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Cognitive Changes in Early Untreated Parkinson's Disease

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Abstract

Cognitive impairment is the most common non-motor symptom patients develop in Parkinson's disease (PD). However, the cognitive profile in early PD remains unclear due to the use of heterogenous samples of disease severity, small sample sizes, and the inclusion of medication effects. This study aims to characterize cognitive changes in early PD using a large, drug-naive sample. This study examined performance on the Montreal Cognitive Assessment and the Hopkins Verbal Learning Test from the Parkinson's Progression Markers Initiative dataset (*n*= 643 patients with PD; *n*= 240 healthy controls). Patients were restricted to ≤ 12 months of disease duration and had not begun chronic dopaminergic therapy. Bayesian analyses of covariance showed Group effects in global cognition, executive function, recall, and retrieval between PD patients and controls. This suggests that early PD patients exhibit multidomain cognitive changes in domains of executive function and memory.

Keywords

Parkinson's disease, De novo, Cognition, Cognitive impairment, Executive function, Memory, Encoding

Summary for Lay Audience

Parkinson's disease (PD) is an age-related, neurodegenerative disorder. PD is commonly recognized for its motor symptoms, whereby patients have trouble in walking, balance, talking, and posture amongst other symptoms. However, patients with PD also experience non-motor symptoms (NMS) that have devastating effects on quality of life. Cognitive impairment is the most common NMS patients develop in PD, with up to one-third of early-disease patients experiencing cognitive changes. Cognitive impairment hinders the ability to think, reason, use logic, remember, and perform other functions that are used in day-to-day living. Although widely studied, the cognitive profile of early PD remains largely unclear. This is due to variability in the disease severity amongst patients in a sample, smaller study samples, and patients taking medication to manage their motor symptoms which can have a side effect on boosting or worsening specific cognitive functions. Thus, it is important to study the profile of cognition, specifically which domains are affected disproportionately, in early PD using a larger, drug-naïve group of patients.

The objective of this study was to create a better profile of cognitive changes present in early PD. We used a large, drug-naïve sample of patients restricted to less than 12 months into disease duration to reduce variability in our sample. We used two different clinical measures to assess several domains of cognition: Global cognition, Executive, Memory Recall, Memory Retrieval, Attention, Learning, Language, Visual abilities, and Orientation to time and space. We compared performance on these measures across early-disease patients with PD and healthy elderly controls. We found patients with PD showed worsened performance on outcome measures of Global cognition, Executive, Memory Recall, and Memory Retrieval. Thus, the profile of cognitive alterations in PD in early disease seems to be multidomain impairment in executive functions and memory.

Co-Authorship Statement

Kunj Patel completed all experimental and written work for this thesis project. This included study design, participant recruitment, data analysis, and writing the written work. Data was collected and obtained permission to use from the Parkinson's Progression Marker's Initiative.

Dr. Penny MacDonald contributed to all aspects of this thesis project including the formulation of the research question, consultation with experiment design, data analysis, interpretation, and editing of the written work.

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

PD	Parkinson's Disease
AD	Alzheimer's Disease
MCI	Mild Cognitive Impairment
SNc	Substantia Nigra pars compacta
DS	Dorsal Striatum
VS	Ventral Striatum
GPi	Globus Pallidus interna
VTA	Ventral Tegmental Area
HrQoL	Health Related Quality of Life
RBD	REM Sleep Behaviour Disorder
PD-NC	Parkinson's Disease Normal Cognition
PD-MCI	Parkinson's Disease Mild Cognitive Impairment
PDD	Parkinson's Disease Dementia
SCC	Subjective Cognitive Complaints
PD-non-MCI	Parkinson's Disease non Mild Cognitive Impairment
L-DOPA	Levodopa
AADC	Aromatic-L-amino-acid decarboxylase
COMT	Catechol-O-methyltransferase
DLB	Dementia with Lewy Bodies
MDS	Movement Disorder's Society
PPMI	Parkinson's Progression Marker's Initiative
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating
HC	Age-matched Healthy Controls
MoCA	Montreal Cognitive Assessment
HVLT-R	Hopkins Verbal Learning Test – Revised
GDS	Geriatric Depression Scale
STAI	State Trait Anxiety Inventory
STAI-S	State Trait Anxiety Inventory- State Measure
STAI-T	State Trait Anxiety Inventory- Trait Measure
GCP	Good Clinical Practice

ICH	International Conference on Harmonization
SC	Screening
BL	Baseline
IR	Immediate Recall
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance

Chapter 1

1 Introduction

1.1 Cognitive Functioning in Humans

Cognition refers to a large array of mental processes involved in acquiring, understanding, storing, and using information to perform responses, as well as simple or complex acts (Craik & Rose, 2012; Miyake et al., 2000; Zelazo & Carlson, 2020). Cognitive abilities and processes underlie functions and behaviours that ensure human survival and create thriving societies. Every task from the mundane, to higher-order problem-solving, relies on a surprising number of separate but interacting cognitive processes, most of which engage disparate brain regions, pathways, and networks.

For example, even seemingly simple tasks such as brushing one's teeth are achieved through the culmination and combination of many separate but interacting cognitive processes. In childhood, we *learn* to *recognize* the *object* that is a toothbrush, and to *chain responses* and perform appropriate *utilization behaviours* upon *judging* the correct context. This involves applying toothpaste, adding water, finally concluding in the *motor act* of cleaning one's teeth with the toothbrush. At first the *performance of this motor task* is clumsy but through practice and *procedural learning,* it becomes fluid, well-calibrated, and automatic. The *decision* to adopt the routine practice of teeth brushing requires higher-order information processing to *understand* the health and societal *benefits*, weighed against the time and financial *costs* of this ritual. This is a decision that can evolve over time and differ between people, depending on *appreciating* and *integrating values* and *priorities*, which are variable and changeable, and upon which *rewards*, such as compliments on a brilliant smile, versus *punishments*, such as painful and costly cavities, also impinge. Finally, even once the decision is made to incorporate this practice as a routine, faithful implementation requires prospectively *remembering* to perform the act at the specified time, and occasionally, *overcoming inertia* (i.e., *motivation*) or *suppressing competing drives or interests* to achieve the task.

This example illustrates how a wide array of cognitive processes converge to accomplish even relatively simple and mundane tasks. Furthermore, it reveals that impairment in performing the task can owe to deficiencies in widely diverse cognitive

operations. These realizations have motivated the development of a plethora of tests and tasks that have aimed to isolate cognitive processes through highly simplistic, or repeated probing, versus contrived scenarios, conditions, or responses that best reveal targeted functions despite the limited ecological validity of these experimental techniques (Jobe, 2003). Over decades of investigation, through a) statistical means yielding shared components, b) increasingly by recognizing similarities in neural bases, and c) common sensitivities/responses to environmental, physiological, or disease states, *domains* of cognition have emerged (Baddeley, 2004; Baddeley & Logie, 1999; Broadbent, 1954; Craik & Rose, 2012; Diamond, 2013; Miyake et al., 2000; Tulving, 1972; Zelazo & Carlson, 2020) The development of a tractable number of cognitive domains has greatly improved our ability to understand cognitive impairment across aging, injury, and neurological and systemic diseases. These conditions can impair cognition globally or in a domain-specific manner, which we are beginning to explore (Fonesca et al., 2012; Hecht et al., 2013; Hsieh et al., 2016; Vallesi et al., 2021; Wynn et al., 2021; Xiao et al., 2020; Zelazo & Carlson, 2020). Increased understanding of cognitive domains has further spurred development of useful screening tools and neuropsychological tests, some of which are clinically validated and extensively normed (Benedict et al., 1998; Nasreddine et al., 2005). These measures will accelerate cognitive research in aging, disease, and even for understanding the impact of sex (Benedict et al., 1998; Julayanont & Nasreddine, 2017).

1.1.1 Cognitive domains

Cognition refers to a wide range of mental processes, as well as covert and overt behaviours. Cognitive processes are classified into those that underlie memory, attention, language, or executive functioning (Broadbent, 1954; Craik & Rose, 2012; Miyake et al., 2000; Tulving, 1972; Vallesi et al., 2021; Zelazo & Carlson, 2020). Others include more bottom-up processes involving sensory and perceptual operations, important for organizing spatial maps of surroundings, enabling appropriate responding. Top-down processes involve more executive functions that can involve integrating prior and new knowledge to reason or problem-solve (Fonesca et al., 2012; Manes et al., 2002; Miyake et al., 2000; Nejati et al., 2018; Zelazo & Carlson, 2020). Cognitive domains and abilities

are not independent of each other, with executive tasks often requiring the integration of multiple sensory, perceptual, attentional, language, and other functions(Churchwell et al., 2009; Draheim et al., 2018; Hsieh et al., 2016; Long & Kuhl, 2019; MacLeod & MacDonald, 2000; Nejati et al., 2018; Xiao et al., 2020). A brief portion of this introduction will review cognitive domains and specific examples of abilities encompassed within each. Though helpful, these domains are pragmatic heuristics evolving as our understanding increases, given our still incomplete understanding of cognition, as well as the limitations and biases of our tools and tests.

Executive functions (EF) refer to a collection of higher-order, top-down complex skills such as reasoning, problem solving, decision making, and suppression of unwanted habitual or inappropriate responses that are necessary to pursue and achieve goals, as demonstrated by lesions, neuroimaging, and transcranial direct stimulation studies (Bechara et al., 1994; Cristofori et al., 2019; Fonesca et al., 2012; Manes et al., 2002; Miyake et al., 2000; Nejati et al., 2018; Zelazo & Carlson, 2020). Emotionally neutral executive skills involving more lateral parts of the prefrontal cortex (PFC), known as "cool EFs" typically are measured behaviourally as inhibitory control, working memory, and cognitive flexibility (Diamond, 2013; Miyake et al., 2000). Motivationally significant skills, involving incentive value (i.e., delay of gratification or delay discounting) and reversal learning (i.e., reversing strong approach-avoidance tendencies), are known as "hot EFs" and involve neural systems connecting ventral and medial PFC with mesolimbic parts including striatum and amygdala (Bjork et al., 2009; Churchwell et al., 2009; Dias et al., 1996; Hecht et al., 2013; Rolls et al., 1994; Zelazo & Carlson, 2020).

Attentional functions generally refer to the abilities to direct or sustain attention to stimuli in the environment, as well as to avoid distracting information in a goal-directed manner (Draheim et al., 2018). Stimuli can be visual, auditory, somatosensory, or a combination of a multi-sensory stimulus. Broadbent (1954), originally proposed that information in working memory (an executive function) can be stored temporarily and give rise to a selective response (Broadbent, 1954), as well attention can also be switched between two tasks (i.e., attentional switching) or split to filter one stimuli from an input of multiple stimuli (Broadbent, 1958). Since then, numerous studies have investigated sustained attention and inhibition in younger and older adults (Brache et al., 2010;

Carriere et al., 2010; Heilbronner & Münte, 2013; Hong et al., 2014; Hsieh et al., 2016; MacLeod & MacDonald, 2000; Staub et al., 2015; Vallesi et al., 2021). Additionally, working memory, specifically attentional shifting, have been better understood through investigations in individuals with alterations in attention due to neurodegenerative disease (Cools et al., 2003; Draheim et al., 2018; Lange et al., 1992; Lewis et al., 2005; Shook et al., 2005; Unsworth et al., 2005).

Another important cognitive domain, memory, is complex and the multifaceted and disparate processes that contribute to its many manifestations suggest that this encompasses multiple cognitive domains. Overall memory performance is attributed to the functioning of three stages: encoding, storage, and retrieval (Craik & Rose, 2012). Encoding is the ability to learn new information, taking the information contained in working memory and processing it for long term storage (Baddeley, 2004; Craik & Rose, 2012). Storage is the retention of information over time, with successfully encoded information being able to recalled at variable post encoding time periods (Baddeley, 2004; Craik & Rose, 2012). Retrieval is the process through with information can be brought out of long term storage into working memory after encoding through recognition or recall (Baddeley, 2004; Craik & Rose, 2012). Encoding and retrieval are highly linked processes and numerous studies have investigated these paradigms through behavioural tasks, neuroimaging, and diseased states (Long & Kuhl, 2019; A. A. MacDonald, Seergobin, et al., 2013; Pillon et al., 1993; Siquier & Andrés, 2021; Smith et al., 2022; Weintraub et al., 2004; Wynn et al., 2021; Xiao et al., 2020).

Unsurprisingly, given the broad range of functions that constitute cognition, cognitive impairment either globally or at least within some domains appears to be a feature of most neurological diseases (Galasko, 2017; Orad & Shiner, 2022). Though our insights of cognitive impairments in aging and neurological illnesses are imperfect due to weaknesses in most studies (e.g., heterogeneity of patient groups, between-study contrasts use different tests, small convenience samples), it seems that the types of cognitive deficits and spared functions—the *cognitive profiles*—are different across conditions such as Parkinson's disease (PD), Alzheimer's disease (AD), mild cognitive impairment (MCI), Huntington's disease, Frontotemporal dementia, vascular dementia, and many others.

1.2 Parkinson's disease

1.2.1 Parkinson's disease pathology

PD is the second most common and fastest-growing neurodegenerative disorder affecting 6.1 million people and mounting worldwide (Bloem et al., 2021). PD is considered a movement disorder because the diagnosis depends on the onset of tremor, rigidity, and bradykinesia, though patients with PD experience a plethora of symptoms, some prior to diagnosis, others simultaneously with motor symptom onset, and others later in disease evolution. Pathologically, the characteristic motor symptoms of PD arise due to the degeneration of nigrostriatal dopaminergic neurons and consequent dopamine restriction to motor-control subregions of the striatum. The presence of Lewy bodies, neuronal inclusions of misfolded α-synuclein protein, has been linked to pathogenesis of PD (Aarsland et al., 2017). Subregions of the striatum, comprising the caudate nucleus, putamen, and nucleus accumbens, are dopamine restricted to greater and lesser extents throughout the progression of PD pathology. In the early stages of the disease, the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) differentially dopamine depletes the dorsal striatum (DS), whereas the ventral striatum (VS) supplied by the ventral tegmental area (VTA) is relatively dopamine replete (Hiebert et al., 2020; Kish et al., 1988; P. A. MacDonald & Monchi, 2011). As the disease progresses, more of the DS, as well as the VS, related to beginning VTA degeneration become dopamine deficient (Hiebert et al., 2020; Kish et al., 1988; P. A. MacDonald & Monchi, 2011). Understanding the differential loss of dopaminergic input that characterizes the pathology of PD is important to understanding the motor and non-motor symptoms of PD and developing strategies to manage them.

Braak's hypothesis is a model of PD pathology proposed that presents a staging system associated with the spread of α-synuclein and Lewy body accumulation in PD based on a specific pattern of spread beginning in the lower brain regions and spreading ultimately to the entire neocortex (Braak, Rüb, et al., 2003; Braak, Tredici, et al., 2003). This model has been proposed to explain the evolution of symptoms in PD. Stages 1 and 2 are characterized by spread of Lewy Body-inclusion bodies primarily to lower brain

structures such as the medulla oblongata and pontine tegmentum. The lower and upper brainstem, including the midbrain, comprising the SNc which causes the motor symptoms, and VTA, as well as some portions of the anteromedial temporal mesocortex are affected in Stages 3 and 4. The SNc is affected in the midbrain in Stages 3 and 4 and as well, while the neocortex is expected to be largely spared. Lastly, Stages 5 and 6 are characterized the by the spread of the PD-inclusion bodies to the neocortex and high order cortical areas (Braak, Tredici, et al., 2003). It is postulated that cognitive impairment and dementia arise at this stage of PD.

1.2.2 Motor and Non-Motor Symptoms (excluding Cognition)

The loss of dopaminergic neurons in the SNc leads to various motor symptoms such as bradykinesia, rigidity, tremor (Xia & Mao, 2012)—the cardinal motor symptoms of PD. Rigidity and bradykinesia are required for the clinical diagnosis, and two-thirds of PD patients also evidence rest tremor (Bloem et al., 2021; Xia & Mao, 2012). Further degeneration of dopaminergic neurons and progression to affect other neural regions, at later stages of disease, cause gait impairments and postural instability at later stages of disease. In general, motor symptoms worsen over disease progression and can pose severe functional impairment ultimately. Motor symptom severity is estimated by the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, with higher scores indicating greater motor impairment and disease severity (Goetz et al., 2008).

PD patients also experience a range of non-motor symptoms, many of which precede motor symptoms in the 'pre-motor' phase of the disease such as REM sleep behaviour disorder (RBD; Sauerbier et al., 2016). Virtually every patient experiences some non-motor symptoms, which are a major determinant of health-related quality of life (HrQoL) for patients and their caregivers (Sauerbier et al., 2016). Non-motor symptoms often present in early disease and worsen throughout disease progression. Some non-motor symptoms include apathy, anxiety, depression, sleep disturbances, lower limb pain, olfactory dysfunction, gastrointestinal disturbances (constipation), and fatigue (Sauerbier et al., 2016; Xia & Mao, 2012). These symptoms are not clearly responsive to dopaminergic therapy, and most worsen with disease progression.

1.2.3 Parkinson's disease treatment

Parkinson's disease has no cure. Given that motor symptoms in PD related to dopamine-deficiency to the DS, however, motors symptoms are improved through dopamine supplementation or medications that mimic the effect of dopamine on synaptic receptions (Lee & Yankee, 2022; Rizek et al., 2016).

Dopamine itself cannot easily cross the blood brain barrier, but its precursor, levodopa (L-DOPA) can (Koller & Rueda, 1998; Lee & Yankee, 2022). L-DOPA, when taken orally by patients, is metabolized in the small intestine and is converted to aromatic-L-amino-acid decarboxylase (AADC) and catechol-O-methyltransferase (COMT), which can then be stored in nigrostriatal terminals in the pathways supplying dopamine to the striatum (Lee & Yankee, 2022). Responsiveness to L-DOPA is very good in idiopathic PD, with 80% of patients responding with improvement of motor symptoms such as bradykinesia and rigidity (Lee & Yankee, 2022; Rizek et al., 2016). L-DOPA has a short half-life, so patients are required to take multiple doses throughout the day. However, L-DOPA does have long-term complications, the most common being dyskinesias and motor fluctuations overserved in about 40-50% of patients within five years of chronic L-DOPA treatment (Lee & Yankee, 2022; Rizek et al., 2016).

