Cognitive Reserve, Cholinergic White Matter Pathways and Cognition in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder identified by its motor symptoms. Cognitive impairments and eventual dementia are now acknowledged as common occurrences in PD and one potential cause of this cognitive decline may be related to cholinergic dysfunction. Deficits in the cholinergic nucleus basalis of Meynert (NBM) may influence cognitive decline in PD. Cognitive reserve (CR) is developed through life experiences and protects against disease-related brain changes by maintaining cognition/function in the presence of brain changes. Specifically, CR is suggested to moderate the effect of disease-related brain changes on clinical severity. Recent advances now allow in vivo imaging of the NBM using MRI. This study uses volumetric MRI and high angular resolution diffusion imaging (HARDI) to investigate NBM volume and NBM tract connection density in 110 PD (classified as PD with normal cognition (PD-N), PD with mild cognitive impairment (PD-MCI), and PD with dementia (PDD)) to 31 healthy elderly controls. Specifically, the influence of CR (as measured by both premorbid IQ and education) on the effect of NBM integrity MRI metrics on global cognition and cognitive domains in PD-N and PD-MCI was investigated. NBM volume was smaller in controls than PD. However, NBM-related brain metrics were not related to cognitive impairments and CR did not moderate the relationship between any NBM brain metric and cognitive measures. These preliminary findings require further investigation with NBM cholinergic measures that are more related to cognition and suggest that CR may not moderate in PD or may not play a large role in the cholinergic system.

1 Introduction

1.1 Parkinson's Disease – Overview

Parkinson's disease (PD) is a neurodegenerative disorder with debilitating symptoms that have a severe impact on the patient, their caregivers and poses an increasing burden on health resources (Dorsey & Bloom, 2018; Myall, Pitcher, Pearson, Dalrymple-Alford, Anderson & MacAskill, 2017). With changing population demographics, the number of people with a PD diagnosis is expected to double by 2040, including in New Zealand (NZ; Dorsey et al., 2018; Myall et al., 2017). In NZ approximately 1000 people are diagnosed with PD per year, with about 11,000 current cases (Myall et al., 2017).

PD is diagnosed by its motor symptoms, revealed by difficulties in executing voluntary movements, such as walking, as well as tremor, rigidity and impaired balance (Postuma et al., 2015). Non-motor symptoms include neuropsychiatric problems and disturbed sleep, which impose additional burden on patients' quality of life (Chaudhuri & Schapira, 2009). Most commonly, however, it is often declining cognition, especially when the decline is severe, that has the greatest impact on patients and their caregivers (Leroi, McDonald, Pantula & Harbishettar, 2012; Jones et al., 2017). Cognitive deficits are heterogeneous across patients and can occur in all cognitive domains, including executive function, attention, memory, visuoperceptual function and - perhaps less frequently - basic language function (Aarsland, Brønnick & Fladby, 2011; Cosgrove et al., 2015).

Dementia is very common in PD; dementia is present in over 80% of 20-year-survivors (Hely, Reid, Adena, Halliday & Morris, 2008). To address this issue, the Movement Disorder Society Task Force (MDS-TF) established research criteria to identify PD patients with mild cognitive impairment (PD-MCI; Litvan et al, 2012). A classification of PD-MCI is anticipated to reflect a stage before the onset of dementia, when cognitive impairment is beyond that of

age-expected norms, but everyday cognitive function is not significantly impaired. Meeting criteria for PD-MCI has been confirmed as a predictor of conversion to PD with dementia (PDD; e.g. Broeders de Bie et al., 2013; Hobson et al., 2015; Wood et al., 2016; Pedersen et al., 2017; Nicoletti et al., 2019). Large multinational retrospective studies have shown the risk of PDD is elevated in PD-MCI patients beyond the influence of age, sex, education, motor severity and depression (Hoogland et al., 2017; Hoogland et al., 2019). MDS-TF Level II PD-MCI criteria require the assessment of at least two tests in each of five cognitive domains (executive function, attention and working memory, episodic memory, visuospatial function and language); Level I criteria require a different pattern of assessment, such as fewer than two tests per domain or the use of global mental status tests (Litvan et al., 2012). However, the probability of detecting impairments to classify PD-MCI does not necessarily increase when more than two tests per cognitive domain are used (Goldman, Aggarwal & Schroeder, 2015). A recent analysis of the NZ Brain Research Institute's cognitive test battery determined the two neuropsychological test measures in each domain that were the best predictors of conversion to PDD, when using the common cut-off of -1.5 SD below normative values to signify impairment (NZBRI internal data analysis, Dr. Myall). Using only these two tests in each of the five cognitive domains reduced the total number of patients classified as PD-MCI but improved the specificity for conversion to PDD in a four-year period. These NZBRI criteria were used to classify the non-dementia PD patients in the current study.

Abnormal α-synuclein is a key neuropathology that defines Lewy body disorders such as PD (Sardi, Cedarbaum & Brundin, 2018). Alpha-synuclein normally plays a role in regulating neurotransmitter release. Abnormal metabolism and lack of clearance can lead to Lewy neurites and aggregated accumulations called Lewy bodies (Sardi et al., 2018). Dysfunction in various organelle processes as well as inflammatory responses are implicated (Lang & Espay, 2018). How α-synuclein aggregation and organelle dysfunction may interact

is currently unknown. For example, organelle dysfunction may influence α-synuclein aggregation, be caused by α-synuclein or play a role in other aspects of PD, such as Lewy pathology spread. Lewy pathology is thought to spread in a prion-like fashion from cell to cell and certain neurons such as those with long, poorly myelinated axons are preferentially vulnerable (Braak, Ghebremedhin, Rüb, Bratzke & Del Tredici, 2004; Lang & Espay, 2018).

Braak's proposed staging of progressive α-synuclein neuropathology in PD encapsulates its progression across neural systems (Braak et al., 2006). This emphasises how PD is a multi-system disorder, well beyond the classic motor disorder perspective. Braak's scheme suggests that Lewy pathology spreads in a topographically predictable manner through the brain across vulnerable neurons (Braak et al., 2004). This spread occurs over a long prodromal stage before symptom onset and a long post-symptomatic disease stage (Hawkes, Del Tredici & Braak, 2009). Their key proposal is that Lewy neuropathology begins in the lower brain stem and the olfactory bulb. Pathology then spreads towards areas such as the locus coeruleus and then the substantia nigra, nucleus basalis of Meynert and amygdala (Hawkes et al., 2009). In the post-symptomatic stages, the thalamus and temporal lobe are progressively more affected before these abnormalities extend to higher association areas of the cerebral cortex in the final stages (Braak et al., 2004). Hawkes et al. (2010) suggest the early stages correspond with more subtle autonomic symptoms, middle stages with classic motor symptoms and the final stages with severe cognitive impairments and eventually dementia. However, this pattern of spread is variable across patients. Symptoms and clinical severity are often found not to correlate with Braak's stages and key structures in Braak's theory do not always develop Lewy pathology (Jellinger, 2009). Autopsy studies have also found evidence of widespread α-synuclein pathology in healthy elderly with no reported evidence of neuropsychiatric symptoms (Jellinger, 2009). Therefore, the pattern and severity of α-synuclein and non-α-synuclein pathology may influence the manifestation of PD symptoms.

Nevertheless, while PD patients may not always adhere to Braak's stages, they provide a framework that emphasizes the involvement of many systems beyond the nigra-striatal dopaminergic system (Braak & Del Tredici, 2017). Degeneration of key dopaminergic cause decreased dopamine function in structures involved in generating voluntary movement and the core motor symptoms of PD (Guttman, Kish & Furukawa, 2003). These deficits are associated with the core motor symptoms of PD. Clearly, however, Lewy pathology is not limited to specific neurotransmitter systems. There is dysfunction and loss of cells in the locus coeruleus, which impacts noradrenergic systems, and a decline in the nucleus basalis of Meynert, which reduces cholinergic integrity in the forebrain, plus degeneration in other brain structures such as the hippocampus and amygdala (Braak et al., 2006; Gratwicke, Jahanshahi & Foltynie, 2015). These changes undoubtedly influence the cognitive impairments found in PD.

1.2 Cholinergic Impairments in Parkinson's Disease

Dysfunction in cholinergic systems are thought to be particularly relevant for cognitive and other non-motor symptoms in PD (Bohnen & Albin, 2011; Gratwicke et al., 2015; Perez-Lloret & Barrantes, 2016). PD patients have been found to have degeneration in the three main sources of cholinergic projections in the brain: the basal forebrain complex, the pedunculopontine nucleus-laterodorsal tegmental complex (PPN-LDTC) and striatal interneurons (Bohnen & Albin, 2011). Degeneration in these systems is associated with decreased cholinergic markers in the areas that receive inputs from them.

