al., 2011) by reducing spurious effects related to multiple comparisons. Thus, controlling for multiple comparisons was done at the model level by including a specific set of test indices hypothesized to associate with neuroanatomical variables. Statistical corrections for multiple comparisons were also conducted but did not significantly change the results and were not reported.

Third, even though included individuals with Parkinson’s disease were cognitively intact, scoring similarly to Controls on global measures of cognition and orientation, individuals with Parkinson’s disease had smaller left entorhinal cortex volumes when correcting for intracranial volume. While the data are cross-sectional and volumetric changes over time cannot be measured, assuming similar entorhinal volumes before PD and other neurological pathology took hold, individuals with PD lost on average 11% of the volume of the entorhinal cortex. While a number of individuals with PD had intact entorhinal volumes, overall, Control individuals had the largest ERC volumes and
individuals with PD had the smallest ERC volumes. These results seem to provide indirect evidence of Lewy body and other pathological changes occurring in the medial temporal lobe before significant cognitive declines occur. Structural changes are important to quantify because individuals with and without PD who have smaller ERC volumes could be at risk of developing significant memory problems as they age (Rodrique & Raz, 2004).

Fourth, and related to the previous point is that for memory measures there were individuals with PD who scored and measured similarly to their Control peers (15-18% of PD individuals scored at or above the Control mean for verbal memory measures). In fact, the majority of individuals with PD in this study did not have significant memory deficits. On the other hand, there was a significant subgroup who had verbal memory deficits. 20-40% of individuals with PD demonstrated at least moderate impairment on one or more verbal memory index score and 20% (8/40) had moderate verbal memory impairment across both list learning and story memory measures (17.5% with a stricter definition of impairment across both measures). This demonstrates that at least moderate memory deficits are common early in PD without any global cognitive deficits. It also demonstrates, on the other hand, that in the absence of global cognitive changes significant proportions of individuals with PD do not have significant memory difficulties.

Fifth, including both gray and white matter is important for understanding the distributed nature of cognition and the effects that pathological changes of neurological disorders have on the brain. That group differences were seen in entorhinal volume but not the cingulum between entorhinal and retrosplenial cortices might reflect pathological progression (i.e., staging). In other words, significant PD pathological changes might not
have spread beyond the brainstem and MTL, at least to the point of significantly affecting the structure of this section of the cingulum. These results might also signify different levels of α-synuclein and Lewy bodies or neurites by region.

Limitations and Strengths

Verbal memory and Parkinson’s disease. Participants in the present study were well-matched between groups. They averaged 67.9 years old, tended to be highly educated (16.39 years average), had intact global cognition (MMSE = 29.09; DRS-2 = 139.84), had similar estimated premorbid vocabulary skills (WTAR = 108.18), and were without significant health concerns (other than Parkinson’s disease). The lack of significant health concerns was due to strict inclusion and exclusion criteria. Because the groups are well-matched and participants are generally healthy, it is likely that this resulted in an increased sensitivity to memory disturbances in PD (i.e., reduction in Type II error rates) without overestimating memory difficulties. This is evident in that a portion of PD participants only had significant deficits on the Story memory task when using scores from the matched Controls as norms. When compared to the general age-matched population using test publisher norms (Wechsler, 1997), none of the participants with PD experienced significant impairments on the Story memory test. In other words, impairments in Story memory were only seen when using a carefully-matched Control group.

While the groups were well-matched, a potential limitation of the findings is that the participants are not necessarily representative of the broader population and so the findings of this study might not be generalizable to the general PD population. However, in general, the careful matching of individuals with PD with Control participants is a great strength of this project. This is particularly true because rates of memory problems
clinically and scientifically might be under-reported when relying on published norms. This is not to question the validity or usefulness of established norms, rather it is to argue for the utility of using norms based on closely-matched groups.

An additional limitation is that the included individuals were all Caucasian, thus limiting further generalizability. However, because both groups were well-matched, this controls for demographic effects in between-group analyses. In other words, because groups were well-matched, between-group differences are broadly generalizable but within-group findings will have limited applications to other groups of people.

