Cognition, psychiatric symptoms and conversion to dementia in Parkinson's disease.

A thesis submitted in fulfilment of the requirements for a

Degree of Doctor of Philosophy in Psychology

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Abstract

Parkinson's disease (PD) is a complex neurodegenerative disorder which can have a significant effect on a patient's quality of life. Psychiatric symptoms and cognitive decline are common, with dementia (PDD) ultimately occurring in approximately 90% of patients. Mild cognitive impairment in PD (PD-MCI) is an intermediate state of cognitive decline, where patients are at a higher risk of progression to PDD than non-PD-MCI patients. The high rates of patients who develop PDD demonstrate that it is pertinent to have indicators of imminent PDD; particularly should a preventative therapy ever become available. Therefore, the aim of my PhD project was to use cognitive and neuropsychiatric measures to predict cognitive decline within a four-year period.

Firstly, we examined permitted variations within Movement Disorder Society Task Force (MDS-TF) Level II diagnostic PD-MCI criteria. We aimed to identify a PD-MCI criterion which optimally captured individuals who later progressed to PDD. To evaluate this, we followed 121 non-demented PD patients for up to 4.5 years; 21% converted to PDD over this period. Three unique groups of patients were classified as PD-MCI using baseline neuropsychological assessments. Each patient was required to have two impaired cognitive test scores, with impairment defined as (1) -2SD, (2) -1.5SD or (3) -1SD below normative data. Relative risk (RR) of PDD for each criterion was calculated, with the -1.5SD criterion found to be optimal for maximizing progression to PDD over four-years.

Secondly, another variation within the MDS-TF PD-MCI criteria was examined - whether the impaired tests need to occur within a single cognitive domain or only across two or more cognitive domains. The same sample of PD patients was reassessed to determine (1) RR of PDD when two impairments at -1.5SD existed within one cognitive domain, followed

by (2) RR of PDD in the unique group whose two impairments at -1.5SD did not exist within one cognitive domain. The -1.5SD cut-off produced a high RR of PDD only when two impairments were identified within one cognitive domain (7.2, 95% confidence interval (CI) = 3.4–16.6, $p<0.0001$). This suggests that if the intent of a PD-MCI diagnosis is to detect increased risk of PDD in the next four years, optimal criteria should identify at least two impairments at -1.5SD within a single cognitive domain.

Next, we examined the number of tests permitted per cognitive domain by the MDS-TF criteria. We tested a reduced test battery of only two tests per cognitive domain, to determine if it could identify PD-MCI patients who were at risk of PDD within the next four-years. Tests were ranked for each cognitive domain based on the number of PD-MCI level impairments they identified. Subsequently, we used an improved methodology, logistic regression, to select two tests sensitive to PDD over four-years in each of five cognitive domains. The 10 neuropsychological test battery consisted of map search, digit ordering (Attention), Stroop interference, Trails B (Executive), picture completion, Rey copy (Visuospatial), CVLT-II SF free recall, Rey-short delay (Memory), DRS-2 similarities and ADAS-Cog language measures (Language). To determine if at-risk patients could be identified RR was conducted on an updated sample of 138 PD patients; 28 progressed to PDD. Using this 10 neuropsychological test battery, patients who classified as PD-MCI defined by 'two impairments at -1.5SD in one cognitive domain' had an equivalent RR (7.0, 95% CI 3.8-12.6) to the same group classified using the full 24 neuropsychological test battery (RR = 6.9, 95% CI 3.3-14.6). PD-MCI in patients with 'one impairment in each of two cognitive domains' now showed significance (RR = 3.6, 95% CI 1.3-9.5), unlike when the same criterion when applied to the 24 neuropsychological test battery. A modified PD-MCI criterion of 'two impairments in any of the 10 neuropsychological tests' was used and

showed a similar RR (7.1, 95% CI 3.2-16.1) to the PD-MCI 'two impairments in one cognitive domain' criterion. This study demonstrated that a 10 neuropsychological test battery can identify PD patients at-risk of PDD within four-years and demonstrated that a modified PD-MCI criterion ('two impairments in any 10 neuropsychological tests') can be used when the battery consists of tests sensitive to PDD.