Gratwicke et al. (2015) suggest dysfunction of the cholinergic network from the nucleus basalis of Meynert (NBM) is critical in the development of cognitive impairments in PD. This nucleus in the basal forebrain is comprised of at least 90% cholinergic neurons (Mesulam, Mufson, Levey & Wainer, 1983). The NBM has widespread projections to the neocortex, parietal and occipital cortices and the medial temporal lobe (Gratwicke et al., 2015). These projections follow two main, medial and lateral, cholinergic pathways (Selden, Gitelman,

Salamon-Murayama, Parrish & Mesulam, 1998). The medial pathway projects anteriorly from the NBM and extends through the parolfactory and medial orbital gyri before coursing through the rostrum of the corpus callosum anteriorly and reaching the cingulum. It extends posteriorly through the cingulum to the splenium before reaching the retrosplenial white matter (Selden et al., 1998). The lateral pathway splits into capsular and perisylvian divisions. The capsular division extends in a dense bundle through the external capsule before splitting and travelling to the amygdala and temporal stem (Selden et al., 1998). The perisylvian division travels through the claustrum and towards the superior temporal and inferior frontal gyri. Individual fibers in all pathways radiate out to a vast number of areas in the cortex (Selden et al., 1998).

The activity of the NBM influences both bottom-up orienting of attention and top-down orienting of attention (Sarter et al., 2005, as cited by Gratwicke et al., 2015). Cholinergic deficits may also influence impairments in other cognitive domains. For example, deficits in orienting of attention may impair encoding of memories and visual discrimination (Gratwicke et al., 2015). Deficits in executive function may also be influenced by NBM dysfunction because of its dependence on other cognitive capacities, such as arousal and attentiveness. Thus, Gratwicke et al. (2015) suggest that NBM cholinergic network dysfunction is a key aspect of cognitive impairment and especially progression to PDD.

NBM deficits have been well documented in PD. About 32% cell loss has been reported in non-demented PD patients and 54-70% in PDD (Whitehouse et al., 1983, Gaspar & Grey, 1984, Perry et al., 1985, as cited by Gratwicke et al., 2015; Hall et al., 2014). Post-mortem studies have found Lewy pathology in the NBM and associated cortical cholinergic deficits in both non-demented PD and PDD, despite only PDD having cholinergic cell loss in the NBM (Hall et al., 2014). Degeneration of the NBM, measured with MRI has also been found to be a significant predictor of future cognitive decline, specifically small grey matter volume and microstructural alterations (Ray et al., 2017; Schulz, Pagano, Bonfante, Wilson & Politis,

2018). Gargouri et al. (2018) reported that connections between the NBM and the associative prefrontal cortex, occipital cortex and peri-insular cortex were weaker in nondemented PD patients. They also found reduced functional connectivity between the NBM and the right inferior frontal area and the thalami, as well as reduced structural integrity of the NBM. These deficits were associated with tests of global cognition and executive function (Gargouri et al., 2018).

1.3 Diffusion MRI

Gargouri et al. (2018) demonstrated that diffusion imaging can be used to measure cholinergic white matter pathways in PD. Diffusion imaging may provide a non-invasive (compared to PET or SPECT) method to examine cholinergic pathways in the brain. Diffusion MRI utilizes the random diffusion of water molecules in the brain, which the MRI is made sensitive to. Microstructure of the brain can be inferred by mathematical models, based on the direction of diffusion after a diffusion gradient is applied. Diffusion tensor imaging (DTI) is the most commonly applied form of diffusion MRI and models a tensor in each voxel (based on six diffusion directions; Dell'Acqua & Tournier, 2018). However, DTI has a few limitations. The direction of fiber populations can only be estimated in one direction per voxel and estimation is limited by the small number of diffusion directions. The resolution of diffusion imaging is only a few millimeters, which means that crossing, bending and diverging fibers can easily occur in a single voxel. Fibers such as these are thought to occur in 90% of white matter voxels (Jeurissen, Leemans, Tournier, Jones & Sijbers, 2013). High angular resolution diffusion imaging (HARDI) uses diffusion weighting in more directions and uses steeper diffusion gradients (Tuch et al., 2002). Using the increased diffusion data and more complicated diffusion models, HARDI allows for the accommodation of multiple fiber populations in a voxel (Raffelt et al., 2017). Therefore, HARDI was used to allow for more accurate representation of white matter fibers in this thesis.

1.4 Cognitive Reserve

One aspect of variability in how a disease impacts patient function, including heterogeneity in cognitive deficits, may be influenced by resilience to the effects of the disease. This idea is embodied in the concept of "reserve" (Stern et al., 2018). The idea of reserve was proposed after Katzman et al. (1989) discovered advanced Alzheimer's disease (AD) pathology in the brain of healthy elderly (as cited in Stern, 2002). Since then many studies have observed that the extent of brain damage or pathology does not directly correlate with the severity of symptoms across individuals (Stern, 2002).

The key idea behind the cognitive reserve (CR) hypothesis is that CR moderates the relationship between brain changes and clinical severity. This means that a given level of change in brain structure or neuropathology has less of an influence on cognition when someone has high CR (Stern et al., 2018). CR is thought to operate through functional brain processes and is determined by factors such as genetic differences and IQ and developed throughout life by lifestyle factors such as education, occupation and social and physical activities (Stern et al., 2018). The latter measures, as well as premorbid IQ, are often used as proxy measures of CR in research studies. Education is the most commonly used CR measure, followed by occupation and premorbid IQ (Jones et al., 2011). A variety of indexes and questionnaires addressing a range of lifestyle factors also exist as composite measures of CR (Stern et al., 2018).

Studies investigating the role of CR in PD have found that higher education is associated with less severe motor symptoms (Kotagal et al., 2015; Sunwoo, Hong, Lee, Lee & Sohn, 2016; Blume, Rothenfusser, Schlaier, Bogdahn & Lange, 2017). Both higher education and premorbid IQ has been associated with better cognitive performance (Koerts, Tucha, Lange & Tucha, 2013; Hindle et al., 2016; Rouillard et al., 2017; Ciccarelli et al., 2018). A measure of occupational decision-making has also been associated with cognitive function (Rouillard

et al., 2017). Composite CR measures such as the Lifetime of Experiences Questionnaire and Cognitive Reserve Index (which combine information about education, occupation and social activities to get a CR 'score') have been associated with better motor function (Hindle et al., 2017; Guzzetti, Mancini, Caporali, Manfredi & Daini, 2019) and cognitive performance (Sánchez, Rodríguez & Carro, 2002; Ciccarelli et al., 2018; Guzzetti et al., 2019).

However, previous studies that have investigated CR in PD often fail to examine how brain changes affect cognition, a critical aspect of CR theory. This is problematic for two reasons. Critically, CR studies that do not link brain metrics and cognition cannot demonstrate that CR helps to maintain function in the presence of poor brain integrity. Secondly, these studies cannot confirm that any maintained function is not due to having more intact brain measures. That is, studies that investigate the effects of CR should account for brain measures to determine whether any preserved function is due to CR or differences in brain integrity.

Some studies in PD have taken into account brain metrics when investigating CR. For example, Kotagal et al. (2015) controlled for cortical grey matter volume and found that more education was associated with fewer motor deficits in PD. This effect was independent of nigrostriatal dopaminergic denervation. Sunwoo et al. (2016) demonstrated that PD patients with higher education had less dopamine in the putamen despite less severe motor impairments. Rouillard et al. (2017) looked at the effect of four lifelong CR factors on cognitive performance at different levels of global brain atrophy and found that education was most consistently associated with cognitive function and the beneficial effect of CR on cognition was most evident in PD patients with a moderate amount of brain atrophy.

Controlling for brain measures is the first step for isolating the effects of brain changes on cognition or clinical severity from the effect of CR. However, Stern et al. (2018) state that looking at the association between CR and cognition (or clinical severity) does not assess the

moderating effect of CR. Instead it is the interaction effect between CR and a brain measure that is relevant. The interaction effect examines whether CR influences the effect of brain metrics on a clinical outcome. The only study in PD to investigate the moderating effect of CR examined whether education moderated the relationship between β-amyloid accumulation and cognitive impairment (Lucero, Campbell, Flores, Maiti, Perlmutter & Foster, 2015). They found that β-amyloid accumulation was negatively associated with global cognition in PD patients with low education, but not in those with higher education. However, β-amyloid deposition may be less relevant to PD than it is to AD (Melzer et al., 2019). Remarkably, no other studies in PD have explicitly looked at the moderating effect of CR. Thus, the investigation of the moderating effect of CR on brain changes that are critical in cognitive decline in PD provides an exciting opportunity to further our understanding of the complex relationship between brain health, disease, CR, and cognitive impairments in PD.