Another potential limitation is that the included individuals with Parkinson’s disease were generally healthy, as the study had strict inclusion and exclusion criteria. While this results in ‘clean’ data, individuals in general society are not always as healthy. This limitation, however, should not affect between-group results. What having well-controlled groups does is increase the probability that deficits seen in individuals with PD are due to the disease process and not extraneous comorbidities. Having ‘clean’ groups does limit the potential variability in verbal memory scores. This variability is also limited because individuals were recruited only if they had intact global cognition at baseline evaluation. While this allowed for a greater understanding of verbal memory relatively early in the Parkinson’s disease process, it possibly limited the relationships with neuroanatomical variables. This speaks to performing larger and longitudinal studies or ones that include wider ranges of cognitive variability.

Related to this, while it was expected that there would be stronger relationships between the volume of the entorhinal cortex and individual scores from the included verbal memory tests, it is possible that other structures are more important for the
measured components of verbal memory than the entorhinal cortex is in this particular sample. In other words, it is possible that other brain regions or functions become more salient in the memory process in a mixed population of PD and healthy older adults (Cabeza, 2002). This might be the case because as one area (e.g., entorhinal) dysfunctions, other areas might start to compensate for that dysfunction. Researchers assessing memory and other cognitive functions in cognitively intact older adults have demonstrated that there appears to be less functional asymmetry in older adults compared to younger adults (termed Hemispheric Asymmetry Reduction in Older Adults {HAROLD}). It is beyond the scope of this dissertation, however, to address this hypothesis but it is interesting to speculate whether older adults in general (particularly neurologically compromised individuals) might not rely on broader brain networks for cognitive and memory functions, thus reducing relationships between individual components of networks (e.g., entorhinal cortex or entorhinal to retrosplenial white matter) and memory and cognition. This hypothesis gives support for continuing to measure and quantitatively track more and more complex brain areas and networks.

**Neuroimaging.** The following potential shortcomings are largely true for any diffusion MRI analysis and are not unique to this project but are discussed briefly in order to underscore the complexity of diffusion analyses.

Diffusion MRI is susceptible to artifacts as the result of subject motion (Leemans & Jones, 2009; Rohde et al., 2003), head position in the scanner, Echo Planar Imaging (EPI) distortion (Bammer et al., 2002), and partial volume averaging as the result of voxel size (Vos et al., 2011). Voxel size is particularly important when seeking to visualize fiber pathways that are similar in width to or smaller than the in-plane
resolution of the diffusion weighted imaging voxels. Whereas in the present analysis 64 streamlines (‘fibers’) were calculated for each 8 mm³ cube of brain matter, there are thousands to tens of thousands axons in the same space. Because of methodological limitations to visualizing and analyzing the white matter, there is a need for fiber tracking at higher spatial resolutions (which will be discussed briefly at a later point) in order to reduce partial volume effects. Higher resolutions should increase sensitivity to change in the white matter; it does, however, come at a cost of time, signal-to-noise, movement, and other factors (Pfefferbaum et al., 2004). For a concise review of difficulties of white matter diffusion analyses refer to Jones and Cercignani’s (2010) recent article.

Fiber tracking is a relatively new method of brain imaging analysis. While the underlying mathematical model and method of tracking used in this analysis is established (Jian et al., 2007), mapping of the fiber networks and connections between regions is an area under development and not without challenges (see Jones, 2010, for a review of challenges faced by researchers performing fiber tracking analyses). Refer to Figure 4-1 for examples of fiber tracking with sub-optimal results (compare to Figure 3-9). The fibers match anatomic structures but the number of calculated streamlines is limited.

In spite of potential limitations to diffusion imaging in general and fiber tracking specifically, the tracking results match known anatomy; further, reasonable steps were taken in order to minimize error so tracking results are thought to be valid. Further reliability and validity studies are planned in future work in order to continue to improve methodology.
Future Directions

It will be important to look at other parts of the memory network in order to start to build a more complete picture of the relationships between segments of memory networks and components of verbal memory. Future work can include tracking between entorhinal cortex and the hippocampus (perforant pathway; see Augustinack et al., 2010; Christidi et al., 2011, for example), tracking the fornix, tracking the uncinate fasciculus, and other brain regions. It is technically possible to track the entire Papez circuit in order to see relationships between each set of connection diodes (e.g., ERC to RSC, ERC to hippocampus, hippocampus to mammillary bodies, etc.) and verbal memory index scores. It could also be important to measure the integrity of the entire system to assess for relationships with verbal memory. These analyses are important for detecting early brain changes that might predict future memory decline, or at least discover individuals at greater risk of developing memory deficits in the future and as such have significant clinical relevance.