Dopamine agonists (i.e., rotigotine, pramipexole, apomorphine) are another dopaminergic medication often prescribed to patients with PD. Unlike L-DOPA which is a precursor in the dopamine metabolic pathway, dopamine agonists exert their action on postsynaptic receptors, by-passing the need for dopamine production (Koller & Rueda, 1998; Lee & Yankee, 2022). Apomorphine, a non-selective dopamine agonist, is often used as a drug for patient suffering from motor fluctuations (Lee & Yankee, 2022).

Technological advancements have also led to the development of deep brain stimulation (DBS) surgery for the management of levodopa-responsive symptoms (i.e., tremor, bradykinesia, rigidity). This approach involves delivering unceasing high frequency electrical stimulation to the basal ganglia through electrical probe implants. The primary targets for DBS are the subthalamic nucleus (STN) and globus pallidus interna (GPi) (Lee & Yankee, 2022). Due to the invasive nature of DBS, candidates generally have severe dyskinesia impairing quality of life, medication-resistant tremor,

and have reasonable cognitive function (Rizek et al., 2016). Patients who undergo DBS can sustain benefits for at least 10 years (Rizek et al., 2016).

1.3 Cognition in Parkinson's disease

1.3.1 Epidemiology of cognitive impairment in Parkinson's disease

Cognitive impairment is the most common NMS patients with PD develop throughout disease progression. Cognitive impairment in the form of mild cognitive impairment (PD-MCI), and dementia (PDD) show clear propensity to worsen with disease progression (Aarsland et al., 2021; Poletti et al., 2012; Weintraub et al., 2024). The MDS has published a set of clinical criteria for stages of cognitive decline in PD, to promote uniformity amongst this field of research. Diagnosing PD-MCI is based on the following criteria being met: a) the patient has a diagnosis of PD, b) the patient, informant, or clinician reports a gradual cognitive decline, c) patient shows cognitive impairment on comprehensive neuropsychological testing or a scale of global cognition validated in PD, and d) cognitive impairment is not sufficient to interfere with daily functional independence (Litvan et al., 2012). More specifically, characterizing degree of cognitive impairment for diagnosing PD-MCI has two levels. Level I implies a brief assessment and level II includes a more comprehensive measure with at least two tests for each of the following cognitive domains: executive function, visuospatial, attention, language, and memory (Litvan et al., 2012). If Level II testing can be done, the patient must show impairments in two tests in one cognitive domain or one impaired test in two different cognitive domains to be diagnosed with PD-MCI (Litvan et al., 2012). PD-MCI is considered the prodromal state to PDD and can provide an opportunity to prevent or delay the progression to PDD, as well as to understand the transition from PD-MCI to PDD.

PDD is diagnosed on the following criteria: a) the patient has a diagnosis of PD, b) demonstrates a slow progressive cognitive decline that developed after establishing a PD diagnosis, and c) impairment in more than one cognitive domain and is severe enough to impair daily functional independence (Emre et al., 2007). Additionally, to separate PDD from other dementias, PDD is often diagnosed using the '1-year rule'. Dementia occurring after one-year of motor symptom onset is diagnosed as PDD, whereas dementia

occurring before or within one-year of motor symptoms onset can be diagnosed as another syndrome such as Dementia with Lewy Bodies (DLB) (Aldridge et al., 2018). Both PD-MCI and PDD are associated with HrQoL of both the patient and the caregiver and require early recognition for better management.

Longitudinal investigations suggest that most patients with PD will develop dementia beyond ten years of disease duration (Aarsland et al., 2017; Aarsland et al., 2021).The reported prevalence of cognitive impairment in PD varies widely across studies due to differing criterion for judging impairment, as well as the broad range of patient symptoms in quality and severity, and of disease stage, coupled with small samples relative the vast within-sample heterogeneity (Gonzalez-Latapi et al., 2021). Using the MDS task force level criteria (Emre et al., 2007; Litvan et al., 2012), the incidence of PD-MCI ranges broadly from 21-50% (Baiano et al., 2020; Chung et al., 2014; Hobson & Meara, 2015). In terms of risk factors for MCI, Age, Education (Nicoletti et al., 2019), and more severe motor symptoms (Baiano et al., 2020; Monastero et al., 2018) were associated with PD-MCI prevalence. Interestingly, Sex was a not a predictor for the progression to PD-MCI in newly-diagnosed patients (Monastero et al., 2018). When comparing specific impairments, the most common phenotype amongst patients showing impairments was amnesic MCI multiple domain (Monastero et al., 2018; Nicoletti et al., 2019)

Dementia in PD is four to six times more common than in healthy age-matched controls (HC) (Aarsland et al., 2001), with a lifetime prevalence of up to 80% (Aarsland et al., 2021; Gonzalez-Latapi et al., 2021; Hely et al., 2008; Hoogland et al., 2019). Moreover, patients with PD-MCI show greater conversion to PDD, as expected given that MCI is a risk factor for dementia (Broeders, de Bie, et al., 2013; Hely et al., 2008; Nicoletti et al., 2019).

Though MCI and dementia are clear in PD, whether cognition is altered at the earliest stages of PD remains unclear. Subjective cognitive complaints are common in early PD, sometimes even at disease onset (Weintraub et al., 2024; Erro et al., 2014). Up to one-third patients with PD reported subjective cognitive complaints amongst the top five most bothersome problems, with domains noted by patients including memory,

language, and concentration/attention, even prior to receiving a formal diagnosis of MCI (Weintraub et al., 2024).

Furthermore, even PD patients who do not meet criteria for MCI or dementia evidence objective impairments on cognitive tests relative to HCs (Aarsland et al., 2017, 2021; Broeders, de Bie, et al., 2013; Chaudhary et al., 2020; Chung et al., 2014; Hoops et al., 2009; Pigott et al., 2015; Wang et al., 2015). Cognitive impairment is one of the most intensely studied manifestations of PD (Aarsland et al., 2010; Biundo et al., 2014; Caviness et al., 2007; Cooper et al., 1991; Curtis et al., 2019; Levin et al., 1989; Lin & Wu, 2015). Nearly all cognitive functions have been found to be impaired, using a variety of tests. PD reveal deficits in working memory (Aarsland et al., 2010; Caviness et al., 2007; Chaudhary et al., 2020; Elgh et al., 2009; Kudlicka et al., 2011; Muslimović et al., 2005; Pfeiffer et al., 2014; Wang et al., 2015; Yu et al., 2012), task-shifting (Cools et al., 2003; A. Costa et al., 2003, 2009; Hayes et al., 1998; Lange et al., 1992; Lewis et al., 2005; Shook et al., 2005; Slabosz et al., 2006; Torta et al., 2009), and memory, though encoding versus retrieval processes are not clearly distinguished (Aarsland et al., 2010; Chaudhary et al., 2020; Chung et al., 2014; Levin et al., 1989; Monastero et al., 2018; Pfeiffer et al., 2014); (Siquier & Andrés, 2021; Weintraub et al., 2004). Impairments in learning associations or the encoding aspect of memory appears to be relatively spared in PD. Studies investigating patients that are withdrawn from or not taking dopaminergic medication, encoding and stimulus-reward learning has been reported to be relatively spared (Hiebert et al., 2014, 2019; A. A. MacDonald, Monchi, et al., 2013; P. A. MacDonald et al., 2011; Vo et al., 2014).

Despite these numerous investigations, however, there is considerable inconsistency in this literature, with many failures of replication (Lin & Wu, 2015; Liu et al., 2015a; Oltra, Segura, et al., 2022; Segura et al., 2013; Siquier & Andrés, 2021) have examined cognitive performance averaged across heterogenous disease durations and severity, making it difficult to compare across studies. Given this heterogeneity and the enormity of this literature (Aarsland et al., 2010; Gonzalez-Latapi et al., 2021; Lin & Wu, 2015; P. A. MacDonald & Monchi, 2011), PD patients have been found to perform worse than non-PD individuals in nearly all cognitive domains. Though, there remain many inconsistencies in this literature. Preponderant findings arise from studies averaging

results across PD patients ranging widely in symptom phenotype and disease duration (Broeders, Velseboer, et al., 2013; Cholerton et al., 2018; Hiebert et al., 2019; A. A. MacDonald, Monchi, et al., 2013; Poletti et al., 2012; Wang et al., 2015; Weintraub et al., 2004, 2005), which is problematic as PD subtypes and disease progression impact severity of cognitive impairment and affected domains (Aarsland et al., 2021; Baiano et al., 2020; Chahine et al., 2018; Lin & Wu, 2015; Schrag et al., 2017). Understanding impacts of the heterogeneity of PD symptoms/subtypes and progression on cognition, the problem of convenience samples is amplified by typically small sample sizes (Miah et al., 2012; Shohamy et al., 2005) and a diversity of cognitive tests across studies, many of which are not clinically normed (Oltra, Segura, et al., 2022). Failure to correct for multiple comparisons can inflate cognitive impairments and cause problems with reproducibility in the literature (Aarsland et al., 2009, 2010; Chaudhary et al., 2020; Elgh et al., 2009; Liu et al., 2015a; Poletti et al., 2012; Siquier & Andrés, 2021; Wang et al., 2015, p. 20; Yu et al., 2012). Finally, testing patients who have been treated chronically with dopaminergic therapy (Aarsland et al., 2010; Chaudhary et al., 2020; Cools et al., 2003; A. Costa et al., 2003; Hiebert et al., 2014, 2019; Lewis et al., 2005; A. A. MacDonald, Monchi, et al., 2013; P. A. MacDonald et al., 2011; Shook et al., 2005; Vo et al., 2014), sometimes even while patients are on their usual dopaminergic therapy (Chaudhary et al., 2020; Levin et al., 1989; Monastero et al., 2018; Pfeiffer et al., 2014; Siquier & Andrés, 2021; Yu et al., 2012) poses a significant challenge for interpreting cognitive findings. Receptor, structural, and functional neural changes related to chronic as well as to acute effects of dopamine therapy could underlie or contribute to cognitive effects (Nutt et al., 1997; Stocchi et al., 2001; Zhuang et al., 2013). Some studies test cognition in the OFF and ON dopaminergic states—withholding regular PD medications for durations of 12-18 hours in the former case and instructing patients to take their medications as usual in the latter (Cools et al., 2003; A. Costa et al., 2003, 2009; Hiebert et al., 2014, 2019; Lewis et al., 2005; A. A. MacDonald, Monchi, et al., 2013; P. A. MacDonald et al., 2011; P. A. MacDonald & Monchi, 2011; Shook et al., 2005; Slabosz et al., 2006; Torta et al., 2009; Tremblay et al., 2010; Vo et al., 2014). Though these latter studies allow for disentangling the acute effects of dopaminergic therapy from main

effects of PD and PD x Medication interactions, the confound of neural changes related to chronic dopaminergic therapy in these studies persists.

1.3.2 Effect of dopaminergic medication on cognition in Parkinson's disease

Dopaminergic medications such as L-DOPA and dopamine agonists, commonly prescribed to manage the motor symptoms of PD, are not prescribed to treat PD-MCI or PDD, though these medications do have complex effects on cognition (Kulisevsky, 2000). Previous literature suggests the basal ganglia mediate different elements of cognition (P. A. MacDonald & Monchi, 2011), with dopaminergic input in the striatum mediating the fronto-striatal functions commonly impaired in PD such as executive function, attention, working memory, and visuospatial abilities (Aarsland et al., 2021). The cognitive effect of dopaminergic medication may be a function of the level of dopamine restriction in different parts of the nigrostriatal supplied cortical and sub-cortical structures (Kulisevsky, 2000). Treatment with dopaminergic medication has been reported to either improve, impair, or not impact cognitive function in PD (Chaudhary et al., 2020; Kulisevsky, 2000; A. A. MacDonald, Seergobin, et al., 2013; P. A. MacDonald & Monchi, 2011). Working memory, attentional, and task-shifting abilities, tested both restricted from and given dopaminergic medication, are reported to improve upon dopamine replacement (Cools et al., 2003; A. Costa et al., 2003; Lewis et al., 2005; Shook et al., 2005; Slabosz et al., 2006; Torta et al., 2009). Sequential learning, requiring patients to learn more than 2-3 blocks of simple stimulus-response associations, is impaired in patients restricted from dopaminergic medication but restored when given dopamine replacement (Shohamy et al., 2005). As well, verbal fluency has also been shown to improve after dopamine replacement in patients with PD (Gotham et al., 1988). suggesting an indefinite role of dopaminergic modulation in fronto-striatal executive tasks. Therefore, it is necessary to disentangle effects of dopaminergic therapy on cognition in PD to better understand the true cognitive profile of PD.

1.3.3 Cognitive complaints in PD

Cognitive complaints in patients with PD are very common, often from disease onset. These complains can precede or coincide with the development of PD-MCI or

PDD. A large number of patients with PD who are *clinically* cognitively normal report subjective cognitive complains (SCC) (Barbosa et al., 2019; Pan et al., 2021). Specifically, PD-non-MCI patients have been shown to perform worse in areas of memory, attention, and executive function (Broeders, de Bie, et al., 2013; Chaudhary et al., 2020), however, the effect of dopaminergic medication in these patients has not been tangled out. Yu et al. (2012), also found early-stage patients with PD to perform worse than HCs in executive functions and psychomotor speed, suggesting cognitive changes can be present from early disease. Investigations of early-stage untreated patients with PD also show cognitive impairments compared to HCs (Aarsland et al., 2009; Cooper et al., 1991; Elgh et al., 2009; Liu et al., 2015b; Miah et al., 2012; Muslimović et al., 2005; Poletti et al., 2012). Although important in highlighting the importance of cognitive symptoms from disease onset, these studies present important limitations that will be discussed in the following section.

Owing to the presence of SCCs and reports of worsened cognitive performance in patients with PD compared to HCs, it is necessary to investigate cognitive symptoms present in early untreated patients further. Defining cognitive symptoms present as cognitive impairment in early disease is also controversial. As described above, if patients do not fulfill MDS criteria for PD-MCI diagnosis, they are considered clinically intact. However, patients themselves disagree and comparisons in many studies show that PD patients perform more poorly than healthy controls. In this way, could the sensitivity of the cognitive tests that are used in clinic be the cause for the conclusion that PD patients are generally cognitively intact at disease onset? To test this, we use tests of cognition that are commonly used by clinicians and that are not terribly sensitive. However, we did so in a large enough sample that we had power to detect differences in overall cognition, or cognitive sub-domains, if they exist, ~~t~~to understand the effect of PD in the earliest stages on cognition. The absence of a diagnosis of clinically-significant cognitively impairment could owe to the poverty of our tests, and it does not dimmish the fact that many patients with PD report SCCs (Barbosa et al., 2019; Pan et al., 2021), which have been shown to be associated with functional cognitive impairment at later stages of disease, as well as persist as the disease progresses (Weintraub et al., 2024). Additionally, cognitive function that is clearly worsened compared to age- and education-

matched non-patients is a crucial tool in identifying cognitive symptoms in PD, perhaps more so than formal neuropsychological evaluations that diagnose MCI which is defined at a stage when cognitive performance has already deteriorate to a point that even basic functions of living are beginning to be impacted. Taken together, defining *cognitive changes* in PD, as early as disease onset, is important to understanding just how integral cognitive symptoms are to PD as well as defining the cognitive domains that are most affected to provide a cognitive profile of PD,

1.3.4 Investigation of cognition in *de novo*, medication naïve patients with Parkinson's disease

The only approach that allows unconfounded evaluation of cognition in PD at the time of diagnosis, as a potential onset symptom, as well as to refute any possibility that cognitive changes results from chronic dopaminergic effects, is to evaluate *de novo*, medication naïve PD patients relative to HCs. In the extensive literature in search of understanding the cognitive profile in PD, only a handful of studies have tested cognition in exclusively *de novo* PD patients prior to the introduction of chronic dopaminergic therapy. Few studies have taken this approach.

De novo patients who have not begun chronic dopaminergic therapy, performed worse than controls on tasks of executive function, including working memory, attention, cognitive sequencing, and semantic fluency (Aarsland et al., 2009; Cooper et al., 1991; Elgh et al., 2009). However, each of these studies incorporates some features that make the interpretation of findings somewhat problematic. For example, in Elgh et al. (2009), *n* = 2/88 patients were taking dopaminergic medication. More concerning, however, the Mini Mental Status Exam was used to rule out MCI, which is known to greatly underestimate MCI in PD. Indeed, 30% of their PD sample, who were normal on the MMSE were deemed to have cognitive impairment that reached a clinically meaningful level. The remainder participated in more than 20 cognitive measures, without correcting for multiple comparisons, challenging the interpretations of these findings.

In addition to executive dysfunction, *de novo,* unmedicated patients perform poorly on experimental tests of selective attention/cognitive control such as the Stroop test, in tests of attention and working memory, such as serially-subtracting by 7s and digit span, as well as measures of planning and cognitive controls trail making (Aarsland et al.,

2009; Cooper et al., 1991; Elgh et al., 2009; Miah et al., 2012; Muslimović et al., 2005; Poletti et al., 2012). However, in Muslimović et al. (2005), only 32% of their total sample (n = 115) was unmedicated, the rest had begun dopaminergic medication, thus their results are confounded with medication effects. Moreover, while Miah et al. (2012), consider an entirely *de novo*, untreated group of patients, their sample is relatively underpowered (n = 23).

Memory impairments in immediate and delayed recall were also present in patients with PD compared to HCs (Aarsland et al., 2009; Cooper et al., 1991; Elgh et al., 2009; Poletti et al., 2012), however, these studies still do not compare performance of HCs to that of PD patients who did not also have MCI at baseline. To reiterate, *de novo* patients with parkinsonism who evidence cognitive impairment on formal tests in the range suggestive of MCI could have diseases other than PD, such as DLB. Including these patients in the analyses could mar our understanding of cognition in PD. Moreover, Aarsland et al. (2009), and Poletti et al. (2012), and Cooper et al. (1991), did not correct for multiple comparisons in their analyses, increasing the likelihood of type 1 error and falsely finding differences between PD patients and HCs.