1.5 Overview of the current study

The current study focused on the NBM and its associated white matter pathways, as the NBM may be a critical structure in the evolution of cognitive decline in PD. The aim for this study was to examine the moderating effect of CR on the impact of changes in the NBM with respect to current cognition, in a cross-sectional study. First, we examined the grey matter integrity of the NBM as well as the connectivity within three primary pathways that arise from the NBM (1) through the cingulate, (2) through the temporal stem and (3) through the external capsule (Selden et al., 1998) by comparing aged healthy (non-PD) controls, PD-N, PD-MCI and PDD groups of patients. High angular resolution diffusion imaging (HARDI) was used to capture the fiber connection density of these tracts. The moderating effect of CR on the association between these measures and cognition was the main focus on this thesis. CR was measured by education and premorbid IQ.

2 Methods

2.1 Participants

As part of an ongoing longitudinal study based at the New Zealand Brain Research Institute (NZBRI), 34 elderly controls and 110 Parkinson's disease received a single high angular resolution imaging (HARDI) scan between 09/05/2015 and 20/05/2017. Exclusion criteria for the NZBRI longitudinal cohort were an atypical Parkinsonian disorder, history of moderate/severe head injury, stroke, major medical or psychiatric illness in the previous 6 months or early-life learning disability, or poor English. PD patients were diagnosed using the UK Parkinson's Society criteria (Hughes, Daniel, Kilford & Lees, 1992), supplemented recently by the MDS criteria (Postuma et al., 2015). To exclude patients with dementia with Lewy bodies, motor symptoms had to be present for at least one year before the onset of cognitive decline. PD-MCI was defined following the Movement Disorders Society Level II criteria for mild cognitive impairment. Specifically, this was defined as having impairments (1.5 SD below normative data) in two neuropsychological tests across any of the five cognitive domains (in a battery of ten tests with two for each domain, see below) but no evidence of significant functional impairments in everyday instrumental activities of daily living (Litvan et al., 2012). PDD was defined as having evidence of significant functional impairment in everyday activities that were not due to motor symptoms, and substantial cognitive impairments, defined as impairments (2 SD below normative data) in at least two of five cognitive domains. Of the 110 PD patients meeting inclusion/exclusion criteria, 39 were classified as PD-N, 61 as PD-MCI and 10 as PDD (Emre et al., 2007; Litvan et al., 2012). Three elderly controls with HARDI scans were excluded for meeting criteria for MCI, leaving a final sample of 31 cognitively normal elderly controls. The study was approved by a local ethics committee of the New Zealand Ministry of Health and all participants provided informed consent.

2.2 Neuropsychological Evaluation

Tests were conducted over two sessions by a team of research fellows at NZBRI who were experienced in conducting neuropsychological tests and interviewing significant others of the PD patients. The author did not conduct any of these tests. Assessments occurred within four months of the HARDI scan. These examined Hoehn and Yahr stage, the Unified Parkinson's disease rating scale (UPDRS III), the Montreal Cognitive Assessment (MoCA), the Clinical Dementia Rating scale (CDR), and the Wechsler Test of Adult Reading (WTAR), as well as a battery of neuropsychological tests in five cognitive domains. This study used the ten cognitive tests that Dr Myall (research fellow at NZBRI) found to be the most predictive of conversion to PDD (NZBRI internal data analysis); there were two tests per cognitive domain and impairment on two tests at -1.5SD below normative data were used to define PD-MCI patients. The Z score of the two tests in one domain were averaged to create domain scores. Executive function was examined using D-KEFS Stroop interference and Trail Making Part B. Attention, working memory and processing speed was measured using digit ordering and TEA map search. Visuoperceptual/visuospatial performance was assessed using Rey Complex Figure Test Copy and judgement of line orientation. Episodic memory was determined by the California Verbal Learning Test-II word list total immediate recall across four acquisition trials and the Rey Complex Figure Test (3-minute short delay). Language was evaluated using the Dementia Rating Scale-2 similarities subtest and the language component of the Alzheimer's Dementia Assessment Cognitive Scale (object and finger naming, commands, comprehension, spoken language and word-finding difficulties). Age, education and sex standardised Z scores were obtained for each neuropsychological test and these were used to create average Z scores for each cognitive domain and a global average Z score for each participant. The WTAR (premorbid IQ) and years of education were used as measures of CR.

2.3 Neuroimaging

2.3.1 MRI Acquisition

MR and diffusion weighted images (DWI) were acquired on a 3-tesla General Electric HDxt scanner with an eight-channel head coil. A volumetric T1-weighted MRI (spoiled gradient recalled echo; TE/TR = 2.8/6.6 ms, inversion time = 400 ms, flip angle = 15°, acquisition matrix = 256 × 256 × 170, field of view = 250 mm, slice thickness = 1 mm), T2-weighted MRI and T2-weighted fluid-attenuated inversion recovery MRI sequence (FLAIR; TE/TR = 105/9,000 ms, inversion time = 2,250 ms, slice thickness = mm, gap = 1.5 mm) were also acquired. High angular resolution diffusion imaging (HARDI) images were acquired using a 2-dimensional diffusion-weighted, spin-echo, echo planar imaging sequence with diffusion weighting in 60 uniformly distributed directions (b = 2,500 s/mm²) and 6 acquisitions without diffusion weighting (b = 0 s/mm²): echo time (TE)/repetition time (TR) =96.1/10,000 ms, flip angle = 90°, acquisition matrix = 128 × 128 × 74, field of view = 250 mm, slice thickness = 2 mm, and voxel size = 1.95 × 1.95 × 2 mm³, phase encoding direction = anterior-posterior, NEX = 1, ungated. An additional b=0 s/mm² image was acquired with reversed phase encoding (posterior-anterior) in order to facilitate susceptibility artefact minimization.

2.3.2 MRI Preprocessing

T1-weighted images were processed using CAT12 (http://www.neuro.uni-jena.de/cat/), an SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/), and Matlab 9.5.0. T1 images were classified into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), bias corrected, spatially normalised to the MNI-registered template in CAT12 via DARTEL and modulated to compensate for spatial normalization. A study-specific structural template was created by averaging the modulated, normalized T1 scans of 34 controls.

HARDI preprocessing was done using MRTrix3 (Brain Research Institute, Melbourne, Australia, http://www.mrtrix.org/) by Megan Stark, PhD student (except for SIFT2). Images

were denoised (Veraart et al., 2016) and adjusted for ringing artefacts using Gibbs-ringing artefact removal (Kellner, Dhital, Kiselev & Reisert, 2016). Eddy current distortions and susceptibility induced distortions were corrected by reversed phase-encoding (Andersson, Skare & Ashburner, 2003; Holland, Kuperman & Dale, 2010). Preprocessing also included movement and bias field correction (Andersson & Sotiropoulos, 2016).

Response functions for white matter and cerebrospinal fluid were calculated in each voxel from the diffusion-weighted images (Dhollander, Raffelt & Connelly, 2016). Constrained spherical deconvolution was used to estimate the fibre orientation distribution (FOD) in each voxel (Tournier, Calamante, Gadian & Connelly, 2004; Tournier, Calamante & Connelly, 2007). FODs underwent global intensity normalisation. To perform Anatomically Constrained Tractography (ACT; this increases the biological plausibility of the streamlines created; Smith, Tournier, Calamante & Connelly, 2012), a 4D preprocessed T1 image with five different tissue types (cortical and subcortical GM, WM, CSF and pathological tissue) was created and co-registered to the diffusion-weighted image (DWI) using FSL (Jenkinson, Beckmann, Behrens, Woolrich & Smith, 2012). This was used to help determine where streamlines could plausibly begin and end. Whole brain probabilistic tractography was used to generate 10 million streamlines for each subject (Tournier, Calamante & Connelly, 2010). The SIFT2 algorithm (Smith, Tournier, Calamante & Connelly, 2015b) assigned each streamline a weight based on the estimated FOD. A study-specific FOD template was created out of 32 participants (eight each of control, PD-N, PD-MCI and PDD groups) as part of the processing pipeline. The average T1 template was non-linearly registered to this FOD template (using FSL's FNIRT) to allow regions of interest (ROIs, see below) to be viewed both in T1 space and HARDI space. For each subject their T1 scan was non-linearly registered to their estimated FOD to allow for visual inspection of ROIs and tract streamlines.

2.3.3 Region of Interest (ROI) Analysis

All ROIs were manually drawn on the study-specific FOD template, with the anterior commissure defined as the origin. The NBM seed regions were based on Selden et al.'s (1998) detailed sectioning of the cholinergic pathways from the NBM. The NBM ROI extended 34mm laterally, starting 3mm from the midline. The superior portion of the ROI began 8mm ventral from the superior edge of the AC and extended 14mm ventrally at its lowest point. The medial section of the ROI extended 4mm posteriorly and 8mm anteriorly from the middle of the AC, while the lateral sections extended 8mm posteriorly and 8mm anteriorly. The ROIs were not made symmetrical due to a head tilt in the study specific FOD template that was consistent with a head tilt from participants when they were in the MRI scanner.