Lastly, the relationship between neuropsychiatric symptoms in PD and progression to dementia was explored. One-hundred-and-twenty-three non-demented PD patients, followed over 3.5-4.5 years were included; 27 progressed to PDD. All received comprehensive Level II neuropsychological testing and neuropsychiatric evaluations. ROC analysis was used to analyse whether neuropsychiatric measures at study entry were associated with future PDD progression. Patient-reported hallucinations was the only neuropsychiatric measure which related to future progression to PDD (PD Questionnaire hallucinations measure: AUC=0.70, CI=0.60-0.80; Unified PD Rating Scale hallucinations measure: AUC=0.69, 95% CI=0.57-0.80). By contrast, hallucinations reported by the patient's significant other on the Neuropsychiatric Inventory did not discriminate patients. Neither patient-reported hallucinations (OR=1.70, 95% CI=0.73-4.03) nor motor function (OR=1.02, 95% CI=0.97-1.09) were found to add any additional useful information above global cognitive ability (OR=26.34, 95% CI=6.44-184.71) and age (OR=1.28, 95% CI=1.11-1.54) for predicting PDD. Cognitive ability and age were stronger predictors of conversion to PDD within the next four-years than any neuropsychiatric measures tested.

The findings of this thesis show that MDS-TF PD-MCI criteria can identify patients at-risk of PDD within a four-year period, even when a reduced 10 neuropsychological test battery is used for classification. Cognition and age were found to be more useful at predicting future PDD than any neuropsychiatric symptom assessed. Hence, specific PD-MCI

criteria may be used as an additional tool to enrich samples for disease modifying

interventions.

Acknowledgements

Completing a PhD is a huge challenge, in my case; it was made easier by the support and encouragement of my primary supervisor Professor John Dalrymple-Alford, and, co-supervisors Professor Tim Anderson, Dr Tracy Melzer, Dr Michael MacAskill and Dr Daniel Myall. They were all invaluable sources of suggestions and advice and always enthusiastic about my project. This enabled me to develop skills as an early career researcher, expand my knowledge and thinking on the issues that were explored in my thesis and taught me to never stop asking questions, no matter now silly they may seem. In particular, John's knowledge across multiple areas of neuroscience and constant suggestions for improvement played a major role in why I upgraded from a Master's to a PhD thesis and has been of an immeasurable value throughout my PhD. I would also like to make a special thank-you to Michael for the additional support and guidance he has provided about navigating the research world here in New Zealand. I would like to express my overwhelming appreciation and thanks to all of my supervisors, you have enabled me to grow as a young neuroscientist.

The financial burden of a PhD is a significant undertaking. This burden was made lighter in 2013 when I received a PhD Scholarship from the New Zealand Brain Research Institute (NZBRI). Receiving this award gave me the ability to focus solely on my research and has significantly increased the amount of work I was able to achieve over the past four-and-a-half years.

Every year of my PhD I have also been lucky enough to travel internationally or domestically to conferences due to sponsorship from the University of Canterbury, the NZBRI, BRNZ, the Movement Disorders Society and travel funding from Prof. Tim Anderson. For this

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Preface

This thesis is submitted for the degree of Doctor of Philosophy at the University of Canterbury, Christchurch, New Zealand. The research was conducted under the primary supervision of Professor John Dalrymple-Alford of the Department of Psychology, University of Canterbury. This thesis was co-supervised by Professor Tim Anderson of the Department of Medicine, University of Otago, Christchurch, Dr Tracy R Melzer in the Department of Medicine, Christchurch, Dr Michael MacAskill of the department of Medicine, University of Otago, Christchurch and Dr Daniel Myall of the New Zealand Brain Research Institute. Material covered in Chapter 3 has previously been published in Wood, K-L., Myall, D. J., Livingston, L., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., Geurtsen, G. J., Anderson, T. J., & Dalrymple-Alford, J. C. (2016). Different PD-MCI criteria and risk of dementia in Parkinson's disease: 4-year longitudinal study. npj Parkinson's Disease, 2, 15027. doi: 10.1038/npjparkd.2015.27.

The data that has been used in this thesis are part of the New Zealand Brain Research Institute's longitudinal Parkinson's disease (PD) cohort which has been collected from Parkinson's patients who live in Canterbury, New Zealand over the past 10-years. Over this period 319 PD patients and 64 healthy-control participants have been assessed. My contribution to this data set has been through the collection of neuropsychological data and the quality control with the storage of this data. I have conducted over 150 detailed neuropsychological assessments of PD patients, their significant others and healthy older adults living in Christchurch, scored over 100 of these assessments and checked that the data was scored and entered correctly into our database for over 950 assessment sessions. I would like to thank everyone who has contributed to this dataset of the past 10-years, but in particular Leslie Livingston, the study co-ordinator, for all of her hard work recruiting and retaining the patients who are part of this study along with her team of excellent research assistants, Sophie Grenfell, Krysta Travis, Bob Young and Maddie Pascoe, who have collected and scored the majority of the neuropsychological data used in this

thesis.