Aarsland et al. (2009), Poletti et al. (2012), and Liu et al. (2015), tested substantial numbers of *de novo*, untreated PD patients but there remain unanswered questions due to some methodological and statistical tactics. Aarsland et al., included a high number of PD-MCI (18.9%) patients in their analyses. This raises concern for the possibility that some patients with DLB patients were included in the sample. This is only discernible with further disease evolution. Despite the high rate of patients scoring in the MCI range, after correcting for Group differences related to depression, and if multiple comparison correction is applied, only measures of verbal learning/memory and Serial 7s were significant, as was a measure of speed of reading and colour-naming without interfering stimuli (i.e., a measure of psychomotor speed/slowing). Poletti et al. (2012), administered an extensive neuropsychological battery, however, they did not measure encoding, an important memory function. Finally, Liu et al. (2015), tested the largest sample of PD patients (n = 414) and they found sex differences on visuospatial and memory batteries. This was mirrored in the HCs with similar sex differences in memory, visuospatial, and attention-processing batteries. This was substantiated by a lack of significant Group x

Sex interaction on any of their measures. Moreover, because their focus was on Sex differences in PD, they did not separately assess cognition of PD-MCI and PD-non-MCI patients relative to performance of HCs. Liu et al. (2015), did not correct for multiple comparisons, which can pose a problem for increasing the chance of Type 1 error. An important domain not directly assessed in any of the above-mentioned studies is learning and encoding abilities. To our knowledge, there have been no investigations of measures that aim to isolate encoding abilities in *de novo*, untreated non-cognitively impaired patients with PD. The profile of cognitive ability, relative to HCs in early-stage (<12 months after disease diagnosis), untreated, PD patients without MCI, is not yet known.

A further issue that needs to be addressed is the problem that statistical methods applied to the study of cognition in PD (i.e., frequentist statistical approaches) have only evaluated cognitive dysfunctions and not functions that are spared (Cholerton et al., 2018). Both components are of clinical importance and therefore developing a full cognitive profile of PD is important. Frequentist approaches, although commonly used, can only are an all-or-none phenomenon and thus only provide probabilities to the data and not the hypotheses themselves (Fornacon-Wood et al., 2022; van den Bergh et al., 2020). Thus, with frequentist approaches we can only reject the null hypothesis based on the probability (i.e., *p*-value) assigned to the data, and more importantly, large *p*-values do not provide evidence for no effect (i.e., accepting the null hypothesis) (Fornacon-Wood et al., 2022). To our knowledge, all studies investigating *de novo* patients with PD have applied frequentist approaches, and thus cannot infer which cognitive functions are spared (Aarsland et al., 2009; Cooper et al., 1991; Liu et al., 2015a; Poletti et al., 2012), though this is important in understanding the cognitive profile of early PD.

Another gap in the literature to understanding the cognitive profile of *de novo* PD is the failure to separate between encoding and retrieval processes in memory paradigms. No study considers encoding, the ability to learn new information and store it in long-term memory, as an independent paradigm (Aarsland et al., 2009; Cooper et al., 1991; Liu et al., 2015a; Poletti et al., 2012). This is problematic, as measuring recall alone does not separate encoded information (i.e., information that was learnt) from retrieval (i.e., how much information is correctly called from long-term memory). This provides a confounded profile of memory impairments or changes in *de novo* PD.

Finally, a gap in the literature investigating the cognitive profile of *de novo* PD is that few studies investigate effects of Age, Education, Anxiety, and Mood differences on cognition. Cooper et al. (1991), and Aarsland et al. (2009), only covaried for depression in their analysis. Whereas Poletti et al. (2012), covary for both age and depression. However, neither of the above-mentioned studies adjust for education or anxiety. Moreover, it is demonstrated that anxiety (Dissanayaka et al., 2017; Ehgoetz Martens et al., 2018) and depression (Norman et al., 2002; Santangelo et al., 2009) impact cognition in PD. Thus, further investigation is needed to understand the differential effects of Age, Education, Anxiety, and Depression on the cognitive profile of *de novo* PD.

1.4 Sex differences in cognition

Sex differences in cognition are present as individuals age normally. Numerous studies have investigated sex differences in cognition in aging. Below we briefly describe a few studies summarizing these cognitive differences, however, due to the focus on PD, an extensive review of sex differences in non-PD older adults is not presented. In two large sample studies of cognitive test performance in older adults, women have been shown to outperform men in verbal learning and memory (Jorm et al., 2004; van Hooren et al., 2007). However, neither of the above-mentioned studies included visuospatial skills, a domain in which men typically have an advantage. In a study of stroke and dementia free US adults, women show higher baseline performance than men in global cognition, executive function, and memory (Levine et al., 2021). Nooyens et al. (2022), investigated cognitive decline in men and women stratified by different birthdate cohorts. Women showed better memory, processing speed, flexibility, and global cognition than men (Nooyens et al., 2022). However, neither Nooyens et al. (2022), nor Levine et al. (2021), investigate visuospatial functions. Studies of clinically normal older adults found women to perform worse than men on visuospatial ability (McCarrey et al., 2016; Munro et al., 2012). Munro et al. (2012), found women and men to perform comparably in attention, category verbal fluency, and executive functioning. Similar results were found in all studies for verbal learning and memory, where women perform better than men (Jorm et al., 2004; Levine et al., 2021; Maller et al., 2007; McCarrey et al., 2016; Munro et al., 2012; van Hooren et al., 2007). Nevertheless, there are important contrasting

findings of note amongst these studies as well. Munro et al. (2012), and van Hooren et al. (2007), show that men and women perform comparable in attention and executive function, however, Levine et al. (2021) show that women perform better in executive function, and Jorm et al. (2004), report men perform better in attentional tasks. Therefore, although there are sex differences in cognition amongst older adults, the studies presented demonstrate that there are replication inconsistences in cognitive performance, specifically in executive function and attentional tasks. It is entirely unclear if executive function and attentional tasks are different between males and females.

The prevalence of PD is almost double in men than in women (Philipe de Souza Ferreira et al., 2022), with the male sex emerging as a risk factor for progression to dementia (Cholerton et al., 2018; Picillo et al., 2022). Male patients with PD have been shown to perform worse than females in global cognition, immediate verbal recall, mental processing speed, semantic verbal fluency, and delayed verbal recall (Bayram et al., 2020; Cholerton et al., 2018; Iwaki et al., 2021; Oltra, Segura, et al., 2022). Further, female patients with PD have been shown to perform worse than males in visuospatial function (Bayram et al., 2020; Cholerton et al., 2018; Gao et al., 2015). However, Cholerton et al. (2018), Gao et al. (2015), and Iwaki et al. (2021), only compare for sex differences amongst patients with PD, therefore lack a comparison with HCs. Thus, neither can conclude if cognition is differentially impacted by sex in PD, or if sex differences present in the PD samples are just representative of differences in HCs. Bayram et al. (2020), and Oltra et al. (2022), compare both PD and HCs for sex differences, however, they find no significant Group x Sex interaction, suggesting that cognition is not differentially affected by sex in PD. Similarly, Liu et al. (2015), contrasted sex differences in early PD and HCs, but found no significant Group x Sex interactions, despite finding differences between men and women in certain cognitive measures. However, there are also contrasting reports of cognitive impairments being more common in female patients than males, with females performing worse in global cognition (Y. Song et al., 2014), visuospatial function, naming, abstraction, and attention (Gao et al., 2015). However, as above-mentioned, Gao et al. (2015), and Song et al. (2014) only compared within patients with PD, and thus lack a comparison is HCs. This deems their findings to be inconclusive about a differential sex effect on cognition in PD

compared to HCs. Therefore, sex differences are an additional heterogeneity in the literature classifying the cognitive profile of early PD. There needs to be direct comparison of PD to HC in a large sample, specifically investigating the Group x Sex interaction to better understand any disproportionate sex effects on cognition that could be attributable to PD pathology and not normal aging.

1.5 Current Study

It is unclear whether cognitive changes leading to impairment occur early in PD or even at PD onset, given conditions that mar interpretation of findings. This literature lacks clarity and certainty due to several factors such as the predominance of convenience samples, confounds related to chronic or even acute dopaminergic therapy, and the non-standardized approach to testing cognition in these studies, which prohibits easy sharing of findings. The cognitive profile in PD seems likely to be multi-domain, with focus on executive, visuospatial, and/or memory processes, based on available evidence and the pathophysiological changes that occur in early PD. Most studies fail to investigate the differential effects of encoding and retrieval processes, which is an aim of the current study. Based on some findings, impairments in attentional processes also occasionally appear in the literature. To understand the cognitive profile in PD, evaluating all broad domains of cognition, in the same participants, at the same time, using a clinically validated, seemed important. Furthermore, given statistical approaches that have to this point been applied, no study has been able to speak truly to spared cognitive processes in PD. This explains the fact that there is often only a mere mention of the domains that were not significantly different between PD patients and comparison groups, without further elaboration. However, to fully apprehend the cognitive profile in PD, we need to uncover impaired as well as spared cognitive functions. The exclusive use, to our knowledge, of Frequentist statistical approaches in this literature, precludes interpreting the results that are not statistically significant given that comparable performance can occur due to determinants that were not controlled by the experimenter and in Frequentist designs, the Type II error rate (i.e., the rate of falsely failing to reject the null hypothesis) is set at 0.20, which means that chance is a very plausible cause of statistically equivalent findings. Toward being able to assert cognitive domains that are truly spared, we plan to

use a Bayesian analysis approach. We were also interested in clarifying whether there were true PD-specific Sex-related cognitive effects, beyond simple Sex effects in all participants, PD and HCs alike, hence we included the Group x Sex interaction as a predictor of our Bayesian models. Finally, we further sought to assess the effects of Age and Education, as well as Anxiety and Depression as potential covariates having impacts on cognition in PD. This allowed us to explore whether the cognitive measures we selected were differentially sensitive to causes known also to affect cognitive performance and whether any of these measures interacted with PD to PD in producing any cognitive deficits. In addition to giving us extra information about the properties of our cognitive measures, this could help us understand whether our PD cognitive profile was disease specific. Finally, we also evaluated the effect of motor symptom severity using the MDS-UPDRS III and of disease duration in months, on cognition in PD patients.

In a large sample of PD-non-MCI, *de novo,* and drug-naïve PD patients (n = 643) and HC (n= 240) participants from the Parkinson's Progression Markers Initiative (PPMI), we compared performance on the Montreal Cognitive Assessment (MoCA), the Hopkins Verbal Learning Test- Revised (HVLT-R; our dissociated measure of memory encoding and retrieval). We also measured Anxiety and Depression given their potential impacts on cognition and possible interaction with PD.

The MoCA has been deemed a good tool for assessing cognition in PD given that it measures multiple domains, not overvaluing the domain of memory. It has good test-retest and interrater reliability, and furthermore, performance on the MoCA correlates well with performance on larger neuropsychological batteries (Gill et al., 2008). It is more sensitive to mild cognitive impairment compared to other screening tools such as the Mini Mental State Exam (MMSE) (Nazem et al., 2009; Vásquez et al., 2019; Zadikoff et al., 2008). Previous work suggests PD patients show impairments in MoCA total and sub-scores of visuospatial abilities, verbal fluency, and delayed recall compared to healthy controls (Luo et al., 2010). Moreover, baseline MoCA performance has also been shown to predict the rate of cognitive decline in PD patients, with patients who have faster-progressing cognitive impairment performing worse on total MoCA, clock drawing, attention, verbal fluency, and abstraction sub-scores compared to patients with

slower cognitive decline (Luo et al., 2010). Furthermore, PD patients with cognitive impairment (i.e., MCI or PDD) score lower on the visuospatial executive, attention, delayed recall, language, and orientation sub-scores than PD patients who are cognitively intact (Hoops et al., 2009; Vásquez et al., 2019). In this way, the MoCA functions not only as a cognitive screening tool, but it also informs and tracks PD-related cognitive impairments across specific domains. Strengths of the MoCA include the facts that it is administered quickly, has clinical validity, and measures cognition across multiple domains in a single test.

The HVLT-R measures memory encoding of an orally presented list of words. Encoding is not assessed by the MoCA. This was the primary motivation for including the HVLT-R in the current study. Furthermore, the HVLT-R allows for a measure that better isolates retrieval from encoding processes. Free recall performance results from the combined influences of memory encoding and retrieval of information that was learned during encoding. Some aspects of the experimental design emphasize the effects of encoding, whereas others stress retrieval processes (A. A. MacDonald, Monchi, et al., 2013; A. A. MacDonald, Seergobin, et al., 2013; P. A. MacDonald et al., 2011). In the HVLT-R, the rate of learning of the repeated list of words provides a measure of encoding, independent of a participant's ability to retrieve words from memory. In contrast, the number of words recalled after a delay, relative to the final number of words successfully recalled in the final IR trial, provides a more isolated measure of retrieval, separate from encoding ability.

The presence of anxiety disorders is widespread in patients with PD, with the average prevalence of anxiety in PD patients being 31% (Broen et al., 2016). The State Trait Anxiety Inventory (STAI) has been extensively for use in healthy non-PD samples as a measure of anxiety, and the MDS recommends the use of the STAI as a screening and outcome measure of anxiety in PD (Leentjens et al., 2008).

Prevalence of depression is much higher in PD patients, with an estimate of 38% (Cong et al., 2022), than the general population (Bromet et al., 2011). The Geriatric Depression Scale (GDS) is shown to work well as a screening tool to distinguish depressed and non-depressed PD patients (Weintraub et al., 2006). The MDS

recommends the use of the GDS in clinical research as a screening instrument for depression (Schrag et al., 2007).

1.5.1 Bayesian Analyses

For all of our analyses, with Group and Sex as predictors and Age, Education, Anxiety, and Depression as covariates, we used model-averaged Bayesian analyses.

Bayesian analysis is a common technique usually applied to statistical problems that aims to develop optimal models that predict real-world data. However, Bayesian analyses can also be used to investigate the effect of including different parameters or predictors in models, on the accuracy of the model to estimate observed data. For Bayesian approaches with multiple predictors (i.e., variables affecting the outcome measure), rather than studying each individual alternate model, we can investigate the effect of any given predictor *averaged over all possible models*. This is known as *Bayesian model-averaging*. Bayesian model-averaging gives the average effect of a predictor across all candidate models.

In model-averaged Bayesian analyses, at the outset, we fix the probability of the effect of including or excluding the predictor, across all possible models, to be equivalent. Effectively this default setting for the *prior inclusion probability* states that any models including the predictor will not have greater accuracy in estimating the actual observed data. Bayesian approaches rely on observed data which is used to continuously update the inclusion probabilities about the effect of the predictor to improve estimation of actual, collected data (van den Bergh et al., 2020). As data accumulate, prior inclusion distributions are updated in terms of models and parameters to jointly achieve the *posterior inclusion probability* for the predictor. The change from the *prior* to the *posterior inclusion probabilities*, is the Bayes Factor for inclusion of the predictor.

The *inclusion Bayes Factor* a) determines whether inclusion of the feature in all models produces an average change in the *posterior inclusion probability* relative to the *prior inclusion probability*, indicated by a value greater than 1, with values below 1 signaling that the data did not change the prior inclusion probability. Unlike frequentist approaches, Bayesian approaches provide a continuous measure of support, and thus are not quantified by imposing an all-or-none cut-off for accepting or rejecting a hypothesis

(van den Bergh et al., 2020). *This allows us to determine whether model performances including or excluding predictors are equivalent (i.e., that the effect of the predictor is null)* and does not simply tell us that we failed to detect a difference, and hence we cannot reject the null, in Frequentist terms. With this approach, we can state the cognitive domains in which PD and HCs perform equivalently and hence we can determine the cognitive functions in PD that are spared as well as impaired. This was our primary motive in applying model-averaged Bayesian analyses.

Inclusion Bayes Factor also b) estimates the magnitude of the averaged effect of including the predictors in all models, with lowest numbers (e.g., < 0.3-0.5) supporting the null hypothesis (i.e., feature does not influence observed outcomes) and highest numbers (e.g., >10-30) indicating strong support. This is an important feature of these analyses in establishing the cognitive domains most or least affected.

1.5.2 Study Purpose

Thus, the objective of this study is to investigate whether cognitive dysfunction is an integral feature of PD through comparing cognitive performance in a cohort of early-disease patients to age- and education- matched HCs. We also aimed to understand the cognitive profile in PD. Using a large sample of PD-non-MCI *de novo*, untreated patients with PD less than one year into disease duration (at the time of testing), we aim to a) investigate cognitive differences in very early PD by comparing to HCs, b) to determine which cognitive domains are disproportionately affected and spared, c) investigate the affect of motor symptom severity and disease duration on cognitive performance, and d) and provide a cognitive profile of early PD that is disentangled from the confounding effects of dopaminergic medication. To our knowledge, no previous study has used such a large sample of *de novo* and drug-naïve patients to investigate cognitive changes in PD prior to the development of clinically diagnosed MCI as early as less than 1 year after diagnosis.

Chapter 2

2 Methods

2.1 Study Design

All data in the current study were collected through the Parkinson's Progression Markers Initiative (PPMI). PPMI is an observational, multi-centred study with an open-access database which includes readily-available information on clinical features, imaging outcomes, genetic markers, and digital markers of PD and its progression from all stages of the disease (*Study Design | Parkinson's Progression Markers Initiative*, n.d.). The dataset provides various disease outcome measures. We focus on select clinical and cognitive measures in this study as will be detailed in subsequent paragraphs in this section.

PPMI's harmonized protocol and standards of operation allow data to be collected across numerous sites internationally and compared as one sample (Marek, 2023). At each visit, participants complete a battery of tests including but not limited to neuropsychological evaluations, clinical measures, motor assessments, imaging, and genetic testing. Participants are followed longitudinally over multiple visits across disease progression changes. In this study, we were only interested in the baseline or screening data, before participants began the use of chronic dopaminergic medication for the management of PD symptoms. This permitted us to evaluate measures of interest, such as cognition, independent of known effects of acute and chronic dopaminergic medication (Chaudhary et al., 2020).