ROI placement is displayed in Figure 1.The cingulate ROIs and sub genu ROIs were adapted from those described by Hong and Jang (2010). The anterior cingulate ROI extended 22mm laterally from the midline at its widest point in the coronal slice containing the posterior edge of the genu of the corpus callosum. The ROI extended 4mm posteriorly and was 26mm dorsal-to-ventral at the most medial edge; it was 12mm dorsal-to-ventral at the lateral edge of the left anterior cingulate ROI and 14mm dorsal-to-ventral at the lateral edge of the right anterior cingulate ROI. The posterior cingulate ROI extended 20mm laterally at its widest point, 1mm from the midline in the coronal slice containing the anterior splenium of the corpus callosum. It extended 4mm posteriorly and was 32mm dorsal-to-ventral at the most medial edge; 14mm dorsal-to-ventral at the lateral edge of the left posterior cingulate ROI and 16mm dorsal-to-ventral at the lateral edge of the right posterior cingulate ROI. The dorsolateral and ventrolateral 'corners' of all the cingulate ROIs were not part of the ROI, giving each cingulate ROI a semi-circle shape.

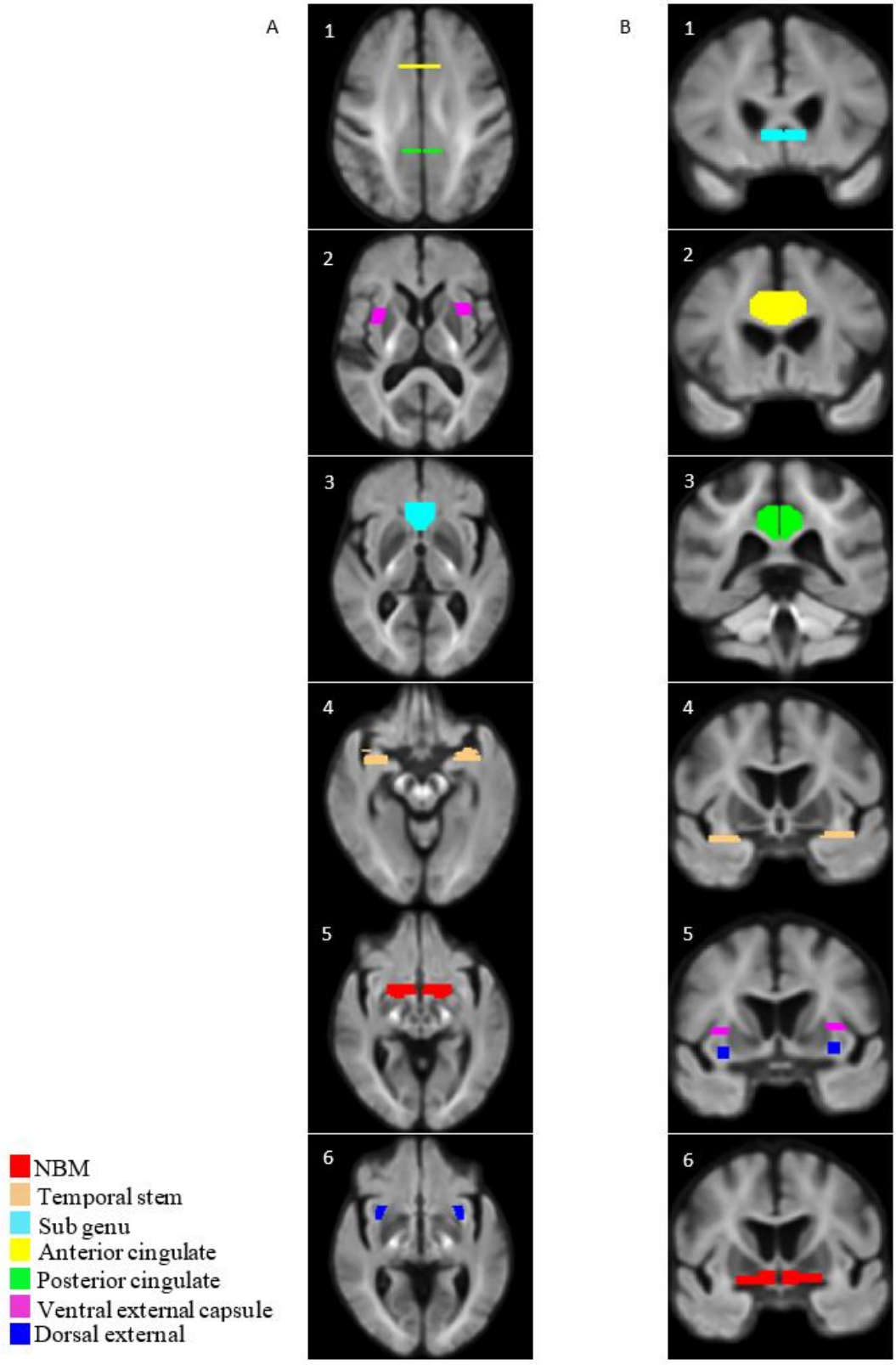

Figure 2-A. ROI placements on the study-specific template. (A) Axial slices from dorsal [1] to ventral [6]. (B) Coronal slices from anterior [1] to posterior [6].

The sub genu ROI was located anteroventral to the anterior cingulate ROI, just ventral to the genu of the corpus callosum. The ventral and dorsal external capsule and temporal stem ROIs were also based off Selden et al.'s (1998) sectioning. The external capsule ROIs were placed on the lateral edges of the putamen (dorsally and ventrally). The temporal stem was located ventrolateral to the NBM and lateral to the dentate gyrus and hippocampus.

NBM volume was obtained from the modulated, normalized GM T1 segments and was calculated by aggregating voxel volume × probability of being GM, for each voxel in the NBM ROI. Intracranial volume (ICV) was also obtained using the automatic reverse brain mask method, in which the SPM brain mask was inverse normalized to each subject's space using DARTEL-derived deformations and nearest neighbour interpolation (Hansen et al., 2015).

The whole brain tractogram was edited to capture only tracts that traversed all inclusion ROIs (using *tckgen*). The cingulate tracts included the sub genu and anterior and posterior cingulate ROIs. External capsule tracks included ventral and dorsal external capsule ROIs. Temporal stem tracts included the NBM and temporal stem ROIs. For the temporal stem tracts, the NBM ROIs were extended 4mm posteriorly to better capture the tracts exiting the posterior part of the NBM. The temporal stem and external capsule tracts were generated to terminate in the ROI so only the tracks between the two ROIs were captured. Tract tracing was performed in left and right hemispheres separately. Streamline weights from SIFT2 of the whole tractogram were included in track editing. Each streamline (in each individual tract) was assigned a weight and these were aggregated to produce a total tract weight based on the estimated FOD. The total tract weight served as a representation of tract connection density (TCD).

2.4 Statistical Analysis

Statistical analyses were completed using the R Statistical Environment (v3.6.2; http://CRAN.R-project.org/doc/). Demographic characteristics, cognition and brain measures were compared across the Healthy Control, PD-N, PD-MCI and PDD groups using ANOVA for continuous variables and χ^2 tests for dichotomous variables. The Tukey HSD test was used for any post-hoc comparisons of group differences.

Cognitive reserve analyses were examined in the PD-N and PD-MCI sample only. The PDD group was excluded because CR effects are not found in populations with significant atrophy (Mungas et al., 2018). Multiple linear regression analyses were used to predict cognitive performance as a function of brain measure and the product of brain measure and CR(i.e. interaction) . Six cognitive performance metrics were investigated: (1) average global Z score, (2) executive function, (3) attention, working memory and processing speed, (4) episodic memory, (5) language and (6) visuoperceptual/visuospatial function. There were four brain measures: (1) relative NBM volume (see below), (2) tract connection density (TCD) of the cingulate, (3) TCD of the temporal stem, and (4) TCD of the external capsule. There were two measures of cognitive reserve: (1) years of education, and (2) IQ as estimated by the WTAR. For each cognitive performance metric (x6), brain measure (x4), and cognitive reserve metric (x2), the following stepwise series of models were conducted:

Model 1 included only age as a predictor of the cognitive performance metric.

Model 2 included age and the brain measure as predictors of the cognitive performance metric.

Model 3 included age, brain measure and the CR measure as predictors of the cognitive performance metric.

Model 4 included age, brain measure, CR measure and the interaction (i.e. product) between the brain measure and the CR measure as predictors of the cognitive performance metric.