During the course of this thesis the following aspects of this research were published and /or presented. Note, my maiden name was 'Wood' and this was used for publication prior to May 2016

Publications

Journal Articles

Wood, K-L., Myall, D. J., Livingston, L., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., Geurtsen, G. J., Anderson, T. J., & Dalrymple-Alford, J. C. (2016). Different PD-MCI criteria and risk of dementia in Parkinson's disease: 4-year longitudinal study. npj Parkinson's Disease, 2, 15027. doi: 10.1038/npjparkd.2015.27.

Abstracts

Horne, K-L., Myall D. J., Macaskill, M. R., Livingston, L., Grenfell, S. F., Melzer, T. R., Pitcher, T. L., Anderson, T. J, & Dalrymple-Alford, J. C. (2017). Patient-reported hallucinations are associated with future progression to dementia in Parkinson's disease, but cognition is more informative. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR)*, Queenstown, New Zealand, 35, Abstract 11.3

Horne, K-L., Myall, D., MacAskill, M., Livingston, L., Grenfell, S., Melzer, T., Pitcher, T., Anderson, T., & Dalrymple-Alford, J.C. (2017). Patient-reported hallucinations and the probability of progression to dementia in Parkinson's disease [abstract]. *Movement Disorder*, 32 (suppl 2). http://www.mdsabstracts.org/abstract/patient-

reported-hallucinations-and-the-probability-of-progression-to-dementia-in-parkinsons-disease/.

Horne, K., Myall, D.J., Livingston, L., Grenfell, S.F., Melzer, T.R., Pitcher, T.L., MacAskill, M.R., Anderson, T.J., & Dalrymple-Alford, J.C. (2016). Risk of dementia in Parkinson's disease: Towards optimal short cognitive testing. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 34, Abstract 6.1

Wood, K., Myall, D.J., Livingston, L., Melzer, T.R., Pitcher, T.L., MacAskill, M.R., Geurtsen, G.J., Anderson, T.J., & Dalrymple-Alford J.C. (2015). Progression to Dementia in Parkinson's disease over four-years: Risk with alternative MCI criteria. *A Proceedings of the Scientific Meeting of the Health Research Society of Canterbury,* New Zealand Medical Journal, 128 (1421), 4 September

Wood, K., Livingston, L., Myall, D. J., Grenfell, S. F., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., Anderson, T. J., & Dalrymple-Alford, J. C. (2015). Neuropsychiatric status and different MCI criteria in Parkinson's disease. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 33, Abstract 5.3

Wood, K., Myall, D., Livingston, L., Melzer, T., Pitcher, T., MacAskill, M., Anderson, T., & Dalrymple-Alford, J. (2014). Comparing mild cognitive impairment criteria in Parkinson's disease: influence on dementia onset. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 32, Abstract 6.4

Wood, K. L., Livingston, L., Myall, D. J., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., Anderson, T. J., & Dalrymple-Alford, J. C. (2014). Alternative criteria for mild cognitive impairment in Parkinson's disease: Relevance to dementia onset [abstract]. *Movement Disorders*; 29 (Suppl. 1: 1002)

Wood, K., Livingston, L., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., Anderson, T. J., & Dalrymple-Alford, J.C. (2013). Criteria for Parkinson's disease with mild cognitive impairment associated with increased progression to dementia. *A Proceeding of the 31st Australasian Winter Conference on Brain Research (AWCBR)*, Queenstown, 31, Abstract 58

Dalrymple-Alford, J. C., Livingston, L., Melzer, T. R., **Wood, K.,** Goh, T. J., Pitcher, T. L., Graham, C. F., Keenan, R. J., MacAskill, M. R., & Anderson, T.J. (2013). Current perspectives on Parkinson's disease: Cognition to the fore. *A Proceeding of the 31st Australasian Winter Conference on Brain Research (AWCBR)*, Queenstown, Volume 31, Abstract 29

Newspaper

Morton, Jamie. (2016, 4 September). Brain detectives: 10 amazing Kiwi insights, New Zealand Herald. Retrieved from **http://www.nzherald.co.nz/lifestyle/news/article.cfm?c_id=6&objectid=11702413**

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Poster Presentations

2017, 10th August, Health Research Society of Canterbury Annual Recycled Poster Evening,

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2014, 8th – 12th June, 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden.

2013, 24th -28th August, 31st International Australasian Winter Conference on Brain Research, Queenstown, New Zealand.