2.2 Participants

Baseline or screening data collected from n= 643 *de novo* patients with PD (n= 231 females) and n= 240 healthy age-matched controls (HC) (n= 89 female) from the PPMI database were included in this study. Only participants who evidenced normal cognition as detailed below, were included in the analyses. Participating PPMI sites received ethical approval from their respective ethics review boards. All participants provided written informed consent to participate in this study in accordance with the current Good Clinical Practice (GCP) regulations and International Conference on

Harmonization (ICH), and local regulatory requirements. We obtained permission to perform the current study from PPMI.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria to participate in this study for the patient group was a) a PD diagnosis ≤ 12 months. Exclusion criteria for the patient group were a) introduction of dopaminergic medications for the treatment of PD symptoms, and b) genetic variants of PD (LRRK2, SNCA, GBA, PARKN, PINK1), and c) presence or history of another serious neurological disease, including dementia, or systemic comorbidity, other than PD. Exclusion criteria for the HC group were a) first degree relative with PD, b) presence or history of any serious neurological disease, including dementia, or systemic comorbidity. An additional inclusion criterion for inclusion in our analysis for both PD and HC was a MoCA total score ≥ 24, to screen individuals out for mild cognitive impairment (MCI). This has been recommended as the cut off for MCI based on meta-analysis as it has been shown to improve diagnostic accuracy and reduce false positive rates (Carson et al., 2018). Thus, 9.4 % (n = 67/710) of PD and 1.2 % (n = 3/243) of HCs participants were excluded from our analyses due to MoCA Total scores < 24/30.

2.4 Clinical and Cognitive Measures

All participants completed a battery of clinical, genetic, imaging, and neuropsychological evaluations, as per the PPMI protocol (Marek, 2023), with many measures repeated at study visits. Data collection of all measures at each visit could be distributed across multiple days. However, these days were sufficiently close in time that they constituted a single visit. For the purposes of this study, we consider only the Screening or Baseline visit, and data collection procedures on selected clinical and neuropsychological evaluations will be described in subsequent paragraphs.

As per PPMI protocol, at the time of Screening (SC) or Baseline (BL) visits, all patients were dopamine-therapy naïve. That is, no patients had yet begun taking chronic dopaminergic medication for the management of PD symptoms. Furthermore, no HC participants were taking dopaminergic therapy. In this way, we analyzed measures in participants who were successfully enrolled in the PPMI study, had completed a SC or BL visit, were reporting no current or previous use of chronic dopaminergic medication

at the time of their testing, and for PD patients, they were evaluated within 12 months of their diagnosis.

The following paragraphs describe the clinical and cognitive measures from the PPMI database that were included in our analyses in this study.

2.4.1 MDS-UPDRS Part III – Motor Assessment

Participants completed the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Motor Assessment at the SC or BL visit (Goetz et al., 2008). MDS-UPDRS Part III is a standardized clinical assessment of motor signs of PD, which measures the presence and severity of PD motor manifestations including but not limited to speech production, facial expression, fine motor functions of the upper and lower limbs, gait, postural stability, as well as postural, kinetic, and rest tremors (Goetz et al., 2008). The MDS-UPDRS Part III comprises 18 items, with 33 specific measures related to scoring some items bilaterally and/or axially, whereas other items include a summary of bilateral and axial findings (e.g., global rating of hypokinesia/bradykinesia). Each of these 33 aspects of movement that are measured are scored on a scale ranging from 0-4, with 0 indicating no manifestation of disease and 4 indicating very severe disease, in some cases indicating total disability of the assessed function, for a maximal total possible score on the UPDRS-III of 132 (Goetz et al., 2008). The higher the overall score, the more severe the PD motor dysfunction (Skorvanek et al., 2017).

2.4.2 Montreal Cognitive Assessment

Participants also completed the Montreal Cognitive Assessment (MoCA), a widely used screening tool used to assess cognitive function in many neurological disorders including PD (Nasreddine et al., 2005; Vásquez et al., 2019). The MoCA is scored out of 30 and has been divided by the authors into the following sub-scales: visuospatial-executive (e.g., trail making, clock drawing), naming (e.g., identifying animals based on their drawing), attention (e.g., digit span forward and backward), language (e.g., verbal fluency), abstraction (e.g., identifying the semantic relation

between two items), delayed recall (e.g., recall of a list of words after a short delay), and orientation (e.g., participant's awareness of where s/he is in time and space).

2.4.3 Hopkins Verbal Learning Test- Revised

In addition to the MoCA, a subset of participants performed the Hopkins Verbal Learning Test- Revised (HVLT-R). The HVLT-R is a short verbal learning and memory test that is easy to administer, providing measures of memory encoding, recall, and recognition (Benedict et al., 1998). In this test, an examiner reads a list of 12 target words belonging to three semantic categories, after which, participants immediately freely recall as many words as possible. This constitutes the first Immediate Recall (IR) trial. This process is repeated two more times, with the examiner reading the same list of target words on each trial. Following a delay of 20-25 minutes, from the third and final IR trial (i.e., HVLT-R IR Trial 3), participants are asked to freely recall as many words as possible from the list of target words, constituting the Delayed Recall trial. A recognition memory phase follows the Delayed recall trial, which we have not included in our analysis. In the HVLT-R, the rate of learning of the repeated list of words provides a measure of encoding, independent of a participant's ability to retrieve words from memory. In contrast, the number of words recalled after a delay, relative to the final number of words successfully recalled in HVLT-R IR Trial 3, provides a more isolated measure of retrieval (i.e., HVLT-R Retrieval), separate from encoding ability.

2.4.4 State Trait Anxiety Inventory

As per the PPMI protocol, participants completed the State-Trait Anxiety Inventory (STAI; Skapinakis, 2014) at their BL visit. The STAI is a 40-item self-administered questionnaire that aims to assess both state and trait anxiety. State anxiety is considered to be a transitory emotional condition, whereas trait anxiety is a more stable personality characteristic that can predispose individuals to experience anxiety at baseline as well as in stressful situations (Skapinakis, 2014). The STAI consists of two sub-scores, the state anxiety (S-anxiety) and trait anxiety (T-anxiety) scales, each consisting of 20 items. The S-anxiety scale consists of questions related to unpleasant feelings of tension, worry, nervousness, and physiological manifestations of anxiety specifically describing

how the participant feels in the moment (e.g., “I feel calm”, “I feel nervous”, or “I feel jittery”) (Skapinakis, 2014). The T-anxiety scale asks questions related to more stable aspects of anxiety proneness and tendencies to perceive situations as threatening (i.e. “I am calm, cool, and collected”, “I am happy”, “I worry too much over something that really doesn’t matter”; Skapinakis, 2014). Each item on both sub-scales is answered on a 4-point Likert scale with a range from 1 (“not at all” for S- or “almost never” for T-anxiety) to 4 (“very much so” for S- or “almost always” for T-anxiety) (Skapinakis, 2014). Scores in each sub-scale range from 20-80, with a higher score indicating more severe anxiety. Scores ranging between 20-37 are considered ‘little to no anxiety’, scores between 38-44 are considered as having ‘moderate anxiety’, and scores above 45 are interpreted as having ‘high anxiety’ (Kayikcioglu et al., 2017).

2.4.5 Geriatric Depression Scale- Short

As part of the PPMI protocol, participants completed the Geriatric Depression Scale (GDS; (Yesavage & Sheikh, 1986) short version at BL visit to assess for depression symptoms. The GDS short is a screening questionnaire consisting of a series of 15 yes/no answer items and can be either researcher- or self-administered. Questions relate to feelings of contentment, satisfaction, worth, helplessness, and overall quality of life (e.g., “Are you basically satisfied with your life”, “Do you feel happy most of the time”, “Do you feel your situation is hopeless”), with total scores ranging from 0-15. Scores ranging from 0-4 suggest no concern for depression, however scores greater than or equal to 5 suggest potential mild depression. With greater scores suggesting greater severity of depression (Greenberg, 2007).

2.5 Statistical Analysis

2.5.1 Outcome measures from the MoCA data

The MoCA was administered and scored by the PPMI research personnel, and results were available to the open-source database in an Excel spreadsheet. To avoid learning effects, the MoCA was not administered at both SC and BL visits, as these were approximately within 60 days of one other. A total of n = 643 PD patients and n = 240

HC were tested. The following measures were included in our analyses: a) MoCA total score (out of 30), b) MoCA Executive sub-score, consisting of the trail making, verbal fluency, and abstraction items (out of 4), c) MoCA Visuospatial sub-score, consisting of the cube drawing and clock items (out of 4), d) MoCA Language sub-score, comprising the animal naming and sentence repetition measures (out of 3), e) MoCA Attention consisting of digit span, serial subtraction by seven, and a finger-tapping vigilance test, (out of 6), f) MoCA Recall, consisting of delayed free recall of words (out of 5), and g) MoCA Orientation subscale to time and place (out of 6). This assembly of MoCA subscales assessing six cognitive domains, thus forming the six-factor model, was originally proposed by Nasreddine et al. (2005), and further validated using Construct Factor Analysis (Freitas et al., 2012) and the Rasch Partial Credit Model (Freitas et al., 2015). These latter studies demonstrate the psychometric adequacy of the six-factor model grouping of the items on the MoCA into the cognitive domains described above and validate its use in discriminating between clinical and control populations. Figure 1 presents the ensemble of measures for each sub-score from the MoCA used for our analyses.

2.5.2 Outcome measures from the HVLT-R Data

The HVLT-R was administered and scored by the PPMI research personnel and was available to the open-source database in an Excel spreadsheet. HVLT-R performance scores for all participants were extracted. Data from a subset of participants who completed both the MoCA and HVLT-R, a total of $n = 611$ patients with PD and $n = 240$ HC, were also analyzed. We derive a measure of encoding in the HVLTR-R by calculating the slope of the change in the number of words recalled across the three IR trials. The words, read aloud by the experimenter, were the same on each trial and therefore the increase in number of words recalled probed encoding processes, given that the retrieval pressures on the immediate recall trials should have been similar. To calculate the slope, we used the =SLOPE() function in Microsoft Excel Version 2404. This function generates the slope for the line of best fit over the three data points: IR Trial 1, IR Trial 2, and IR Trial 3. The formula for slope calculation was as follows:

$$slope = \frac{\left(\text{slope}_{IR\ Trial\ 3-IR\ Trial\ 2}\right) + \left(\text{slope}_{IR\ Trial\ 2-IR\ Trial\ 1}\right)}{2}$$

$$slope = \frac{\left(\frac{IR\ Trial\ 3 - IR\ Trial\ 2}{3-2}\right) + \left(\frac{IR\ Trial\ 2 - IR\ Trial\ 1}{2-1}\right)}{2}$$

The slope for learning new items across trials provided a more targeted estimate of memory encoding processes (i.e., HVLT-R Slope). To investigate whether the possibility that effects on slope could result from participants reaching ceiling (i.e., twelve words) on IR Trial 3, which would obviously blunt the slope at different rates related to Group or Sex, we also investigated absolute number of items recalled on IR Trial 3 (i.e., HVLT-R IR Trial 3). Thus, we used two measures of encoding in our study, the slope and the absolute learning score at IR Trial 3. We further evaluated memory retrieval processes by subtracting the total number of words freely recalled after a delay of 20-25 minutes from the total number of words encoded and immediately, freely recalled on IR Trial 3—the final IR trial (i.e., HVLT-R Retrieval). This relative measure was intended to isolate retrieval processes, correcting for differences between individuals and groups in terms of encoding capabilities.

2.5.3 Statistical Analyses

We used the Bayesian approach to assess the likelihood that Group (PD vs. HCs), Sex (F vs. M), Group x Sex interaction, Age, and Education affect cognitive performance using the MoCA and the HVLT-R.

For the MoCA and HVLT-R measures, all demographic and clinical variables (i.e., Age, Education, STAI-T and GDS) were assessed in 2 x 2 factorial analyses of variance (ANOVAs) with Group (PD vs. HC) and Sex (Female vs. Male) as between-subject factors. For all ANOVAs, α was set at $p < 0.05$.

We performed two-way model-averaged Bayesian Analyses of Covariance (ANCOVAs) with Group (PD vs. HCs) and Sex (F vs. M) as between-subject factors, and Age and Education as covariates on a) MoCA total score, and b) MoCA Executive, c) MoCA Visuospatial, d) MoCA Language, e) MoCA Attention, f) MoCA Recall, and g) MoCA Orientation, h) HVLT-R Slope, i) HVLT-R IR Trial 3, and j) HVLT-R Retrieval measures. Given known effects of anxiety and depression on cognition and expected

differences in these symptoms in PD patients and HCs, we performed these ANCOVAs with and without the STAI-T and GDS scores—measures of anxiety and depression, respectively—as covariates, in case they impacted cognitive performance. We performed analyses with and without outlier removal, using +/-2.5 SD from Group and Sex means. For simplicity, we planned to report these results without STAI-T and GDS and without outlier removal if these had no impact on results.

All analyses were performed using JASP version 0.18.3.0. For each ANCOVA, we report the prior inclusion [P(incl)] and exclusion [P(excl)] probabilities, which were set using the default in JASP to designate predictors as having 'no effect' in estimating the observed data. Posterior inclusion [P(incl|data)] and exclusion [P(excl|data)] probabilities represent the average effect of all models that include versus exclude predictors/covariates, in accurately estimating the scores and measures obtained as our dependent variables. The Bayes Factor for inclusion (BF_{incl}) indicates whether a change in predictors' probabilities from the P(incl) to the P(incl|data) has occurred, based on model-averaged effects, estimating observed outcomes. $BF_{incl} < 1$ indicates that the P(incl|data) for predictors based on observed data are unchanged relative to their P(incl). $BF_{incl} > 1$ indicates that the outcome data have rendered different the P(incl|data) for predictors relative to the P(incl). BF_{incl} also provides information about the magnitude of effects. BF_{incl} associated with lowest numbers (e.g., < 0.3) strongly support the null hypothesis (i.e., no influence of predictor on observed outcomes; P(incl) and P(incl|data) are equivalent), and highest numbers (e.g., >10-30) indicate strong support for the alternative hypothesis (i.e., effect of predictor on observed outcomes; P(incl) and P(incl|data) are different).

We also investigated the effect of PD a) motor severity, estimated with MDS-UPDRS Part III scores, and b) disease duration, measured as the time in months since receiving a PD diagnosis relative to study date. Toward these goals, we correlated MDS-UPDRS Part III scores and Months since diagnosis with a) MoCA total score, and b) MoCA Executive, c) MoCA Visuospatial, d) MoCA Language, e) MoCA Attention, f) MoCA Recall, and g) MoCA Orientation sub-scores, as well as a) HVLT-R Slope, b) HVLT-R IR Trial 3, and c) HVLT-R Retrieval measures. We set the α level for

significance at $p< 0.05$. We applied a Bonferroni correction ($p_{adjusted}$ <0.005), correcting family-wise, for multiple comparisons.

Figure 1 shows the design of this study and the data analysis plan.

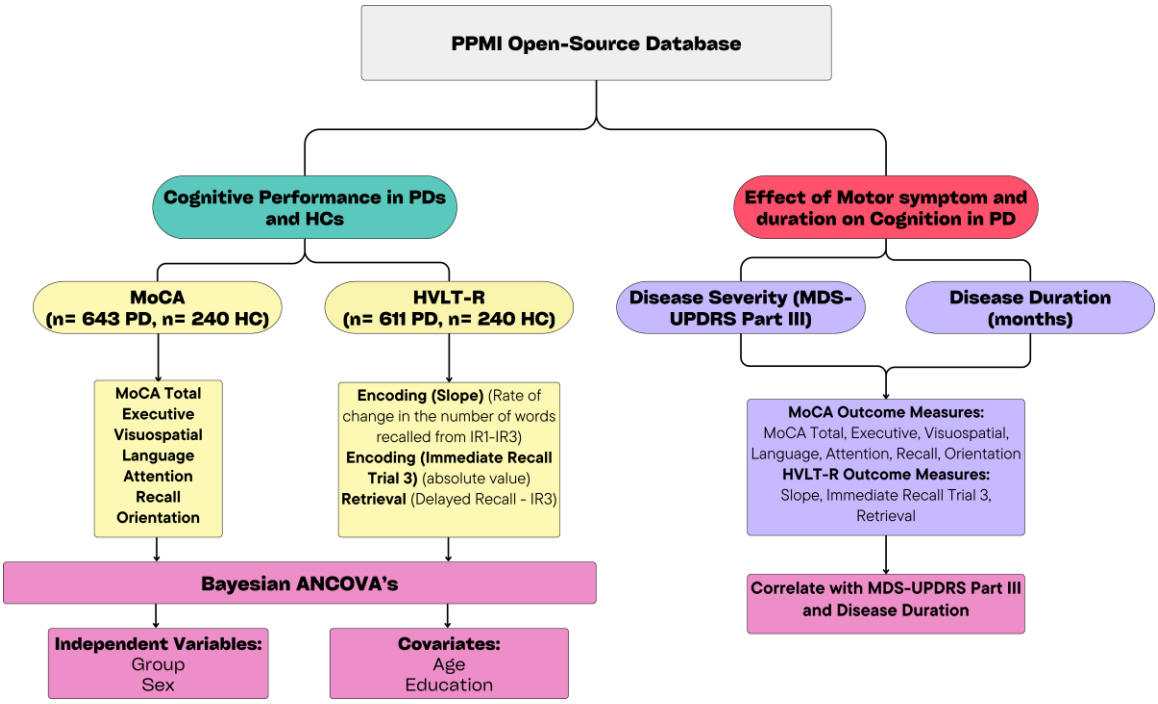

Figure 1. Flow chart illustrating Group stratification and planned analyses.

11 independent model-averaged Bayesian ANOVAs were run on MoCA Total and subscores and HVLT-R measures. These measures were correlated with MDS-UPDRS III and Months since diagnosis.

Chapter 3

3 Results

3.1 Demographic and Clinical Features

Tables 1 and 2 present demographic and clinical features with means [± Standard Deviation (SD)] for PD and HCs, separated by Sex. Table 1 presents descriptive variables for patients who completed the MoCA. Table 2 presents descriptive variables for the large subset of patients who completed both the MoCA and the HVLT-R. For the MoCA participants and the MoCA + HVLT-R participants, separately, all variables were assessed in 2 x 2 factorial Analyses of variance (ANOVAs) with Group (PD vs. HC) and Sex (Female vs. Male) as between-subject factors. For all ANOVAs, α was set at $p < 0.05$, correcting for family-wise multiple comparisons.