For each series of models used to predict each cognitive performance metric, models were compared using the Akaike information criterion (AIC) to select the model with the best fit. Only the model with the lowest AIC is reported for each cognitive performance metric.

To account for the strong correlation between NBM volume and ICV, a relative NBM volume was calculated (NBM volume divided by ICV). For all models, education, premorbid IQ, age, relative NBM volume, and cingulate, temporal stem and external capsule TCD were mean-centred. Premorbid IQ, age, relative NBM volume and cingulate TCD were divided by ten. Temporal stem and external capsule TCD were divided by one hundred. These were done to make estimates from the regression models more interpretable.

3 Results

3.1 Group differences in demographics

Demographic characteristics and cognitive performance of the controls, PD-N, PD-MCI and PDD groups are displayed in Table 3-A. Group differences were found in premorbid IQ estimated with the WTAR ($F(3,137) = 3.47$, $p = 0.018$). Post hoc comparisons indicated that the mean WTAR score of the control group was significantly higher than the mean premorbid IQ of the PD-MCI and PDD groups, but not significantly higher than the PD-N group. There were no significant differences in years of education across the four groups. As expected significant differences were found in global cognition ($F(3,133) = 125.7$, $p < 0.001$), executive function ($F(3,135) = 77.96$, $p < 0.001$), attention and working memory ($F(3,135) = 68.54$, $p < 0.001$), episodic memory ($F(3,133) = 50.71$, $p < 0.001$), visuospatial/visuoperceptual function ($F(3,134) = 39.96$, $p < 0.001$) and language ($F(3,135) = 27.1$, $p < 0.001$). Post hoc comparisons indicated that for global cognition, attention and episodic memory, the healthy control group had significantly higher scores than all PD groups, the PD-N group had higher scores than PD-MCI and PDD groups, and the PD-MCI group had higher scores than PDD group. For executive function, visuospatial/visuoperceptual function and language, the healthy control group had significantly higher scores than PD-MCI and PDD groups, the PD-N group had higher scores than the PD-MCI and PDD group, and the PD-MCI group had higher scores than the PDD group.

3.2 Group differences in brain metrics

MRI metrics of each group are presented in Table 3-B. Only NBM volume was significantly different across groups ($F(5,132) = 19.4$, $p < 0.001$) when age and ICV were controlled for. Post hoc tests indicated that the mean NBM volume of both PD-N and PD-MCI groups was significantly smaller than the mean NBM volume of the controls. The PDD group did have smaller NBM volumes than the control group but the differences were not significant, likely

Table 3-A. Demographic, Clinical and Cognitive Characteristic (mean(s.d.)

	Controls	PD-N	PD-MCI	PDD
Sample size	31	39	61	10
Age (years)[g]	73.77 (7.99)	69.49 (7.22)	71.95 (6.46)	76.54 (5.38)
Gender (M/F)	22/9	28/11	43/18	8/2
MoCA[f]	26.58 (2.41)	25.72 (2.41)	22.39 (2.97)	16.20 (3.55)
Education (years)	14.00 (2.78)	13.21 (2.84)	13.02 (2.84)	12.40 (2.32)
Premorbid IQ (WTAR)[g]	113.97 (8.55)	111.15 (9.31)	108.46 (10.12)	104.80 (9.94)
Symptom duration (years)		10.35 (4.93)	10.48 (5.75)	9.88 (6.05)
Hoehn & Yahr stage[g]		2.37 (0.64)[a]	2.56 (0.56)	3.00 (0)[b]
UPDRS III[f]		34.97 (12.00)[a]	40.62 (14.17)	51.50 (8.43)[b]
LED (mg/d)		825.06 (457.90)	960.33 (627.16)[c]	1072.60 (550.39)
CDR[f]	0.02 (0.09)[e]	0.20 (0.25)[a]	0.40 (0.23)[d]	1.25 (0.54)
Global Z score[f]	0.60 (0.42)	0.09 (0.52)[a]	-1.04 (0.49)[c]	-2.11 (0.47)[b]
Executive function[f]	0.87 (0.36)	0.39 (0.60)	-1.07 (1.03)	-2.77 (0.58)[b]
Attention and working memory[f]	0.11 (0.69)	-0.46 (0.68)	-1.59 (0.64)	-2.55 (0.54)[b]
Episodic memory[f]	1.59 (0.97)	0.70 (1.12)[a]	-0.79 (0.98)[c]	-1.79 (1.00)[b]
Visuoperceptual/ visuospatial[f]	0.26 (0.64)	-0.14 (0.64)[a]	-1.16 (0.87)	-2.10 (0.72)[b]
Language[f]	0.15 (0.36)	-0.02 (0.47)	-0.56 (0.59)	-1.33 (0.75)[b]

Abbreviations: CDR, clinical dementia rating; LED, Levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson's disease rating scale (motor component); WTAR, Wechsler test of adult reading.

[a] n = 38; [b] n = 8; [c] n = 60; [d] n = 57; [e] n = 28. UPDRS III, Hoehn & Yahr stage were not collected in one PD-N due to recent surgery and the Rey Complex Figure Test (copy and immediate recall) was not collected for unknown reasons. LED was not collected in one PD-MCI. Two PDD underwent short assessments that did not assess UPDRS III, Hoehn & Yahr stage or neuropsychological measures. Rey Complex Figure Test (immediate recall) was not collected in one PD-MCI for unknown reasons. Three control, one PD-N and four PD-MCI did not have CDR because significant other sessions were not completed. Missing data in the domain scores prevented calculation of Global Z score for one PD-N, one PD-MCI and two PDD.

Significant analysis of variance/χ^2 across groups, $p < 0.01$ [f], $p < 0.05$ [g]

because of the small PDD sample size. An example of the streamlines extracted for each tract in displayed in Figure 3-A. Connection density of the cingulate ($F(3,119) = 0.30$, $p = 0.81$), external capsule ($F(3,128) = 0.27$, $p = 0.84$) and temporal stem ($F(3,131) = 1.98$, $p = 0.11$) tracts and ICV ($F(3,137) = 0.25$, $p = 0.85$) were not significantly different between groups.

3.3 Influence of cognitive reserve

3.3.1 NBM

The interaction between CR (premorbid IQ or education) and NBM volume was never associated with any cognitive performance metrics. Only age and premorbid IQ were significantly associated with the cognitive measures across models.

For global Z score, Model 3 with premorbid IQ as the CR variable was selected. Age was significantly negatively associated ($b = -0.59$, $p = 0.03$) and the WTAR was significantly directly associated ($b = 0.20$, $p = 0.007$) with global Z. However, NBM volume did not reach significance ($b = 0.11$, $p = 0.27$).

For executive function, Model 1 had the lowest AIC. Age was negatively associated ($b = -0.40$, $p = 0.02$). For the attention domain, Model 2 was selected, but only age was significantly negatively associated ($b = -0.34$, $p = 0.01$); although Model 2 produced the lowest AIC, NBM volume itself showed no significant association with the attention domain score (b = 0.19, p = 0.11).

Model 3 with premorbid IQ as the CR measure was selected for visuospatial/visuoperceptual function. Only the WTAR was significantly directly associated ($b = 0.24$, $p = 0.01$), NBM volume ($b = -0.09$, $p = 0.48$) and age were not ($b = -0.11$, $p = 0.45$).

Model 3 with premorbid IQ as CR was the best at predicting episodic memory, with only the WTAR being significantly positively associated ($b = 0.31$, $p = 0.02$). NBM volume ($b = -0.27$, $p = 0.14$) and age ($b = -0.13$, $p = 0.51$) were not significantly associated.

Table 3-B. MRI Metrics (mean(s.d.)

	Controls	PD-N	PD-MCI	PDD
Sample size	31	39	61	10
NBM volume[i] (mm^3)	1484.04 (132.28)	1429.63 (152.07)[e]	1404.32 (130.36)[h]	1402.17 (116.58)
Cingulate TCD	63.34 (47.29)[a]	57.14 (41.86)[c]	62.82 (47.35)[f]	73.16 (59.88)
Temporal stem TCD	384.43 (160.80)[a]	443.83 (154.88)[e]	467.05 (157.62)[g]	404.12 (112.43)
External capsule TCD	290.08 (139.53)[b]	266.08 (118.31)[d]	280.63 (134.12)[g]	301.64 (163.29)
ICV	1557.11 (144.33)	1579.98 (138.69)	1564.61 (136.39)	1589.35 (121.68)

Abbreviations: TCD, track connection density; ICV, intracranial volume

[a] n = 28; [b] n = 30; [c] n= 31; [d] n = 36; [e] n = 38; [f] n = 54; [g] n= 56; [h] n = 59. For each brain metric, outliers that were 1.5× the interquartile range above the upper quartile were excluded from the analysis.