Future directions also speak to the need to better understand the relationship between PD pathology progression, verbal memory, and structural brain changes. Such efforts will require close multidisciplinary efforts. All are important research areas in order to better understand the in vivo progression of Parkinson’s disease and other neurodegenerative disorders with the goal of earlier and more effective interventions.
Figure 4-1. Representative images showing suboptimal arcuate fasciculus fiber tracking. A) participant with lowest AF edge weight – note the few streamlines calculated; B) participant with low AF edge weight – also has few streamlines.
APPENDIX A
PARTICIPANT INCLUSION AND EXCLUSION CRITERIA

- **Diagnosis**
  - Non-demented Idiopathic PD ‘on’ medication
  - Diagnosis based on United Kingdom PD Society Brain Research Center criteria (Gibb & Lees, 1988)
  - Hoehn and Yahr scale range 1-3 (Hoehn and Yahr, 1967).

- Patients are excluded if they match criteria for comorbid neurodegenerative disorders (see below)

- ‘Normal’ Age/Education Matched Adults

- See exclusion criteria below

- Ethnicity/race: all ethnic and racial groups.

- Sex/gender: men and women

- Age: 60 and up. There is no upper age limit imposed.

- Handedness: Right handed

**PD Exclusion Criteria**

- Underlying medical disease likely to limit lifespan or confound outcome analyses.

- Other neurodegenerative disorders.

- Patients are excluded at baseline if they present with signs of a dementia as indicated by DSM-IV criteria and a Dementia Rating Scale-2nd Edition age and education corrected scale score < 8.

- Psychiatric Exclusions: A major psychiatric disorder. Also, patients who meet criteria for Major Depression or experience a Major Depressive Episode within three months prior to study recruitment will be excluded. We did not exclude patients reporting mild depression or anxiety for many PD patients report such symptoms.

- Conditions or behaviors (e.g., claustrophobia) likely to affect imaging or cognitive testing.
Parallel Control Group Exclusion Criteria

Exclusion criteria for this group match that of the PD patients except that it will be required that they do not have symptoms of PD. Scores on the Dementia Rating Scale-Revised will be within the average range [age and education scale score > 8; (Jurica et al., 2001)] and scores on the Mini Mental State Exam will be in the normal range [total score > 27; (Folstein et al., 1975; Lezak, 1995)].
APPENDIX B
MAGNETIC RESONANCE IMAGE PROCESSING WORKFLOW
APPENDIX C

AIM 2 WITHIN-GROUP SUB-AIM: SIDE OF ONSET AND LATERALIZED DIFFERENCES

25/40 PD participants had right side symptom onset, 14/40 had left side onset, and 1/40 experienced axial/gait changes first. When comparing left and right side onset PD participants, there were no significant differences in brain structure volumes or fiber integrity (see Table C-1).

<table>
<thead>
<tr>
<th>Table C-1. Parkinson’s disease side of onset group contrast</th>
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<tbody>
<tr>
<td>Measure</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Left ERC/ICV</td>
</tr>
<tr>
<td>Left ERC-RSC EW</td>
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<tr>
<td>Left AF EW</td>
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Note: ERC/ICV = Entorhinal cortex volume corrected for intracranial volume X 10000; ERC-RSC EW = Entorhinal cortex to retrosplenia cortex edge weight normalized and adjusted for intracranial volume; AF EW = Arcuate Fasciculus edge weight normalized and adjusted for intracranial volume.
REFERENCE LIST


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BIOGRAPHICAL SKETCH

Jared J. Tanner grew up in Arizona in a family of seven children. He attended Brigham Young University where he earned a Bachelor of Science in psychology, with a minor in gerontology. He also earned a Master of Science degree from Brigham Young University in psychology. His thesis was entitled *Measuring Reliable Change in Acute Respiratory Distress Syndrome*.

Currently, Jared is a graduate student at the University of Florida in the Clinical and Health Psychology Ph.D. program with an emphasis in neuropsychology. Jared is a member of Catherine Price’s laboratory with a focus on neuroimaging and cognition and memory in neurological disorders and after major surgery. His clinical internship was completed at the Duke University Medical Center in the Department of Psychiatry and Behavioral Sciences.