There were no significant main effects of Group, F (1, 881) = 0.349, $p > 0.05$, or Sex F (1, 881) = 2.48, $p > 0.05$, nor a significant Group x Sex interaction, F (1, 881) = 0.857, $p > 0.05$, in terms of age in those participants who completed the MoCA (Table 1). There was no significant effect of Group (F (1, 881) = 0.103, $p > 0.05$), or significant Group x Sex interaction effect, F (1, 881) = 1.995, $p > 0.05$, on years of education achieved in participants who completed the MoCA. We did find a significant main effect of Sex (F (1, 881) = 10.579, $p = 0.001$, $\eta^2_p = 0.012$) on years of education, with lower levels of educational achievement in female [*M(±SEM)* = 15.65 (3.276)] relative to male [*M(±SEM)* = 16.304 (3.135)] participants.

As expected, given that anxiety and depression are symptoms of PD, there were significant Group differences in STAI-S scores, F (1, 881) = 48.612 , $p < .001$, η^2_p = 0.052, STAI-T scores, F (1, 881) = 25.325, $p < .001$, $\eta^2_p = 0.028$, and GDS scores, F (1,881) = 27.727, $p <.001$, $\eta^2_p = 0.031$, in participants who completed the MoCA (Table 1). These main effects were due to higher STAI-S, STAI-T, and GDS scores in PD patients, [*M(±SEM)* = 32.378 (10.050), *M(±SEM)* = 31.68 (9.082), and *M(±SEM)* = 2.299 (2.629)] respectively, compared to HC participants, [*M(±SEM)* = 27.275 (7.590), *M(±SEM)* = 28.275 (7.174), and *M(±SEM)* = 1.212 (2.086)] respectively. There was a significant effect of Sex in STAI-T scores F (1, 881) = 6.206, $p = 0.013$, $\eta^2_p = 0.007$, but

not in STAI-S F (1, 881) = 0.556, $p > 0.05$, or GDS scores F (1, 881) = 0.85, $p > 0.05$ (Table 1). This was due to higher STAI-T scores in female, [*M(±SEM)* = 31.762 (9.464)], compared to in male, [*M(±SEM)* = 30.181 (8.244)], participants. There was no significant Group x Sex interaction on STAI-S scores F (1, 881) = 0.090, $p > 0.05$, STAI-T scores (F (1, 881) = 0.041, $p > 0.05$), or in GDS scores F (1, 881) = 1.196, $p > 0.05$.

Table 1. Demographics and clinical measures for patients with PD and HCs who have completed the MoCA separated by sex.

		PD (n= 643)	HC (n= 240)	P_{Group}	P_{Sex}	$P_{Group\ x\ Sex}$
Age						
	f	62.139 (9.166)	61.056 (9.969)	0.555	0.116	0.355
	m	62.602 (8.694)	62.841 (9.542)			
Education						
	f	15.771 (3.356)	15.337 (3.052)	0.748	**0.001**	0.158
	m	16.231 (3.172)	16.503 (3.035)			
Disease duration (m)						
	f	4.965 (3.153)	--	--	--	--
	m	3.893 (3.084)				
MDS-UPDRS Part III (/132)						
	f	21.597 (9.422)	--	--	--	--
	m	21.442 (9.113)				
STAI -S (/80)						
	f	32.874 (10.418)	27.483 (8.064)	**< .001**	0.456	0.765
	m	32.100 (9.839)	27.152 (7.322)			
STAI-T (/80)						
	f	32.667 (9.753)	29.416 (8.268)	**< .001**	**0.013**	0.84
	m	31.126 (8.646)	27.603 (6.377)			
GDS (/15)						
	f	2.277 (2.662)	1.461 (2.523)	**< .001**	0.357	0.274
	m	2.311 (2.614)	1.066 (1.773)			

Note. Values are presented as Means (+/-SD). Age is presented in years. Education represents years of education completed by participant. Disease duration is presented in months. MDS-UPDRS Part III = Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III, with a total possible score of 132. STAI-T= State Trait Anxiety Inventory- Trait, with a total possible score of 40. GDS= Geriatric Depression Scale, with a total possible score of 15. *p*-values arise from 2 x 2 factorial ANOVAs, with between-subject factors of Group (PD vs. HCs) and Sex (Female vs. Male).

Analogously, in the participants who completed the MoCA and HVLT-R (Table 2), there were no significant main effects of Group, F (1, 849) = 0.121, $p > 0.05$, or Sex, F (1, 849) = 2.857, $p > 0.05$, nor a significant Group x Sex interaction, F (1, 849) = 0.625, $p > 0.05$, in terms of age. There was no significant effect of Group F (1, 849) = 0.217, $p > 0.05$, or significant Group x Sex interaction, F (1, 849) = 2.508, $p > 0.05$, on years of education achieved in participants who completed the MoCA and the HVLT-R. We did find a significant main effect of Sex F (1, 849) = 9.219, $p = 0.002$, $\eta^2_p = 0.011$ on education, with fewer years of education in female [*M(±SEM)* = 15.702 (3.288)] relative to male [*M(±SEM)* = 16.299 (3.125)] participants.

As expected, given that anxiety and depression are symptoms of PD, there were significant Group differences in STAI-S scores F (1, 849) = 49.905, $p < .001$, $\eta^2_p = 0.056$, STAI-T scores F (1, 849) = 24.994, $p < .001$, $\eta^2_p = 0.029$, and GDS scores F (1, 849) = 25.748, $p < .001$, $\eta^2_p = 0.03$, in participants who completed the MoCA and HVLT-R (Table 2). These main effects were due to higher STAI-S, STAI-T, and GDS scores in PD patients, [*M(±SEM)* = 32.463 (10.035), *M(±SEM)* = 31.651 (9.036), and *M(±SEM)* = 2.27 (2.610)] respectively, compared to HCs [*M(±SEM)* = 27.275 (7.590), (*M(±SEM)* = 28.275 (7.174), and *M(±SEM)* = 1.212 (2.086)] respectively. There was a significant effect of Sex in STAI-T scores F (1, 849) = 6.157, $p = 0.013$, $\eta^2_p = 0.007$, but not in STAI-S F (1, 849) = 0.571, $p > 0.05$, or GDS scores F (1, 849) = 0.632, $p > 0.05$ (Table 2). This was due to higher STAI-T scores in female, [*M(±SEM)* = 31.699 (9.384)] compared to male, [*M(±SEM)* = 30.149 (8.228)] participants. There was no significant Group x Sex interaction on STAI-S F (1, 849) = 0.097, $p > 0.05$, STAI-T scores, F (1, 849) = 0.042, $p > 0.05$, or in GDS scores, F (1, 849) = 1.485, $p > 0.05$.

Table 2. Demographics and clinical measures for patients with PD and HCs who have completed the MoCA and HVLT-R, separated by sex.

		PD (n= 611)	HC (n= 240)	P_{Group}	P_{Sex}	$P_{Group\ x\ Sex}$
Age						
	f	62.000 (9.166)	61.18 (9.995)	0.728	0.091	0.429
	m	62.648 (8.677)	62.967 (9.541)			
Education						
	f	15.854 (3.376)	15.337 (3.052)	0.641	**0.002**	0.114
	m	16.221 (3.172)	16.503 (3.035)			

Disease duration (m)						
	f	4.981 (2.818)	--	--	--	--
	m	5.113 (2.859)				
MDS-UPDRS Part III (/132)						
	f	21.789 (9.350)	--	--	--	--
	m	21.714 (8.928)				
STAI-S (/80)						
	f	32.981 (10.383)	27.483 (8.064)	**< .001**	0.450	0.755
	m	32.186 (9.845)	27.152 (7.322)			
STAI-T (/80)						
	f	32.653 (9.672)	29.416 (8.268)	**< .001**	**0.013**	0.838
	m	31.116 (8.642)	27.603 (6.377)			
GDS (/15)						
	f	2.216 (2.617)	1.461 (2.523)	**< .001**	0.427	0.223
	m	2.299 (2.610)	1.066 (1.773)			

Note. Values are presented as Means (+/-SD). Age is presented in years. Education represents years of education completed by participant. Disease duration is presented in months. MDS-UPDRS Part III = Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III, with a total possible score of 132. STAI-T= State Trait Anxiety Inventory- Trait, with a total possible score of 40. GDS= Geriatric Depression Scale, with a total possible score of 15. *p*-values arise from 2 x 2 factorial ANOVAs, with between-subject factors of Group (PD vs. HCs) and Sex (Female vs. Male).

3.2 Investigating the effects of Group, and Sex on MoCA and HVLT-R

We performed two-way Bayesian ANCOVAs to assess the effects of Group (PD vs. HC), Sex (Female vs. Male), and Group x Sex interaction, with Age and Education as covariates on cognitive performance measured with the MoCA (i.e., MoCA total, MoCA subscores) and HVLT-R (i.e., HVLT-R Slope, IR Trial 3, and HVLT-R Retrieval measures). As we had planned, we also performed these ANCOVAs a) with and without STAI-T and GDS as covariates, given that anxiety and depression are symptoms of PD, and the potential impact of these symptoms on cognition, and b) with and without outlier removal using Group and Sex means +/-2.5 SD cutoffs. The results were invariant whether or not we included STAI-T or GDS as covariates, and whether or not these analyses were performed on data with outlier removal. Hence, for the sake of simplicity,

we report the results without STAI-T and GDS as covariates, and on data without outlier removal below.

In Tables 3-7, we present the P(incl) and P(excl)—the prior probabilities for including or excluding predictors, P(incl|data) and P(excl|data)—posterior probabilities calculated based on observed data when predictors were included or excluded, and $BF_{incl.}$—the magnitude of the change from the prior to the posterior inclusion probabilities, for all predictors on MoCA and HVLT-R measures. Figure 2 presents the cognitive measures where impairments were evident for PD patients relative to HCs, as well as histograms of these measures. Figure 3 presents the cognitive measures, and accompanying histograms, for which Sex was a predictor that increased accuracy in predicting observed results.

3.2.1 Effect of Group on MoCA and HVLT-R

In model-averaged Bayesian ANCOVAs with Group (PD vs. HCs) and Sex (Female vs. Male) as between-group factors, and Age and Education as covariates, we found models that included Group as a predictor provided superior estimates of observed data, relative to models that excluded Group, in the following measures: a) MoCA total (BF_{incl} = 669.375), b) MoCA Executive (BF_{incl} = 36.67), c) MoCA Recall (BF_{incl} = 3.397), and d) HVLT-R Retrieval measure (BF_{incl} =8.433). In all cases, PD worsened performance on these measures, with large effect sizes. BF_{incl} indicates the number of times more likely models containing Group, relative to models excluding it, accurately predicted observed scores. In contrast, scores observed on all other cognitive measures (MoCA subscales: Visuospatial, Language, Attention, Orientation, HVLT-R Slope measure, IR Trial 3) were not more likely to be predicted by models including than excluding Group as a parameter. In these cases, the null hypothesis was supported. Hence, PD patients and HCs performed equivalently on these measures of cognition. Table 3 presents the effect of Group on all cognitive measures. For summary, Figure 2 presents the measures in which PD altered cognitive performance. We present accompanying histograms to reveal the distribution of the results for PD vs. HCs.

Table 3. Model-averaged Bayesian effects of Group on MoCA Total and subscores, as well as HVLT-R performance.

	P(incl)	P(excl)	P(incl|data)	P(excl|data)	BF_{incl}
MoCA Total	0.4	0.4	0.769	0.001	**669.375**
Executive	0.4	0.4	0.892	0.024	**36.67**
Visuospatial	0.4	0.4	0.116	0.879	0.132
Language	0.4	0.4	0.098	0.901	0.108
Attention	0.4	0.4	0.125	0.873	0.143
Recall	0.4	0.4	0.651	0.197	**3.297**
Orientation	0.4	0.4	0.141	0.856	0.165
Slope	0.4	0.4	0.272	0.725	0.376
IR Trial 3	0.4	0.4	0.228	0.734	0.31
Retrieval	0.4	0.4	0.815	0.097	**8.433**

Note. All predictors of interest are listed in the Effects column. P(incl) and P(excl) show the prior probabilities of the effect of including or excluding the predictor. We computed inclusion/exclusion probabilities using matched models only, such that all models with the interaction effect were compared to models with the same predictors excluding the interaction effect. P(incl|data) and P(excl|data) shows the posterior inclusion and exclusion probabilities, respectively. This represents the average effect of all models that include versus exclude predictors in estimating the observed outcomes. BF_{incl} is the Bayes Factor for inclusion of the predictor across all averaged models, quantifying the change from prior to posterior inclusion probabilities. Values >1 represent the number of times more likely that models including versus excluding Group as a parameter, accurately predicted the observed data.

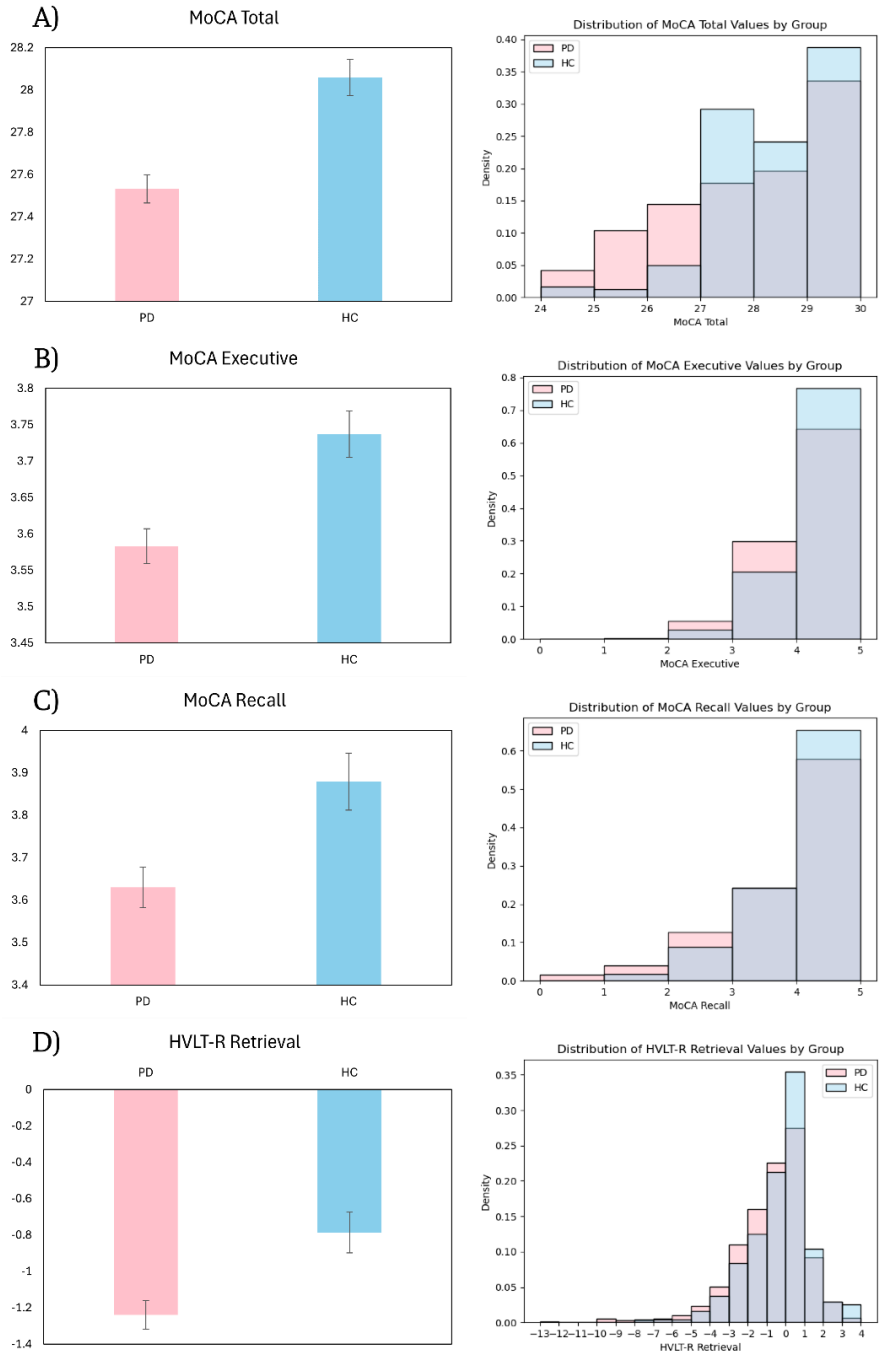

Figure 2. Mean (±SEM) scores and density distributions comparing performance on cognitive measures affected by Group (PD vs. HC).
Left panels represent mean values for each score on the y-axis, and right panels represent a histogram of density distributions for each score on the y-axis. A) Montreal Cognitive Assessment (MoCA) Total with a maximum attainable score of 30, B) MoCA Executive subscore with a maximum attainable score of 5, C) MoCA Recall subscore with a maximum attainable score of 5, and D) Hopkins Verbal Learning Test-Revised (HVLT-R) Retrieval measure. HVLT-R Retrieval was calculated as the difference in the Delayed Recall and Immediate Recall Trial 3 scores. Negative values indicate the number of words 'forgotten'. MoCA n_{PD} = 643, HVLT-R n_{PD} = 611, n_{HC}= 240.

3.2.2 Effect of Sex on MoCA and HVLT-R

Models including, versus excluding, Sex as a parameter, more reliably predicted the scores obtained on a) MoCA Total (BF_{incl} = 14.304), b) MoCA Recall (BF_{incl} = 15762.93), c) HVLT-R IR Trial 3 (BF_{incl} = 910303.8), and d) HVLT-R Retrieval (BF_{incl} = 6.681). Females performed better, on average, than males using these tests. Table 4 presents the effect of Sex on all cognitive measures. For summary, Figure 3 presents the measures, with accompanying histograms revealing distribution of results, in which Sex altered cognitive performance.

Table 4. Model-averaged Bayesian effects of Sex on MoCA Total and subscores, as well as HVLT-R performance.