[i] Significant analysis of variance across group, controlling for age and ICV, $p < 0.001$

For language function, Model 4 with premorbid IQ (WTAR) as CR was selected. Only the WTAR had a significant association with language performance ($b = 0.18$, $p = 0.004$). Age ($b = -0.14$, $p = 0.12$), NBM volume ($b = 0.12$, $p = 0.16$) and the WTAR x NBM volume interaction ($b = 15$, $p = 0.16$) were not significantly associated with language function.

3.3.2 Cingulate tract connection density

The model with the interaction between CR (premorbid IQ or education) and cingulate TCD was never selected as the best predictor of any of the cognitive performance metrics. For cingulate tract connection density, age was associated with cognitive performance the most and premorbid IQ was only associated with visuospatial/visuoperceptual function. When predicting global cognitive ability (global Z score), Model 1 with age ($b = -0.23$, $p = 0.05$) as the only predictor, produced the lowest AIC and was selected. Model 1 was also selected for executive function ($b_{age} = -0.45$, p = 0.01) and attention ($b_{age} = -0.36$, p = 0.009).

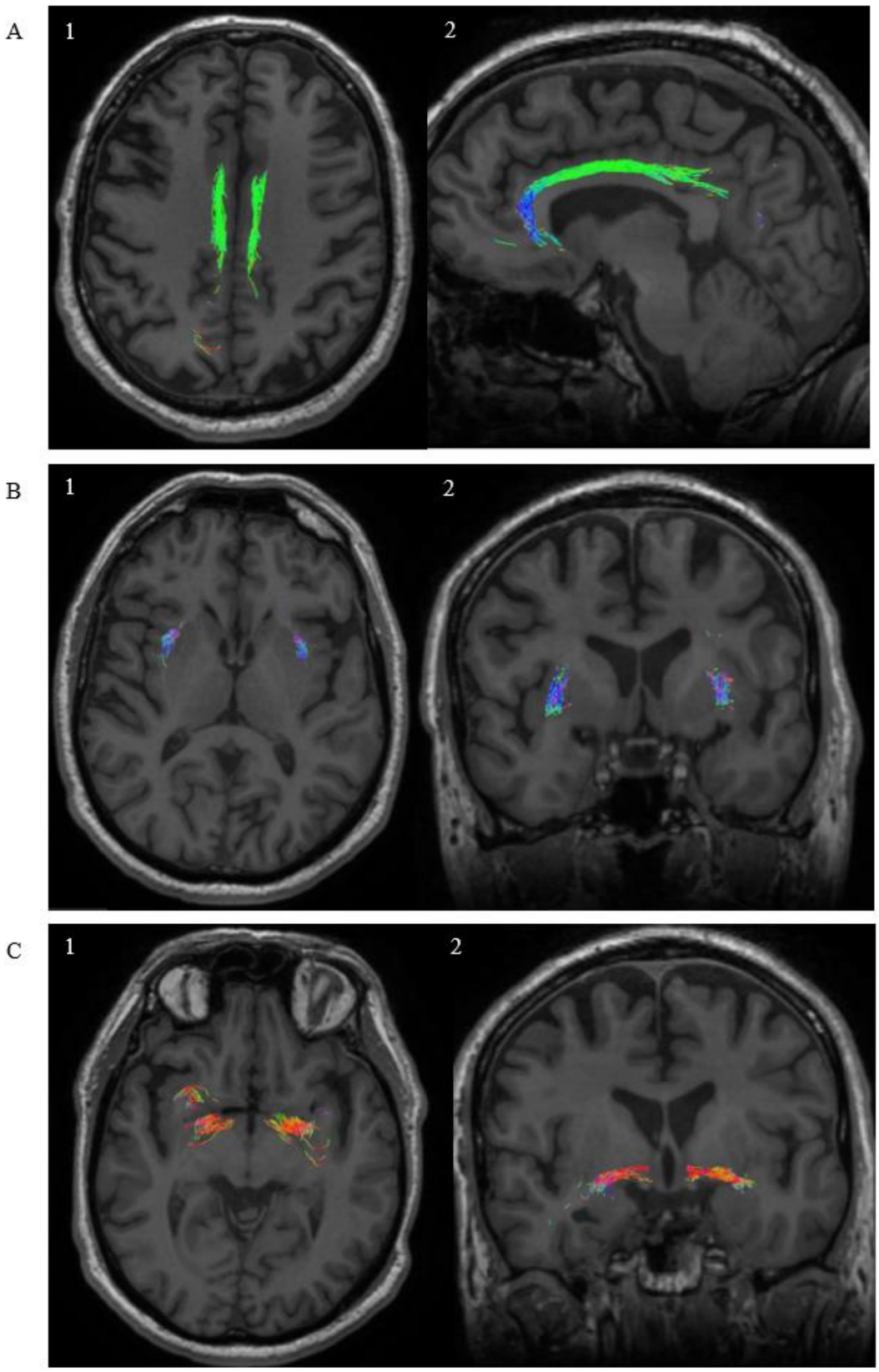

Figure 3-A. Example of Streamlines Captured in each Tract on a T1 Scan of 65-year-old Healthy Control(A) Axial [1] and sagittal [2]

For visuospatial/visuoperceptual function, Model 3 with premorbid IQ as CR was selected. Only the WTAR was significantly positively associated (b = 0.25, p = 0.02). Age (b = -0.04, p = 0.79) and cingulate TCD (b = -0.01, p = 0.54) did not reach significance.

For memory function, Model 1 with only age was selected (b_{age} = -0.12, p = 0.56) and this was also the case for language function (b_{age} = -0.15, p = 0.10).

3.3.3 Temporal stem tract connection density

The interaction between CR (premorbid IQ or education) and temporal stem TCD had a trend towards being associated with visuospatial/visuoperceptual function. This was the only time Model 4 was selected to explain cognitive measures. Premorbid IQ was associated with global Z, memory and language performance. For the global Z score, Model 3 with premorbid IQ as the CR variable was selected. Both age (b = -0.28, p = 0.009) and the WTAR (b = 0.21, p = 0.005) reached significance, but temporal stem TCD did not reach significance (b = 0.01, p = 0.70). Model 1 with age only was selected for executive function (b_{age} = -0.44, p = 0.00) and attention (b_{age} = -0.41, p = 0.001).

For visuospatial/visuoperceptual function, Model 4 with premorbid IQ was chosen, where premorbid IQ was significant (b = 0.26, p = 0.008) and the interaction between temporal stem TCD and the WTAR approached significance (b = -0.14, p = 0.05). Age (b = -0.08, p = 0.53) and temporal stem TCD (b = 0.26, p = 0.14) were not significant.

Model 3 with premorbid IQ was selected for episodic memory. The WTAR was significantly associated with memory (b = 0.34, p = 0.01), but age (b = -0.23, p = 0.20) and temporal stem TCD (b = 0.11, p = 0.19) were not.

For language function, Model 3 with premorbid IQ as CR was also selected and the WTAR was significantly associated with language performance (b = 0.16, p = 0.01). Age (b =

-0.14, p = 0.11) and temporal stem TCD (b = -0.06, p = 0.08) however, were not significantly associated with language performance.

3.4 External capsule tract connection density

The interaction between CR (premorbid IQ or education) and external capsule TCD was never associated with any cognitive performance metrics. Age and premorbid IQ were the most consistently associated with cognitive performance. For global Z, Model 3 with premorbid IQ as CR was selected. Both age (b = -0.31, p =0.006) and the WTAR (b = 0.21, p = 0.006) were significantly associated with global Z, but external capsule TCD was not (b = -0.03, p = 0.54).

For executive function, Model 1 was selected, and age was significant (b = -0.43, p = 0.01). Model 1 was also selected for attention and age was significant (b = -0.40, p = 0.002).

For visuospatial/visuoperceptual function, Model 3 with premorbid IQ as CR was selected. The WTAR was significant (b = 0.26, p = 0.007), but age (b = -0.18, p = 0.18) and external capsule TCD (b = -0.07, p = 0.35) were not.

Model 3 with premorbid IQ as CR was the best at predicting episodic memory with only the WTAR being significant (b = 0.33, p = 0.01), while age (b = -0.28, p = 0.15) and external capsule TCD (b = -0.05, p = 0.63) were nonsignificant.

Model 3 with premorbid IQ as CR was selected for language function and the WTAR was significant (b = 0.18, p = 0.003). Age (b = -0.15, p = 0.07) and external capsule TCD (b = -0.02, p = 0.63) did not reach significance.

4 Discussion

4.1 Summary of Findings

This study focused on the NBM and its associated white matter pathways in PD. These cholinergic pathways may play a significant role in PD-related cognitive decline (Gratwicke et

al., 2015; Ray et al., 2017; Schulz et al., 2018). NBM volume and connection density of related tracts were assessed in PD patients with varying cognitive status and in healthy controls. The role of these cholinergic brain metrics and cognitive reserve in PD participants who had different cognitive abilities were also assessed, with the aim to examine how CR influences cognitive outcomes in PD. Specifically, how CR moderates the effect of NBM volume (and tract connection density) on cognition was investigated. In this study we found NBM volume, but not connection density of the tracts derived from HARDI MRI, differed between controls and PD participants. NBM volume was smaller in the PD-N and PD-MCI group compared to controls, but not significantly so in the PDD group relative to controls. CR did not moderate the relationship between brain measures and global cognition or cognitive domain scores. NBM volume and connection density of the tracts did not influence global Z scores or cognitive domain performance in the PD-N and PD-MCI groups. Premorbid IQ was found to be associated with global Z scores, memory, language and visuospatial function, however education was not significantly associated with any of the cognitive performance metrics.

4.2 Group differences compared to the literature

Controlling for age and intracranial volume, gray matter volume of the NBM was significantly smaller in the PD-N and PD-MCI groups than in the control group. This was also true for the PDD group, but the difference did not meet the significance threshold. This lack of significance in the PDD group was surprising considering cell loss in the NBM in PDD is well documented (Hall et al., 2014; Gratwicke et al., 2015) and degeneration of the NBM has been found to be predictive of future cognitive decline (Ray et al., 2017; Schulz et al., 2018). Numerically, the PDD group did exhibit reduced NBM volumes; the smaller number of PDD (n = 10) in the study compared to the other groups (39 PD-N and 61 PD-MCI), could have reduced statistical power, and therefore may help explain why reduced NBM volumes in the PDD group did not meet the statistical threshold when compared to controls. It was also surprising that differences

were found in the NBM volume of PD-N compared to controls as other studies have not observed this (Schulz et al., 2018) or only found differences between controls and PD-MCI (Ray et al., 2017).

Contrary to what was expected, no group differences were found in the TCD of the cingulate, temporal stem or external capsule. Gargouri et al., (2018) found differences between controls and nondemented PD patients in the connection density between the NBM and the associative prefrontal cortex and the occipital cortex. According to Selden et al., (1998) cholinergic fibers from the capsular division of the lateral NBM pathway supply these cortices. The cholinergic tracts through the external capsule extend both anteriorly to the dorsal and lateral prefrontal cortex and posteriorly (some through the temporal stem) to the occipital lobe (Selden et al., 1998). The lack of differences between groups in the external capsule and temporal stem TCD is therefore contradictory to their findings. However, like this study, Gargouri et al. (2018) also found no group differences in the temporal stem TCD which could suggest that the connection density of the NBM and associative temporal cortices do not differ between groups. However, Gargouri et al. (2018) looked at the connection density between the NBM and cortical regions regardless of the pathways between them. Therefore, the connection density variables are not directly comparable, and which may explain why group differences were found in their study.

4.3 Cognition and cognitive reserve compared to the literature

For the CR analysis regarding the NBM volume (adjusted for ICV), premorbid IQ was associated with global Z score, memory, visuospatial/visuoperceptual function and language function. In all these models, however, NBM volume and the interaction between NBM volume and both CR measures (premorbid IQ or education) were not associated with any measure of cognitive performance. Microstructural integrity of the NBM has been associated with performance on the Stroop test and Trail Making test (Gargouri et al., 2018) and others have

found low GM volume of the NBM to be predictive of future cognitive decline (Ray et al., 2017; Schulz et al., 2018). The lack of association between the NBM and any of the cognitive measures is therefore contradictory to these findings, although cognitive performance was not examined cross-sectionally in Ray et al.'s (2017) and Schulz et al.'s (2018) studies. Interestingly, microstructural integrity of the NBM is a better predictor of cognitive decline than NBM GM volume (Schulz et al., 2018). Cognition may be more related to the microstructural integrity (as measured by DTI metrics) of the NBM than the volume of the NBM. DTI metrics from the NBM could not be calculated in the current study as the tensor model was not appropriate for the HARDI acquisition sequence used here (with the high b=2500s/mm2). At higher b values (generally >2000s/mm2), the diffusion-weighted signal attenuation deviates from the linear diffusion function assumed by the tensor model; accordingly, metrics derived from the diffusion tensor (for example, fractional anisotropy and mean diffusivity) are biased and inappropriate (Steven, Zhuo & Melhem, 2014). Future work may benefit from a diffusion acquisition that allows both tensor and more advanced diffusion modelling which could better assess the relationship between NBM metrics and cognition.

In the CR analysis relating to the connection densities of the cingulate, temporal stem and external capsule tracts, TCD was not associated with any cognitive measures in any of the tracts. Gargouri et al. (2018) found that connection density between the NBM and associative prefrontal cortex was associated with MMSE scores but not domain-specific cognitive measures. The connection density between the NBM and other cortical regions were not associated with any measures of cognition (Gargouri et al., 2018). As mentioned above the connection density variables in Gargouri et al. (2018) were derived differently are not directly comparable, which may explain why no associations were found in this study.

While there was no evidence of a moderating effect of years of education or premorbid IQ (WTAR) on the effect of NBM volume on cognitive performance, premorbid IQ was

associated with global cognition, memory, visuospatial/visuoperceptual function and language ability. However, IQ was not associated with executive function or attention in the current study. Ciccarelli et al. (2018) found that higher premorbid IQ (as measured by the National Adult Reading Test; NART) was associated with better performance on word fluency and digit span (backward) tests in non-demented PD participants. Koerts et al. (2013) found that higher premorbid IQ (NART) was associated with better performance on tests of memory (Rey Auditory Verbal Learning test [RAVLT; immediate and delayed recall] and digit span forward) and executive function (Trails B, Stroop interference and letter fluency). While neither of these studies examined global cognitive performance, language or visuospatial/visuoperceptual function, it was strange that premorbid IQ was not found to be associated with executive function in this study. This was especially surprising since the NBM integrity measures have been associated with executive function in the past (Gargouri et al., 2018).

Across all three tract connection density measures, premorbid IQ was never associated with executive function or attention. Across all tracts, age was the best predictor of performance in these domains. When the cingulate tract and CR were assessed, premorbid IQ was only associated with performance in the visuospatial/visuoperceptual function. CR analyses related to the temporal stem and external capsule tracts showed that premorbid IQ was associated with global cognition, memory, visuospatial/visuoperceptual function and language. There was a trend towards an association between the temporal stem TCD and premorbid IQ and visuospatial/visuoperceptual performance. While the analyses were not corrected for multiple comparisons and thus even significant results should be treated with caution, this result supports Selden et al.'s (1998) finding that cholinergic fibers from the lateral pathway extending from the NBM may pass through the temporal stem on the way to the occipital cortex and adjacent areas. Degradation of the NBM tracts through the temporal stem could influence visuospatial and visuoperceptual function due to decreased cholinergic function in the occipital

lobe. Premorbid IQ therefore could moderate the influence that deficits in these tracts have on visuospatial and visuoperceptual deficits.

Education was not associated with any metric of cognition, nor did it significantly interact with any brain measure. Higher education in non-demented PD (when participants have been split into high and low education groups) has been associated with higher MMSE scores (Sunwoo et al., 2016) and better performance on the Visual Verbal Test (Armstrong et al., 2012). Higher education based on a 10-point scale (where years of education, having higher education and maximum level of higher education was taken into account) has been associated with higher MMSE scores and verbal fluency and visuospatial domain scores in the Addenbrooke's Cognitive Examination Revised (Hindle et al., 2016). Rouillard et al. (2017) found years of education was associated with RAVLT and the phonemic fluency task, while Lucero et al. (2015) found an interaction between education and β-amyloid deposition was associated with MMSE score. It was therefore surprising not to find an association between years of education and any cognitive measure in this study.

However, most studies which have reported an association in PD have split participants into high and low education groups, using thresholds ranging from 8 to 12 years of education (Sánchez et al., 2002; Sunwoo et al., 2016). Lucero et al. (2015) found the protective effect of education to occur at 16 years of education and more. The cut-off points for high and low education are often variable and arbitrary, motivating the decision to investigate education as a continuous variable (ranging from 8 years - 19 years) in this study. Furthermore, unlike this study Armstrong et al. (2012) and Hindle et al. (2016) did not investigate whether any brain changes or neuropathology had an influence on cognition. This could be why education was found to be significant in their study. Sunwoo et al. (2016) and Lucero et al. (2015) found education to be associated with the MMSE, however the MMSE is a crude measure of global cognition (Dalrymple-Alford et al., 2010). In the current cohort, the WTAR was a superior

predictor of global cognition than years of education, however this is unsurprising as years of education is also a rather crude measure of global cognitive ability.