	P(incl)	P(excl)	P(incl|data)	P(excl|data)	BF_{incl}
MoCA Total	0.4	0.4	0.72	0.05	**14.304**
Executive	0.4	0.4	0.184	0.733	0.251
Visuospatial	0.4	0.4	0.306	0.689	0.445
Language	0.4	0.4	0.075	0.924	0.082
Attention	0.4	0.4	0.114	0.884	0.129
Recall	0.4	0.4	0.848	5.378×10^{-5}	**15762.931**
Orientation	0.4	0.4	0.129	0.868	0.149
Slope	0.4	0.4	0.082	0.916	0.089
IR Trial 3	0.4	0.4	0.962	1.056×10-6	**910303.843**
Retrieval	0.4	0.4	0.793	0.119	**6.681**

Note. All predictors of interest are listed in the Effects column. P(incl) and P(excl) show the prior probabilities of the effect of including or excluding the predictor. We computed inclusion/exclusion probabilities using matched models only, such that all models with the interaction effect were compared to models with the same predictors excluding the interaction effect. P(incl|data) and P(excl|data) shows the posterior inclusion and exclusion probabilities, respectively. This represents the average effect of all models that include versus exclude predictors in estimating the observed outcomes. BF_{incl} is the Bayes Factor for inclusion of the predictor across all averaged models, quantifying the change from prior to posterior inclusion probabilities. Values >1 represent the number of times more likely that models including versus excluding Sex as a parameter, accurately predicted the observed data.

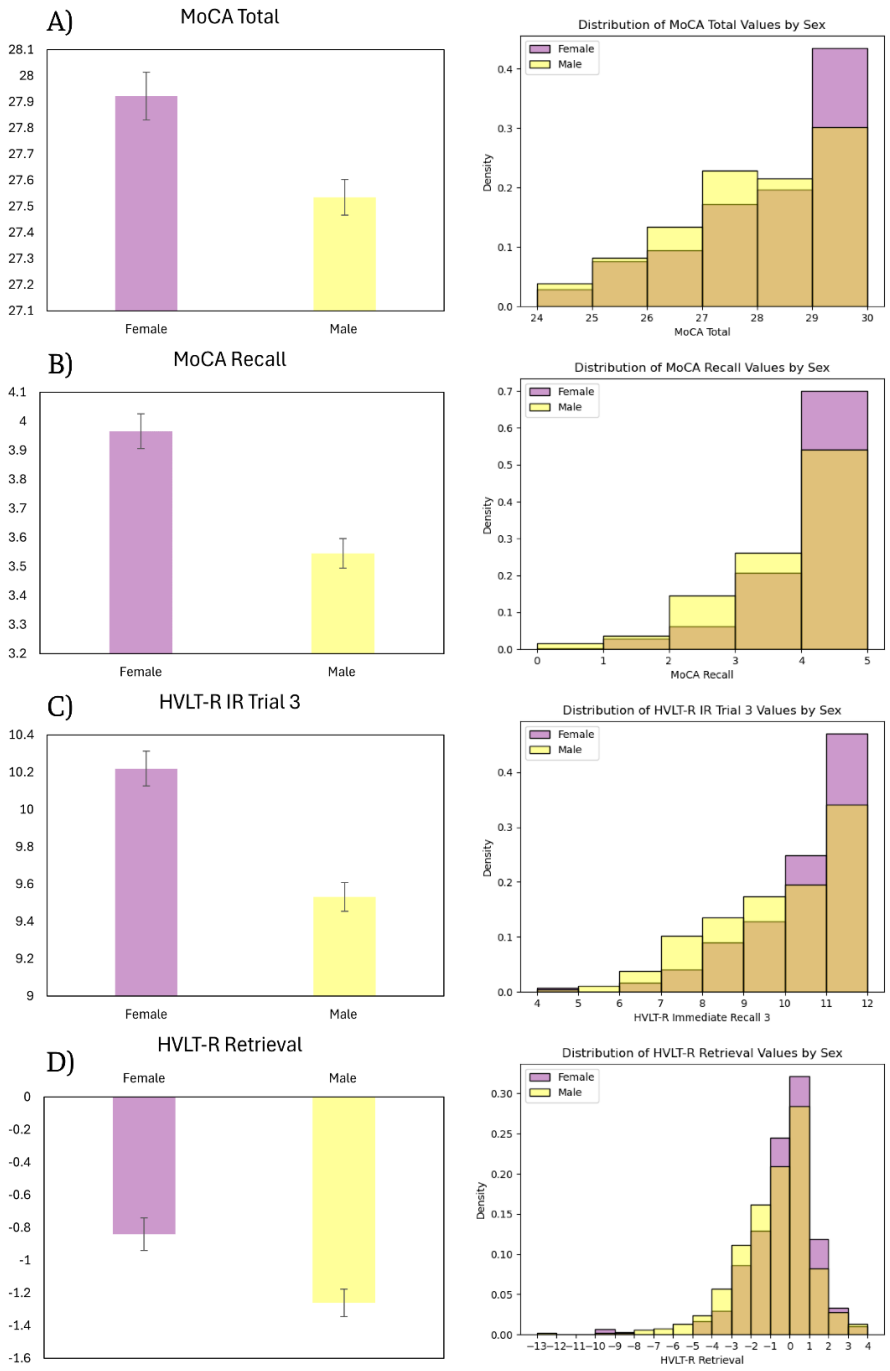

Figure 3. Mean (±SEM) scores and density distributions comparing performance on cognitive measures affected by Sex (Female vs. Male).
Left panels represent mean values for each score on the y-axis, and right panels represent a histogram of density distributions for each score on the y-axis. A) Montreal Cognitive Assessment (MoCA) Total with a maximum attainable score of 30, B) MoCA Recall subscore with a maximum attainable score of 5, C) Hopkins Verbal Learning Test-Revised (HVLT-R) Immediate Recall (IR) Trial 3 score with a maximum attainable score of 12, and D) HVLT-R Retrieval measure. HVLT-R Retrieval was calculated as the difference in the Delayed Recall and Immediate Recall Trial 3 scores. Negative values indicate the number of words 'forgotten'. MoCA n_{Female} = 320, n_{Male}= 563. HVLT-R n_{Female} = 302, n_{Male}= 549.

3.2.3 Effect of Group x Sex on MoCA and HVLT-R

Models including, versus excluding, Group x Sex interaction were not more accurate in predicting scores on any cognitive outcomes, either using the MoCA or the HVLT-R. The null hypothesis was supported with respect to all measures. In this way, though PD is a neurodegenerative disease with a strong male preponderance, there was no differential effect of Sex in PD on cognition. See Table 5 for the details.

Table 5. Model-averaged Bayesian effects of Group x Sex on MoCA Total and subscores, as well as HVLT-R performance.

	P(incl)	P(excl)	P(incl|data)	P(excl|data)	BF_{incl}
MoCA Total	0.2	0.2	0.23	0.718	0.32
Executive	0.2	0.2	0.084	0.179	0.468
Visuospatial	0.2	0.2	0.005	0.036	0.142
Language	0.2	0.2	9.908×10^{-4}	0.007	0.137
Attention	0.2	0.2	0.002	0.014	0.151
Recall	0.2	0.2	0.152	0.65	0.234
Orientation	0.2	0.2	0.002	0.018	0.132
Slope	0.2	0.2	0.003	0.023	0.118
IR Trial 3	0.2	0.2	0.038	0.228	0.169
Retrieval	0.2	0.2	0.088	0.708	0.125

Note. All predictors of interest are listed in the Effects column. P(incl) and P(excl) show the prior probabilities of the effect of including or excluding the predictor. We computed inclusion/exclusion probabilities using matched models only, such that all models with the interaction effect were compared to models with the same predictors excluding the interaction effect. P(incl|data) and P(excl|data) shows the posterior inclusion and exclusion probabilities, respectively. This represents the average effect of all models that include versus exclude predictors in estimating the observed outcomes. BF_{incl} is the Bayes Factor for inclusion of the predictor across all averaged models, quantifying the change from prior to posterior inclusion probabilities. Values >1 represent the number of times more likely that models including versus excluding Group x Sex as a parameter, accurately predicted the observed data.

3.3 Investigating the effect of covariates Age and Education on MoCA and HVLT-R

3.3.1 Effect of Age on MoCA and HVLT-R

Models including, versus excluding, Age as a predictor were more likely to achieve the outcomes observed on a) MoCA Total (BF_{incl} = 4950.773), b) Visuospatial (BF_{incl} = 144.965), c) Recall (BF_{incl} = 215.203), and e) HVLT-R IR Trial 3 (BF_{incl} = $1.536\times10^{+8}$). In all cases, older age was associated with poorer performance. Table 6 presents the details of these analyses involving Age.

Table 6. Model-averaged Bayesian effects of Age on MoCA Total and subscores, as well as HVLT-R performance.

	P(incl)	P(excl)	P(incl|data)	P(excl|data)	BF_{incl}
MoCA Total	0.5	0.5	1	2.019×10^{-4}	**4950.773**
Executive	0.5	0.5	0.129	0.871	0.148
Visuospatial	0.5	0.5	0.993	0.007	**144.965**
Language	0.5	0.5	0.093	0.907	0.103
Attention	0.5	0.5	0.205	0.795	0.258
Recall	0.5	0.5	0.995	0.005	**215.203**
Orientation	0.5	0.5	0.111	0.889	0.125
Slope	0.5	0.5	0.091	0.909	0.1
IR Trial 3	0.5	0.5	1	6.511×10-9	**1.536×10+8**
Retrieval	0.5	0.5	0.343	0.657	0.521

Note. All predictors of interest are listed in the Effects column. P(incl) and P(excl) show the prior probabilities of the effect of including or excluding the predictor. We computed inclusion/exclusion probabilities using matched models only, such that all models with the interaction effect were compared to models with the same predictors excluding the interaction effect. P(incl|data) and P(excl|data) shows the posterior inclusion and exclusion probabilities, respectively. This represents the average effect of all models that include versus exclude predictors in estimating the observed outcomes. BF_{incl} is the Bayes Factor for inclusion of the predictor across all averaged models, quantifying the change from prior to posterior inclusion probabilities. Values >1 represent the number of times more likely that models including versus excluding Age as a parameter, accurately predicted the observed data.

3.3.2 Effect of Education on MoCA and HVLT-R

Years of Education was a significant predictor of measures collected on a) MoCA Executive (BF_{incl} = 4782.752), b) MoCA Visuospatial (BF_{incl} = 14.064), c) MoCA Language (BF_{incl} = 2.461), and d) MoCA Attention (BF_{incl} = 5.878) and, e) HVLT-R IR Trial 3 (BF_{incl} = 50449.61), with better performance for models that include versus

exclude Education as a parameter. Superior performance was noted in all cases for those participants with more years of education. Table 7 provides the details of these analyses.

Table 7. Model-averaged Bayesian effects of Education on MoCA Total and subscores, as well as HVLT-R performance.

	P(incl)	P(excl)	P(incl|data)	P(excl|data)	BF_{incl}
MoCA Total	0.5	0.5	0.231	0.769	0.301
Executive	0.5	0.5	1	2.090×10^{-4}	**4782.752**
Visuospatial	0.5	0.5	0.934	0.066	**14.064**
Language	0.5	0.5	0.711	0.289	**2.461**
Attention	0.5	0.5	0.855	0.145	**5.878**
Recall	0.5	0.5	0.196	0.804	0.244
Orientation	0.5	0.5	0.089	0.911	0.098
Slope	0.5	0.5	0.434	0.566	0.767
IR Trial 3	0.5	0.5	1	1.982×10-5	**50449.614**
Retrieval	0.5	0.5	0.141	0.859	0.164

Note. All predictors of interest are listed in the Effects column. P(incl) and P(excl) show the prior probabilities of the effect of including or excluding the predictor. We computed inclusion/exclusion probabilities using matched models only, such that all models with the interaction effect were compared to models with the same predictors excluding the interaction effect. P(incl|data) and P(excl|data) shows the posterior inclusion and exclusion probabilities, respectively. This represents the average effect of all models that include versus exclude predictors in estimating the observed outcomes. BF_{incl} is the Bayes Factor for inclusion of the predictor across all averaged models, quantifying the change from prior to posterior inclusion probabilities. Values >1 represent the number of times more likely that models including versus excluding Education as a parameter, accurately predicted the observed data.

3.3.3 Summary of Main effects

In summary, Group, Sex, Age, and Education have different impacts on cognitive measures, with varying magnitudes of these effects. Table 8 presents a summary of the cognitive domains, measured with MoCA and HVLT-R, differentially affected by our predictors. The measures are presented based on the magnitude of the effect of predictors, estimated with model-averaged BF_{incl}, in descending order.

Table 8. Summary of the Bayesian model-averaged effects of each predictor on cognitive outcomes, organized by effect size (largest effect to smallest effect).

Group	Sex	Age	Education
MoCA Total	Immediate Recall Trial 3	Immediate Recall Trial 3	Immediate Recall Trial 3

(BF_{incl} = 669.375)	(BF_{incl} = 910303.8)	(BF_{incl} = 1.536×10+8)	(BF_{incl} =50449.61)
Executive (BF_{incl} = 36.67)	Recall (BF_{incl} = 15762.93)	MoCA Total (BF_{incl} = 4950.773)	Executive (BF_{incl} = 4782.752)
Retrieval (BF_{incl} = 8.433)	MoCA Total (BF_{incl} = 14.304)	Recall (BF_{incl} = 215.203)	Visuospatial (BF_{incl} = 14.064)
Recall (BF_{incl} = 3.297)	Retrieval (BF_{incl} = 6.681)	Visuospatial (BF_{incl} = 144.965)	Attention (BF_{incl} = 5.878)
			Language (BF_{incl} = 2.461)

3.4 Investigating the effect of PD motor symptom severity and disease duration on cognitive performance on the MoCA and HVLT-R

3.4.1 Disease severity

Disease severity was measured through the MDS-UPDRS Part III motor assessments, with higher scores indicating more severe motor symptoms. We correlated MDS-UPDRS Part III scores with measures of cognitive performance. We applied a Bonferroni ($p_{adjust} < 0.05/10$) correction and an α value was set a $p < 0.005$, to correct for family-wise multiple comparisons. There was no significant correlations between MDS-UPDRS III and any of the outcome measures: a) MoCA Total Score $r(1,641) = -0.077$, $p = 0.049$, b) MoCA Visuospatial $r(1,641) = -0.093$, $p = 0.018$, c) MoCA Executive $r(1,641) = 0.02$, $p = 0.621$, d) MoCA Language $r(1,641) = -0.091$, $p = 0.022$, e) MoCA Attention $r(1,641) = 0.003$, $p = 0.938$, f) MoCA Recall $r(1,641) = -0.022$, $p = 0.579$, g) MoCA Orientation $r(1,641) = 0.052$, $p = 0.201$, h) HVLT-R Slope $r(1,609) = 0.027$, $p = 0.503$, i) HVLT-R IR Trial 3 $r(1,609) = -0.082$, $p = 0.043$, and j) HVLT-R Retrieval $r(1,609) = -0.031$, $p = 0.444$ measures. PD patients in our study were restricted to those who were assessed within 12 months of disease duration, restricting the range of our disease severity (0-60 on the MDS-UPDRS Part III in our sample).

3.4.2 Disease duration

Months since diagnosis was our measure of disease duration, which was correlated with all cognitive measure. We found that Months since diagnosis, in our restricted range, did not correlate with any cognitive measures, all $p > 0.05$: a) MoCA Total Score $r(1,641) = 0.037$, $p = 0.344$, b) MoCA Visuospatial $r(1,641) = 0.037$, $p = 0.345$, c) MoCA Executive $r(1,641) = 0.011$, $p = 0.772$, d) MoCA Language $r(1,641) = 0.021$, $p = 0.6$, e) MoCA Attention $r(1,641) = 0.024$, $p = 0.543$, f) MoCA Recall $r(1,641) = 0.017$, $p = 0.663$, g) MoCA Orientation $r(1,641) = 0.006$, $p = 0.878$, h) HVLT-R Slope $r(1,609) = 0.016$, $p = 0.687$, i) HVLT-R IR Trial 3 $r(1,609) = -0.053$, $p = 0.189$, and j) HVLT-R Retrieval $r(1,609) = -0.008$, $p = 0.849$ measures.

Chapter 4

4 Discussion

We provide evidence of cognitive changes in a large sample of *de novo* [i.e., < 12 months since diagnosis, mean disease duration (months) = 3.955 (± 3.108)], drug-naïve PD patients (n = 643), who have no concurrent diagnosis of MCI or dementia, relative to HCs (n = 240). These data were collected through the multicentred PPMI database. In our sample, 9.4 % of PD and 1.2 % of HCs participants were excluded from our analyses due to MoCA Total scores < 24/30, which has been shown to be an appropriate cut-off for detecting MCI (Carson et al., 2018). Chi-squared analysis is significant ($\chi^2 = 17.896$, $p < .001$), confirming higher proportion of MCI in PD relative to HCs. In the sample included in our analysis, PD patients evidenced impairments in the MoCA Total, MoCA executive, and MoCA Recall, as well as in the HVLT-R Retrieval measure. In contrast, performance on the MoCA Visuospatial, MoCA language, MoCA attention, MoCA orientation to time and place, as well as on HVLT-R Slope and HVLT-R IR Trial 3 scores were *equivalent* in PD patients and HCs. By using a model-averaged Bayesian approach, we could test hypotheses about the impact of PD on performance of various measures of cognitive function, to discern the full profile of impaired *as well as* spared cognitive functions in *de novo* PD, without the confound of dopaminergic therapy, given that patients were treatment naïve.

We also sought to investigate the effects of Sex across cognitive domains. In terms of main effects, we found that female participants had superior performance on MoCA Total, MoCA Recall, HVLT-R IR 3 score, and HVTL-R Retrieval. Overall, cognitive differences related to Sex seemed attributable to memory effects. Though MoCA Recall reflects the combined effects of encoding and retrieval processes, the HVTL-R allows for measures that emphasized encoding and retrieval processes differentially. Though the slope of learning from HVLT-R IR 1 to 3 was equal between the sexes, female participants immediately recalled more words than male participants following the three learning trials with 0.8 mean word difference, compared to a 0.4 mean word difference in the number of words recalled after a 20-minute delay, corrected for total number of words encoded at HVLT-R IR 3. Taken together, it seems that

females have superior encoding and retrieval. Female and male participants performed equivalently on all other cognitive measures.

Our principal aim in assessing the effect of Sex was to investigate whether Sex differentially impacted cognition in PD patients. Though PD is a disease to which females and males are differentially susceptible, with male preponderance (Oltra, Uribe, et al., 2022; Philipe de Souza Ferreira et al., 2022), surprisingly we found no Group x Sex interactions. That is Sex impacted cognition *equally* in PD and HCs. In our Bayesian analyses, in all cognitive domains, the null hypothesis (i.e., that there were no differential effects of Sex on PD) was strongly supported.

We found significant effects of Age and Education, with impairment related to older age and to lower educational attainment, on the MoCA Visuospatial and HVLT-R IR 3. Older age also caused impairment on MoCA total and MoCA Recall. Lower levels of educational attainment were related to MoCA Executive dysfunction, as well as impairment on MoCA Attention and Language scores.

Anxiety and depression measures had no predictive value on cognitive scores. Based on this, to simplify our models, we reported our results without anxiety and depression as covariates. Finally, histograms reveal that our results were not related to extreme scores. Results with or without outliers of +/- 2.5 deviation for Group and Sex mean were equivalent and, again, to simplify our models, we report our findings without outlier removal.

We also explored the relationship between motor disease severity, assessed with MDS-UPDRS III and of disease duration on cognitive performance. We found that neither motor impairment nor disease duration (in months) were correlated with any of our cognitive measures. It should be noted that our current sample of PD patients was restricted to < 12 months disease duration, affecting disease severity as well as disease duration. Consequently, these measures might have impacts on cognitive performance at more advanced stages of PD.

4.1 *De novo*, drug naive patients with PD reveal cognitive changes in multiple domains compared to HCs

We found that *de novo* drug-naïve patients with PD who did not have concurrent MCI or dementia revealed alterations in multiple domains, with worsened performance in executive function and memory compared to HCs. Similar to our findings, studies investigating patients with PD with normal cognition (i.e., PD-non-MCI), who were are more advanced disease stage, however, revealed multidomain cognitive differences when compared to HCs (Broeders, de Bie, et al., 2013; Chaudhary et al., 2020; Pigott et al., 2015; Wang et al., 2015). Broeders et al. (2013) and Chaudhary et al. (2020), found changes in attention and memory in PD-non-MCI patients compared to HCs. Chaudhary et al., also found alterations in language for PD patients. Wang et al. (2015), found differences in attention and semantic fluency in PD-non-MCI patients compared to HCs. In our study, PD patients exhibited dysfunction in memory, but not in attention and language. Neither Broeders et al. (2013), Chaudhary et al. (2020), nor Wang et al. (2015), corrected for multiple comparisons in their analyses, thus increasing the chances of falsely rejecting the null hypothesis and claiming cognitive differences. Lastly, Pigott et al. (2015), do not compare patients with PD to HCs, but rather found that executive function and memory dysfunction at baseline were predictors of greater cognitive decline longitudinally. These findings were complementary to ours as these domains were the only ones that were impaired relative to HCs in our study in early, *de novo* and drug-naïve D PD patients.

In previous studies of *de novo* patients with PD, multidomain cognitive changes are also reported (Aarsland et al., 2009; Cooper et al., 1991; Poletti et al., 2012). Aarsland et al. (2009), Cooper et al. (1991), and Poletti et al. (2012), show worsened performance in tasks of executive and memory domains comparing *de novo* PD patients and HCs. Miah et al. (2012), show single-domain worsened performance in executive function/working memory in *de novo* patients compared to HCs. All previous did not distinguish PD patients with no co-occurrence of MCI relative to HCs. Our findings therefore fill a gap, revealing that cognitive function is already altered relative to a similarly aged groups of HCs in multiple domains at onset of motor symptoms, far ahead

of when widespread cortical regions are expected to be affected (Mak et al., 2014; S. K. Song et al., 2011).

4.1.1 Patients with PD show executive differences compared to HCs

Patients with PD in our sample performed worse than HCs on combined measures of executive function (Figure 2B), which included the trail making component, verbal fluency, and abstraction scores on the MoCA. Our Bayesian analyses reveal a strong effect of Group (i.e., being a PD patient vs. a HC) as a predictor of poorer performance. The observed data were 669.375 times more likely for models that included Group as a parameter suggesting that it strongly exerted an effect, with poorer performance for PD patients compared to HCs (Table 5).

Though cortex is not expected to be directly structurally altered by PD pathophysiological processes in very early stages of PD, fronto- and parieto-striatal pathways are already affected due to dopamine deficiency (Trujillo et al., 2015). At the time of motor symptom appearance, the DS is already significantly dopamine restricted due to degeneration of the dopamine-producing neurons of the SNc, which supplies the DS (P. A. MacDonald & Monchi, 2011). The SNc, via the DS, forms nigrostriatal pathways with frontal and parietal cortical regions (Aarsland et al., 2021; Sasikumar & Strafella, 2020). These pathways are strongly implicated in cognitive flexibility and cognitive control, which underlie most measures of executive function (Trujillo et al., 2015). This is a plausible mechanism through which these deficits arise, mere months following diagnosis in PD, even in drug naïve patients.

The limited literature in PD-non-MCI patients supports fronto-striatal mediated executive deficits to be characteristic of the cognitive profile in PD, with a few limitations that our findings address. Chaudhary et al. (2020), report PD patients to perform worse in trail-making, a task that we also measured in our executive function subscore on the MoCA. Broeders et al. (2013), Chaudhary et al. (2020), and Wang et al. (2015), did also find attentional deficits in PD-non-MCI patients.

Focusing on a handful of smaller samples of *de novo* patients, previous studies have also found patients to be impaired in inhibition (Aarsland et al., 2009), working memory (Cooper et al., 1991; Elgh et al., 2009), and verbal fluency (Poletti et al., 2012),

all of which constitute executive functions. Cooper et al. (1991), found *de novo* patients with PD to perform worse in semantic fluency, set-formation, cognitive sequencing, and working memory tasks. Poletti et al. (2012), found newly diagnosed drug naïve patients with PD performed worse in an overall frontal assessment battery compared to healthy controls. However, similar to limitations listed above, Aarsland et al. (2009), showed that *de novo* patients perform worse on the Stroop interference task, suggesting a deficit in inhibition, an executive function. Lastly, Miah et al. (2012), show working memory deficits in strategy use tasks in untreated PD compared to HCs. However, some limitations to these findings include heterogenous samples of PD-MCI and PD-non-MCI (Aarsland et al., 2009; Cooper et al., 1991), small sample sizes (Cooper et al., 1991; Miah et al., 2012), and the inclusion of a small proportion of medicated patients (n= 2/88 patients; Elgh et al., 2009). Thus, an advantage to our findings, that further validate these previous studies, is the presence of executive deficits in PD-non-MCI patients specifically using a large, entirely drug-naïve sample.

4.1.2 Recall and Retrieval are changed in patients with PD compared to HCs

We also found memory deficits in patients with PD relative to HCs, specifically on the delayed recall measure in the MoCA and the HVLT-R Retrieval measure (Table 3). Previous reports of worsened memory function (i.e., in immediate and delayed recall) in early, PD-non-MCI patients support our findings (Broeders, de Bie, et al., 2013; Chaudhary et al., 2020). This study provides an advantage over these previous findings by eliminating effects of dopaminergic medication through the use of an entirely untreated *de novo* sample of patients with PD.

Our findings are also in support with studies investigating cognition in untreated patients early in disease progression. Both immediate and delayed recall seem to be affected in drug naïve patients (Aarsland et al., 2009; Cooper et al., 1991; Elgh et al., 2009; Poletti et al., 2012). However, the sample sizes of these investigations fluctuates from as low as n= 60 (Cooper et al., 1991) to a maximum of n = 169 (Aarsland et al., 2009). Our study provides evidence from a much larger sample, allowing for greater power and more accurate estimates of effect size, and offers further confirmation of memory impairment in early PD. Moreover, our results show recall and retrieval memory

deficits in PD-non-MCI patients specifically, whereas previous work considers either a heterogenous sample of cognitively impaired patients (Aarsland et al., 2009), or does not screen for PD-MCI (Cooper et al., 1991). Lastly, Elgh et al. (2009), in addition to not screening for PD-MCI, also contain $n = 2/88$ patients who are taking dopaminergic medication. Due to this, while their sample is majority *de novo,* it cannot be considered exclusively *de novo* and completely spared from any confounds of dopaminergic medication. Thus, our findings suggest memory to be an important domain implicated in early, *de novo* patients with PD.

Additionally, to ensure the detected retrieval deficits were not a function of poor encoding, we measured retrieval as a function of each participants delayed recall score from their immediate recall trial 3 score. In this way, their immediate recall trial 3 score was a measure of encoding (i.e., how much information the participant had learned), and this was subtracted from their recall score, which was an absolute measure and thus could not represent retrieval independently. To our knowledge, no other study of early-disease *de novo* patients with PD has separated retrieval processes from free immediate or delayed recall (Aarsland et al., 2009; Cooper et al., 1991; Elgh et al., 2009; Poletti et al., 2012). This is an added strength of our findings, the ability to demonstrate retrieval memory deficits in early *de novo* PD-non-MCI patients that are separate from any recall deficits.

4.1.3 Patients with PD do not show impairments in encoding when compared to HCs

Encoding, the ability to learn new information, was not affected by early PD in our study (Table 3). To better isolate encoding processes, we calculated the slope (i.e., rate of change) of the number of words correctly recalled over three immediate recall trials on the HVLT-R. We also compared the absolute learning score, through the HVLT-R IR Trial 3. Comparing both the slope and immediate recall measure, there was no effect of Group between patients and controls (Table 3). This is in contrast with Weintraub et al. (2004) who report evidence for both an encoding and retrieval deficit profile in PD. However, there are two important differences of note here. Firstly, the patient samples are different. Weintraub et al. (2004), patient sample consists of individuals taking dopaminergic medication. Literature reports that dopaminergic

medication worsens encoding and learning ability in PD (A. A. MacDonald, Seergobin, et al., 2013) in a similar measure of encoding. Thus, encoding deficits seen in Weintraub et al. (2004), could potentially be attributed to effects of dopaminergic medication. However, more importantly, Weintraub et al. (2004), performed a within group analyses of patients with PD, and thus differential encoding and retrieval profiles arising were relative to other patients with PD of different disease stages. Our studies compared patients to healthy elderly controls, thus providing a means for determining whether encoding is altered by PD at disease onset. Our results are in line with previous literature comparing patients in the OFF medication state with controls, whereby patients perform similarly to controls in trials of stimulus-stimulus or stimulus-reward learning when acutely withdrawn from dopaminergic medication (Hiebert et al., 2014, 2019; A. A. MacDonald, Monchi, et al., 2013; P. A. MacDonald et al., 2011; Vo et al., 2014), suggesting patients are not impaired in encoding. To our knowledge, there is no study of *de novo* drug-naïve PD investigating encoding processes, thus our findings are entirely novel. Furthermore, using Bayesian analyses, we could assert that encoding was actually spared.

The relative retention of encoding ability agrees with the disproportional loss of dopaminergic neurons in early disease. Dopamine producing neurons in the VTA are relatively unaffected in early disease, leaving the VS and its cortical partners in the temporal lobes, amply implicated in memory encoding, relatively replete with dopamine at this stage (P. A. MacDonald & Monchi, 2011). The VS is thought to mediate the learning of new information (P. A. MacDonald & Monchi, 2011), and thus it makes sense why encoding would remain unaffected in early disease.

An important clinical application drawing from our study is the distinction between encoding and retrieval deficits in PD in comparison to other neurodegenerative diseases, namely Alzheimer's. Compared to PD, patients with AD show worse deficits in encoding (Aretouli & Brandt, 2010; Weintraub et al., 2004). In conjunction with these findings, our study further distinguishes these two patients' group by demonstrating patients with PD do not display encoding deficits in early disease stage. This information can prove crucial to distinguishing clinical symptoms of AD and PD related cognitive impairment in early clinical presentations.

4.2 Patients with PD were not changed in attention, language, visuospatial, or orientation domains compared to HCs

Attention on the MoCA, as measured through digit span forward and backwards, serial subtraction by 7 (i.e., serial 7s), and vigilance finger tapping, was not altered in PD in our sample (Table 3). Although attention is reported to be affected in studies with heterogenous samples of disease severity, duration, and medication status (Aarsland et al., 2010; Chaudhary et al., 2020; Pfeiffer et al., 2014), investigations of early, untreated patients report similar findings to ours. Elgh et al. (2009), found patients to perform worse in Trails A and B, however, in our study we grouped Trails on the MoCA into executive function in which there was altered performance in patients compared to controls. Elgh et al. (2009), did not find patients to be different in digit span, similar to our findings in attention on the MoCA. Similarly, Cooper et al. (1991), found patients with PD to perform comparable to HCs in digit span forward, however, they did find patients to be impaired in digit span backward. However, Cooper et al. (1991) also did not screen patients out for MCI, thus it is likely their sample consisted of both PD-MCI and non-PD-MCI patients. Similarly, Aarsland et al. (2009), found patients with PD to be impaired in serial 7s, however, this sample did include PD-MCI patients, who are comparably more impaired than non-PD-MCIs. Therefore, considering the heterogeneity amongst samples in previous studies of untreated patients with PD, our study reports attentional functions, as measured on the MoCA, to be relatively spared in early, non-PD-MCI, *de novo* patients.

Language was not different between patients and controls in our sample, as seen in the Bayesian model-averaging (Table 3). In this study, we measured language as the ability to name animals, and repeat two sentences exactly as they are said by the test administrator. For early disease patients performing similarly to HCs in other domains (i.e., visual), it is not unexpected for there to be no difference in recognizing common animals such as a lion or repeating sentences. In terms of the literature, other studies report minimal to no language deficits in non-demented patients with PD (Caviness et al., 2007; Levin et al., 1989; Muslimović et al., 2005). Many studies do not define a separate domain for language, instead report deficits in specific language functions such as phonemic or semantic fluency (Aarsland et al., 2010; Elgh et al., 2009; Wang et al.,

2015), a feature we analyzed as an executive function. This discrepancy in the literature in understanding language functions in PD likely stems from the fact that language is rarely assessed as a separate domain and its often affected by functioning in other domains such as attention and working memory or executive tasks. For example, phonemic fluency is often indexed as both language and an executive functioning ability (Watson & Leverenz, 2010). We did see patients with PD performing worse in executive functioning on the MoCA, which included phonemic fluency, thus potential differences in language could be represented through executive functioning measures. However, considering language as the ability to name animals and repeat sentences on the MoCA, we found no difference between early disease, *de novo,* non-MCI-PD patients and elderly HCs.

Patients did not show differential performance in the visuospatial domain on the MoCA compared to controls, as seen through no effect of Group on visual performance (Table 3). Cooper et al. (1991) and Aarsland et al. (2009), found that drug naïve patients with PD perform worse in visual reproduction tasks compared to HCs. The cube task on the MoCA is a visual reproduction task, however, Cooper et al. (1991), used a different visual reproduction measure, the Rey-Osterrieth and Taylor complex figures. Additionally, Cooper et al. (1991), grouped the figure copy task into a subset of memory-based measures, suggesting a deficit in figure copy to be attributable to deficits in memory. Moreover, in their study, they also did not find PDs and HCs to differ in visuospatial specific reproduction tasks such as the matchsticks test (Cooper et al., 1991). Aarsland et al. (2009), did find patients with PD to perform worse in a cube copy task, however, their sample consisted of both non-PD-MCI and PD-MCI patients. However, in another study of newly diagnosed patients, Elgh et al. (2009), did not find a difference in visuospatial function in early disease patients. Thus, considering early stage, non-PD-MCI, *de novo* patients with PD, there seems to be a preservation in visuospatial abilities, with deficits in this domain likely arising with disease progression, and potentially at the time of development of PD-MCI or PDD. These findings are somewhat surprising given that it has previously been suggested that visuospatial cognitive processing deficits are distinctly associated with PD (Macdonald & Monchi, 2011), though this literature relies

nearly exclusively on convenience samples that include broadly varying PD groups in terms of disease duration and PD features, on a range of different tasks.

Another domain not affected by PD in our data is Orientation, as seen through the lack of effect of Group on orientation performance (Table 3). This is not unexpected, as orientation has a high likelihood of obtaining the highest possible score and does not discriminate well between clinical and control groups (Freitas et al., 2015), owing to the simple nature of the task. Most participants, especially in early disease who are performing similarly to controls in other cognitive domains, will be spatially oriented in time space simply due to performing other daily tasks such as checking the calendar, going to work, remembering a scheduled study appointment, or even opening their phone screen which indicates the date.

An advantage of our study relative to the interpretation of these measures in which no PD-HCs differences arise is the use of Bayesian model-averaging. Frequentist approaches, employed by all above-mentioned studies of cognition in early, *de novo* PD (Aarsland et al., 2009; Cooper et al., 1991; Liu et al., 2015b; Miah et al., 2012; Poletti et al., 2012) can only provide evidence for the alternate hypothesis (i.e., rejecting the null hypothesis). In contrast, there an be no interpretation when rejection of the null hypothesis fails. (Fornacon-Wood et al., 2022). Failing to reject the null hypothesis can arise due to multiple factors. Therefore, an important limitation to employing Frequentist approaches is that they cannot claim which cognitive domains, if any, are *relatively spared* in early *de novo* PD in comparison to HCs. Through the use of Bayesian model-averaging, we assign probabilities to the hypotheses themselves, and thus can report the *likelihood* of the data being true *given* the hypothesis, allowing direct comparison of the alternative and the null hypotheses. This allows us to not only report which domains are impaired through the evidence of a Group effect, but we can also identify which domains are spared when Group exerts no effect on the likelihood of the observed data. Through the Bayesian approach, we are able to provide a more comprehensive understanding of the cognitive profile in early *de novo* PD through identifying which cognitive domains are impaired and which are spared.