4.4 Potential implications

This study is consistent with evidence that NBM deterioration occurs in PD (Hall et al., 2014; Gratwicke et al., 2015). However, it does not provide support for GM loss in the NBM or connection density of tracts from the NBM as critical in PD-related cognitive impairment. For example, Hall et al. (2014) found a decrease of cortical cholinergic markers in nondemented PD despite no neuronal loss in the NBM. Gargouri et al. (2018) found more associations between functional connectivity (of the NBM and cortical areas) and cognitive performance than between connection density and cognitive performance. It may be that NBM volume and connection density of the tracts emanating from the NBM are not the primary cholinergic deficits that elicit cognitive impairments. Despite the lack of associations between brain metrics and cognitive variables in this study, it is likely that this was the result of other factors (see below, in limitations) rather than because NBM deterioration is not relevant to cognition in PD.

This study also did not find evidence that CR moderated the effect of NBM volume (or tract connection density) on global cognition or cognitive domain scores. In Alzheimer's disease (AD) education has been found to moderate the relationship between medial temporal lobe atrophy and MMSE performance (Perneczky et al., 2009); and premorbid IQ (measured by the American NART) moderates the relationship between Tau in the inferior temporal region and MMSE score (Rentz et al., 2017). In preclinical AD, education has been found to moderate the relationship between CSF β-amyloid and brain metabolism in temporo-parietal and ventral prefrontal areas (Ewers, Insel, Stern & Weiner, 2013). Interestingly, in all these studies the moderating effect involved temporal brain areas. In this study, only the interaction between temporal stem TCD and premorbid IQ came close to influencing performance in visuospatial and visuoperceptual tests, perhaps suggesting a small involvement of cognitive

reserve in temporal areas in PD. This may not have reached significance in this study compared to those in AD because of limitations in the tract connection density measures that are discussed below.

The CR literature in AD is dominated by studies that show the association between CR measures and brain integrity metrics, while controlling for cognition or clinical severity. This is thought to represent a beneficial effect of CR because better cognition is maintained in people with higher CR despite poorer brain integrity. However, this method is much the same as demonstrating CR influences cognition when brain integrity is controlled for and is not the same as moderation. Many studies in AD have shown that higher CR is associated with more white matter hyperintensities (Brickman et al., 2009), abnormal β-amyloid levels (Durmurgier et al., 2010), more advanced tau pathology (Hoenig et al., 2017), and less cerebral blood flow (Scarmeas et al., 2003) when cognition or clinical severity was controlled for. It may be the case that CR influences cognition and clinical outcomes in the presence of a range of brain deficits in both AD and PD, but only moderates the effect of some brain integrity measures. This could be why no moderation effect was found in this study. It is logical to think that CR should protect against the negative effect of a range of brain deficits. However, recent findings that CR proxies can directly maintain brain integrity and that CR has a measurable neural basis (Stern, 2017) highlights the many ways (through either moderation or a simple association) CR could be influencing clinical outcomes.

4.5 Limitations/Future directions

There are many limitations to the TCD measures that may help explain why no associations with cognition and no group differences were found. All participants demonstrated large variability in tract connection density and in the number of streamlines generated from the ROI-based analysis. This was particularly evident in the cingulate tract where six participants failed to generate any streamlines between the ROIs. Because the TCD measures

were obtained by aggregating the streamline weights in each tract, the values are strongly related to the number of streamlines generated in the *tckedit* command in MRTrix3. It is generally accepted that extracting specific pathways of interest will result in a large amount of variance (Smith, 2018). These are likely due to streamline tractography biases, difficulties reconstructing FODs, as well as genuine differences in connectivity strengths, not to mention any underlying disease-related changes; which all may have influenced the large variability in connection density measures.

The ROI transformations from the study-specific template to subject space may have also influenced the number of streamlines that intersected the ROIs. ROIs in normalized space were inverse normalized to each individual's subject space to automate tract tracing. However, placement in subject space depends on accurate normalization parameters. While in general these normalization algorithms are ever improving, they may add noise to the system, which may manifest as increased variability in streamlines. In cases where more severe atrophy had resulted in smaller brain structures, this could have caused the ROIs to encompass more of the structure and in turn capture more streamlines. Visual inspection of track outliers implied this could have been the case.

While the aim was to track the cholinergic pathways from the NBM, streamlines that traversed the NBM and the cingulate, and the NBM and the external capsule ROIs could not be identified using the *tckedit* command. Instead the method of Hong and Jang's (2010) diffusion study was used where ROIs were placed on tracts originating from the NBM (sub genu and ventral external capsule ROIs). This was problematic for all the tracts because there was no way to differentiate which neurotransmitter system each streamline belonged to. However, it was more problematic in the cingulate and external capsule tracts as they could not be connected directly with the NBM. There was also no way to capture streamlines going in one direction (i.e. from the NBM to the temporal stem, but not from the temporal stem to

the NBM). Therefore, some of the streamlines captured would have been projecting the opposite way to the tracts of interest. These undesirable streamlines would have decreased the validity of the TCD measures (as measures of the cholinergic pathways of interest) and could have influenced the lack of group differences and associations with cognitive measures that were expected.

Another part of the processing pipeline that may have influenced the tract measures was the use of anatomically constrained tractography. ACT was used to increase the biological plausibility of the streamlines in the whole brain tractogram (Smith et al., 2012). ACT works by defining where streamlines can plausibly begin, and end based on tissue type and CSF. Streamlines were defined as starting at the boundary of GM and WM. This type of seeding has a shorter mean streamline length and therefore longer pathways are not reconstructed as densely (Smith, Tournier, Calamante & Connelly, 2015a). This may have influenced the reconstruction of the cingulate streamlines and could explain why some participants returned no (or very few) streamlines after the ROI analysis.

As this thesis was a preliminary investigation into cholinergic pathways from the NBM and CR in relation to cognitive impairment, it suffered from some methodological complications. Therefore, further investigation into NBM deficits relative to cognition in PD and moderation through cognitive reserve is warranted. For example, microstructural integrity of the NBM may be more relevant to cognitive outcomes than GM volume in the NBM (Schulz et al., 2018). Gazes et al. (2020) used HARDI to extract tracts of interest and calculated mean, axial and radial diffusivity and fractional anisotropy of those tracts. Examining these diffusion metrics with multi-shell diffusion data (i.e. several non-zero b values) instead of the connection density values may be a better way to quantify the tracts, despite the known shortcomings of the tensor (DTI) model. This would reduce the influence that the variability in the connection density measures presumably had on the results and may be more relevant to cognition.

Future research could also look at how CR influences the connection density between the NBM and cortical structures using connectomics, which was examined by Gargouri et al. (2018). This involves looking at connections between structures of interest based on the start and end points of streamlines, irrespective of which tracts or pathways streamlines followed. Because this study was focused on specific pathways emanating from the NBM rather than their connection with specific cortical regions, it was opted not to look at connection density this way. However, this method would have avoided any normalization issues related to ROI placement and the variability in streamline count that occurs after extracting tracts of interest. The methods used in this study were theoretically sound but based on ongoing research by the MRTrix3 team at the Brain Research Team in Australia that has not been validated. The science of connectomics and random matrix theory are well-developed (Smith et al., 2015a) and more commonly used in HARDI studies (e.g. Shen et al., 2019) and therefore would likely produce more valid results

5 Conclusion

The volume of the NBM was found to be smaller in PD-N, PD-MCI and PDD groups than in the healthy elderly control group, but not significantly smaller in the PDD group. The connection density of cingulate, external capsule and temporal stem tracts that extend from the NBM did not display differences between the groups. This supports the consensus that NBM deterioration occurs in PD but does not indicate how NBM white matter tracts are influenced by this, or which ones are affected. Limitations in the method and processing pipeline used to obtain tract connection density may help explain why the expected differences were not found.

Cognitive reserve, when measured by premorbid IQ and education, was not found to moderate the effect of the NBM-related brain metrics on global cognition or cognitive domain scores (executive function, attention and working memory, episodic memory, visuospatial/visuoperceptual function and language). Premorbid IQ was however, associated with global cognition, episodic memory, language and visuospatial/visuoperceptual function independently of NBM-related brain metrics, which were not related to cognitive performance. This does not support the notion that CR moderates the effect of NBM-related deficits in cognition but does suggest that premorbid IQ influences cognitive outcomes in PD. Limitations in the connection density measures may have reduced the ability to identify an effect of NBM-related brain measures on cognition. Volume of the NBM also may not be especially relevant to cognition in PD compared to microstructural integrity of the NBM. Further research in this area would benefit from using alternative HARDI metrics and methods, such as diffusion metrics for the NBM and NBM tracts or connectomics. This would help in understanding how important cholinergic deficits are for cognition in PD and whether CR moderates this relationship.

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