4.3 Sex effects were restricted to Memory measures in MoCA and HVLT-R

In the current sample, MoCA total and Recall, as well as IR Trial 3 and Retrieval from the HVLT-R were affected by Sex, regardless of patient or controls status (Table 4). Out of the four variables affected by Sex, the largest effects are seen on MoCA Recall and HVLT-R IR Trial 3. In our sample, females performed better than males on all four measures, as seen in Figure 6. This is similar to findings in the literature, whereby females perform better than males in tasks of verbal learning and memory such as immediate and delayed recall (Jorm et al., 2004; Levine et al., 2021; McCarrey et al., 2016; Munro et al., 2012; Nooyens et al., 2022; van Hooren et al., 2007). As well, we see females performing better than males in retrieval memory, which is representative of previous findings of reports of females performing better in measures of memory than males (Levine et al., 2021; Munro et al., 2012; Nooyens et al., 2022). Levine et al. (2021), and McCarrey et al. (2016), also report females performing better than males on global cognition, which we also found through a higher mean MoCA total score in females than males (Figure 6).

4.4 No differential effect of Sex on cognition in PD.

Looking at differential effect of Sex on cognition, we found none. That is, though there were general effects of Sex on cognition, there was no Group x Sex interaction indicating that Sex affected PD or HCs comparably.

Considering the literature for sex differences in cognition in PD, there are only a handful of studies that have investigated either a PD-non-MCI group or *de novo* drug-naïve patients. Pigott et al. (2015), are the only study to our knowledge, to investigate sex as a predictor for cognitive decline in patients who do not have MCI or PDD. Amongst patients with PD who had normal cognition at baseline, they found male sex to be a significant predictor of cognitive decline in a longitudinal follow-up (Pigott et al., 2015). However, no cognitive domains were identified to be specifically impaired in males versus females, and no direct comparison of male and female performance on cognitive measures was reported. Thus, Pigott et al. (2015), only highlight male sex to be a predictor in future cognitive decline in patients with normal cognition. Our findings,

however, compare male and female patients directly across multiple cognitive domains, and show no significant Group x Sex interaction, suggesting that sex does not differentially impact cognition in PD patients compared to HCs.

Similarly, only a handful of studies have investigated sex differences in cognition in PD using exclusively *de novo* patients (Bayram et al., 2020; Liu et al., 2015b; Oltra, Uribe, et al., 2022). Bayram et al. (2020), report females in general (PD or HC) to perform better in verbal memory, and males to perform better in visuospatial function. However, similar to our findings, they did not uncover any significant Group x Sex interactions. Oltra et al. (2022), similarly investigated sex differences in *de novo* PD, and claimed female patients with PD performed better than males in immediate verbal recall and mental processing speed. In the overall participants, combining PD and HCs, females performed better in semantic fluency and delayed recall, and males performed better in visuospatial functions (Oltra, Uribe, et al., 2022). Comparing Group x Sex interaction, only the MoCA total was significant, prior to correcting for multiple comparisons and likely would not survive this correction. In this way, there *post-hoc* analyses in verbal recall and mental processing speed were not appropriate given that they did not reveal any Group x Sex interactions in any of their cognitive subscores. Lastly, Liu et al. (2015), reported sex differences in *de novo* PD in MoCA total and memory, however, they did not find any significant Group x Sex interaction. Thus, although studies of *de novo* PD report sex differences in patients, in line with our findings, Sex effects on cognition are not distinct in PD.

Therefore, after comparing early disease *de novo* PD-non-MCI patients for sex differences, we found no significant Group x Sex interaction, indicating the sex cognitive to be similar in patients with PD and HCs, with no PD specific differences in females and males.

4.5 Age, and Education have distinct effects on cognitive performance

In addition to Group and Sex differences, we saw effects of Age and Education as predictors of cognitive function on the MoCA and HVLT-R measures. Age had an effect on MoCA total, MoCA Visuospatial, and MoCA recall, as well as on HVLT-R IR trial 3

(Table 6). Education had an effect on executive, visuospatial, language, and attention on the MoCA, and immediate recall on the HVLT-R (Table 7).

Comparing the effects on cognition of the predictors Age and Education to those of the predictors of Group or Sex, we see that different domains are affected by each primarily or more secondarily (Table 8).

4.6 Is the MoCA Cognitive Profile of PD specific or related to differential sensitivity and validity of MoCA sub-domains?

We used the six-factor model of the MoCA to assess cognitive performance in our study. This model was originally proposed by Nasreddine et al. (2005), and has since been validated (Freitas et al., 2012). Freitas et al. (2015), demonstrate through a novel Partial Credit Model the psychometric adequacy of each of the six-factor domains. Each domain in the six factor model is significantly more correlated with MoCA total score than with another domain, demonstrating the discriminatory power of the MoCA and its domains (Freitas et al., 2012). The high variability of performance in clinical and control groups in each of the domains is an additional indicator of the validity of the MoCA domains (Freitas et al., 2015). The domains discriminating between a clinical group of AD and mild cognitive impairment (MCI) patients and controls were Executive, Visuospatial, Language, and Attention (Freitas et al., 2015). We found differences in Executive when comparing PD patients and controls. We observed no differences in Visuospatial, Language, and Attention between PDs and HCs in our sample. According to Freitas et al. (2015), the MoCA domain discriminating the least between clinical and controls groups are Recall and Orientation. Recall showed the least likelihood that an individual from the control group would have a cognitive impairment, ascribing the poor discriminant ability of the domain to its difficulty (Freitas et al., 2015). Interestingly, in our sample we saw Group (PD vs. HC) effects in Recall, with controls performing better than patients. This, the complementary finding of reduced HVLT-R Retrieval performance, combined with sparing of slope of learning and absolute number of words learned on HVLT-R IR trial 3, suggest that memory alterations, likely owing to retrieval deficits, are indeed an early feature of PD. Different cognitive domains were affected by Group, Age, Sex, and Education, each evidenced different cognitive profiles, also

suggesting that specific effects of these predictors rather than more general influences on subscales such as overall difficulty or effective distribution, were producing our PD cognitive profile.

Additionally, Bayesian model-averaging allows us to not only identify impaired domains, but also to determine if any cognitive domains are *spared* in PD. All measures in which the domains in cognition as they are differentially affected by all predictors (i.e., Group, Sex, Age, and Education). Understanding this is important to have a full understanding of the cognitive profile in early PD, and how it is affected or spared by the other demographic characteristics. Thus, the validated six-factor model of the MoCA used in our studies identifies meaningful cognitive differences in early PD that warrant further clinical attention.

4.7 Limitations

Though the multi-centred nature of this study is a strength because it increases the sample size and perhaps the representativeness of our sample, a disadvantage is that this can lead to slight protocol variations, including testing time and presentation order, which in turn impact participant alertness and performance. Examiner tone and instruction clarity can also add to this variability across participating centres. The MoCA's standardized administration, however, likely reduces these slight variations in protocol (Nasreddine et al., 2005). Additionally, the MoCA has been reported to be resistant to presentation order effects (A. S. Costa et al., 2012). Therefore, while there is the chance for variation in testing conditions and execution may be attributable to minor effects on cognitive performance, the standardized protocol design for the PPMI study and features of the MoCA help minimize that substantially.

Another challenge to contextualizing our findings to the greater literature is insufficient research on the MoCA six-factor model for assessing cognitive impairment in PD, and related to other factors such as Sex, Aging, or Education. This scarcity of this literature arises not only complicates the contextualization of study findings within existing knowledge but also impedes the validation of our results against previous similar findings. However, the studies (Freitas et al., 2012, 2015; Nasreddine et al., 2005) and meta- justify the six-factor model were well-executed and corroborate our findings.

Lastly, a final limitation in our study was the unequal sex ratio in our sample, exhibiting a greater representation of males than females. Nevertheless, the male-to-female ratio in the patient group was equated with that in the control group, ensuring no disparity in sex ratio between the two groups. Moreover, given PD's predominantly male prevalence, enrolling more male participants than females is statistically more probable and is a factor we cannot control for.

4.8 Conclusions

Overall, these findings reveal that MoCA Total, MoCA subscores, and HVLT-R measures are sensitive to cognitive changes in *de novo* PD relative to HCs. These measures also reveal clear measures that are spared at this stage of the disease. Suggested by the different cognitive profiles, MoCA and HVLT-R are detecting specific effects related to all of our different predictors. These allays any concerns that our PD cognitive profile arose entirely due to differences in task difficulty across the domains.

Therefore, this study concludes that there is cognitive alteration in PD from its earliest stages, prior to the development of PD-MCI. The cognitive profile early non-PD-MCI is multidomain impairment primarily in frontal-executive and memory functions. It is also of utmost important to highlight that these deficits are removed from any confounds of chronic dopaminergic medication, as all the patients in our sample were drug naïve. To our knowledge, this was amongst the few studies to assess cognitive changes in early, *de novo*, non-PD-MCI patients using a substantially larger sample of drug-naïve patients than previously reported in the literature.

Implications of this work are widespread, both in clinical and research applications. Clinically, screening tools such as the MoCA and HVLT-R can be applied easily to index areas of concern that can be followed up with extensive neuropsychological evaluations. This work also provides the groundwork for new research. The domains highlighted in this study can be investigated further in early, drug naïve patients using more sensitive measures for each domain. Follow-up longitudinal studies can be conducted using the same measures to see how well the MoCA and HVLT-R predict cognitive change as PD progresses. Studies of functional MRI can correlate cortical and striatal structures with cognitive tasks in the scanner, providing a

better understanding of brain regions implicated with each cognitive domain in PD pathology. Thus, this understanding of the early cognitive profile of PD in drug naïve patients highlights a starting point for many future directions in further elucidating the cognitive profile of a complicated disease such as PD.

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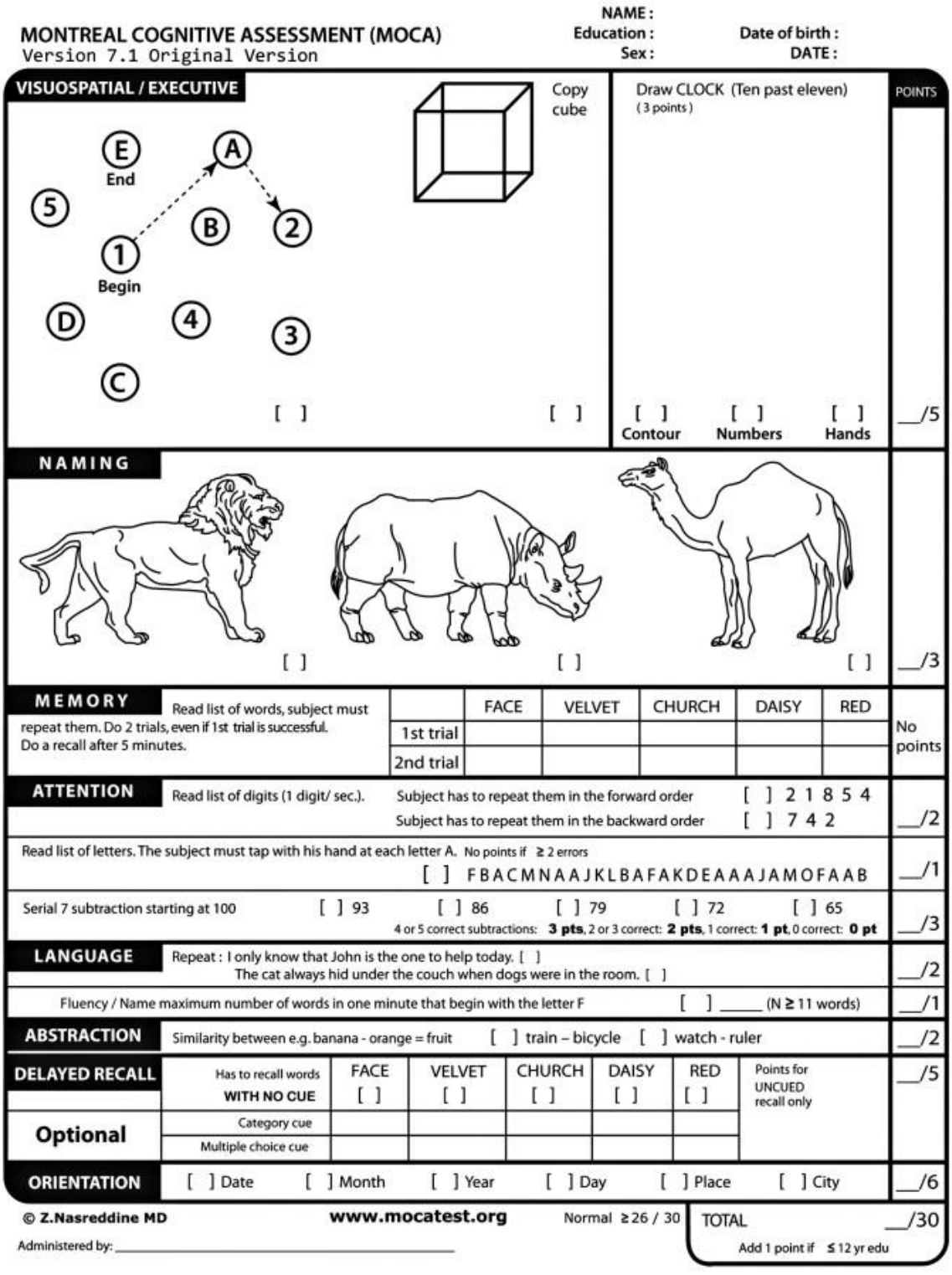
Appendices

Appendix A	Montreal Cognitive Assessment (MoCA)
Appendix B	Hopkins Verbal Learning Test- Revised (HVLT-R)
Appendix C	State Trait Anxiety Inventory (STAI)
Appendix D	Geriatric Depression Scale-Short (GDS)



Appendix A. Montreal Cognitive Assessment (MoCA) Version 7.1.
More versions and information can be found at: **mocacognition.com**

HOPKINS VERBAL LEARNING TEST
Form 1: four-legged animals, precious stones, human dwellings

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
EMERALD	_____	_____	_____
HORSE	_____	_____	_____
TENT	_____	_____	_____
SAPPHIRE	_____	_____	_____
HOTEL	_____	_____	_____
CAVE	_____	_____	_____
OPAL	_____	_____	_____
TIGER	_____	_____	_____
PEARL	_____	_____	_____
COW	_____	_____	_____
HUT	_____	_____	_____
# CORRECT	_____	_____	_____

HORSE	ruby*	CAVE	balloon	coffee	LION
house*	OPAL	TIGER	boat	scarf	PEARL
HUT	EMERALD	SAPPHIRE	dog*	apartment*	penny
TENT	mountain	cat*	HOTEL	COW	diamond*

Part B: Recognition:

 # True-Positives:_____/12

 # False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

Appendix B. Hopkins Verbal Learning Test (HVLT).
This is not an official version of the test. Words on the test vary with the test version administered. Official test can be purchased from: **Hopkins Verbal Learning Test–Revised | HVLT-R (parinc.com)**

State Trait Anxiety Inventory

Read each statement and select the appropriate response to indicate how you feel right now, that is, at this very moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	1	2	3	4
	Not at all	**A little**	**Somewhat**	**Very Much So**
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I feel tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel uncomfortable	1	2	3	4
11. I feel self confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I feel jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Appendix C. State Trait Anxiety Inventory (STAI).

This is not an official version of the questionnaire. This is also not the full-length version of the questionnaire. Official and full-length version can be purchased from: **State-Trait Anxiety Inventory for Adults (STAI-AD) - Assessments, Tests | Mind Garden - Mind Garden**

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	no
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	no
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	no
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

Total Score _____

Appendix D. Geriatric Depression Scale -Short (GDS).
More information on the measure can be found at: **Geriatric Depression Scale (GDS) (apa.org)**

Curriculum Vitae

Kunj Patel

Education

BACHELOR OF MEDICAL SCIENCES (HONORS SPECIALIZATION IN INTERDISCIPLINARY MEDICAL SCIENCES)
Western University, London, ON
September 2018- June 2022

MASTERS OF SCIENCE - NEUROSCIENCE
Western University, London, ON
September 2022 –Present

- Thesis: Biomarkers of Cognitive Impairment in Parkinson's Disease using structural MRI
- Supervisor: Penny MacDonald

Presentations

INSPIRING DIVERSITY IN STEM UNDERGRADUATE CONFERENCE
Western University, London, ON
March 12 & 13, 2022

- (2022). Functional Neuroimaging of Brain Injured Patients in the Intensive Care Unit: A Narrative Review. Inspiring Diversity in Stem Conference, London, Canada

WESTERN RESEARCH FORUM
Western University, London, ON
March 17, 2023

- (2023). Biomarkers of Cognitive Impairment in Parkinson's Disease using Structural MRI. Western Research Form, London, Canada

CLINICAL NEUROLOGICAL SCIENCES RESEARCH DAY
Western University, London, ON
May 16, 2023

- (2023). Biomarkers of Cognitive Impairment in Parkinson's Disease using Structural MRI. Western Research Form, London, Canada

SOCIETY FOR NEUROSCIENCE CONFERENCE 2023
Washington, DC
November 13, 2023

- (2023). Examining sex-differences in cognitive impairment in patients with Parkinson's disease. Society for Neuroscience, Washington, DC, USA.

NEUROSCIENCE RESEARCH DAY 2024
Western University, London, ON
February 23 & 24, 2024

- (2024). Cognitive deficits in Early Parkinson's Disease. Neuroscience Research Day, London, Canada

Related Work Experience

GRADUATE TEACHING ASSISTANT
London, ON
2022-2024

- *Third year physiology and Pharmacology lab (PHYSPHARM3000). Duties included guiding students through experiment design, data collection, data presentation, and*

writing. Marking duties included marking lab reports and assignments, as well as proctoring midterms and final exams.

Academic Achievements

DEANS HONOR ROLL *(Fall/Winter 2018-2022)*
ADMISSIONS SCHOLARSHIP *(Fall/Winter 2018-2022)*

- For an entrance average of 95% or higher
- $10,000 for four undergraduate years

WESTERN GRADUATE RESEARCH SCHOLARSHIP *(Fall/Winter/Summer 2022-2024)*

Text Interviews

December 1, 2021

Tackling London's health challenges through community-engaged learning, NewsSchulich School of Medicine and Dentistry https://www.schulich.uwo.ca/about/news/2021/december/tackling_londons_health_challenges_through_comm