Oral Presentations

2017, 2nd – 6th September, 35th International Australasian Winter Conference on Brain Research, Queenstown, New Zealand.

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Other publications, not directly related to the content of this thesis:

Articles

Jones, A. J., Kuijer, R. G., Livingston, L., Myall, D., **Horne, K.,** MacAskill, M., Pitcher, T.,

Barrett, P. T., Anderson, T. J., & Dalrymple-Alford, J. C. (2017). Caregiver burden is

increased in Parkinson's disease with mild cognitive impairment (PD-MCI).

Translational Neurodegeneration, 6(1). doi: 10.1186/s40035-017-0085-5.

Almuqbel, M., Melzer, T. R., Myall, D. J., MacAskill, M. R., Pitcher, T. L., Livingston, L.,

Wood, K., Keenan, R. J., Dalrymple-Alford, J. C., & Anderson, T. J. (2016).

Metabolite ratios in the posterior cingulate cortex do not track cognitive decline in

Parkinson's disease in a clinical setting. *Parkinsonism and Related Disorders*, 22, 54-

61. doi:10.1016/j.parkreldis.2015.11.008.

Abstracts

Stark, M. R., Melzer, T. R., Keenan, R. J., Myall, D. J., Kaur, G., Livingston, L., **Horne, K.,** Marsh, S., Grenfell, S., Young, B., Macaskill, M. R., Dalrymple-Alford, J. C., & Anderson, T. J. (2017). Parkinson's disease: No association between amyloid PET imaging and cognitive status. A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR), Queenstown, New Zealand, 35, Abstract 14.11

Elias, B., Goh, J., Peterson, E., Livingstone, M., Goulden, M., Myall, D., Melzer, T., Pitcher, T., Livingston, L., **Horne, K.,** Grenfell, S., Young, B., Wilkinson, M., Macaskill, M., Kuijer, R., Mulligan, H., Cutfield, N., Anderson, T., Hale, L., & Dalrymple-Alford, J. (2017). Theory of mind in Parkinson's disease: Improvement after physical and cognitive exercise. A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR), Queenstown, New Zealand, 35, Abstract 14.30

Peterson, E., Goh, J., Wilkinson, M., Livingstone, M., Elias, B., Goulden, M., Myall, D., Melzer, T., Pitcher, T., Livingston, L., **Horne, K.,** Grenfell, S., Young, B., Macaskill, M., Kuijer, R., Mulligan, H., Cutfield, N., Anderson, T., Hale, L., & Dalrymple-Alford, J. (2017). Motor outcomes in Parkinson's disease patients: An RCT of physical exercise and cognitive enrichment. A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR), Queenstown, New Zealand, 35, Abstract 14.31

Livingstone, M., Elias, B., Goh, J., Peterson, E., Wilkinson, M., Goulden, M., Myall, D., Melzer, T., Pitcher, T., Livingston, L., **Horne, K.,** Grenfell, S., Young, B., Macaskill,

M., Kuijer, R., Mulligan, H., Cutfield, N., Anderson, T., Hale, L., & Dalrymple-Alford, J. (2017). Maintaining Independence in Parkinson's disease: Cognitive effects of a combined cognitive and physical exercise intervention. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR)*, Queenstown, New Zealand, 35, Abstract 14.32

Melzer, T.R., Keenan, R.J., Myall, D.J., Kaur, G., Livingston, L., **Horne, K.,** Marsh, S., MacAskill, M.R., Dalrymple-Alford, J.C., & Anderson, T.J. (2016). Amyloid imaging and cognition in Parkinson's disease: Interim report. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 34, Abstract 11.3

Almuqbel M. M., Melzer T. R., Myall D. J., MacAskill M. R., Livingston L., **Horne K-L.,** Pitcher T. L., Keenan R. J., Dalrymple-Alford J. C. & Anderson T. J. (2016) Regional cortical thinning is associated with cognitive status in Parkinson's disease. *22nd Annual Meeting of the Organization for Human Brain Mapping*, Geneva, Switzerland, 26-30 Jun

Almuqbel, M. M., Melzer, T. R., Myall, D. J., MacAskill, M. R., Livingston, L., **Wood, K.,** Pitcher, T. L., Keenan, R. J., Dalrymple-Alford, J. C, & Anderson, T. J. (2016). Cortical atrophy in cognitively impaired Parkinson's disease patients [abstract]. *Movement Disorders*, 31 (suppl 2). http://www.mdsabstracts.org/abstract/cortical-atrophy-in-cognitively-impaired-parkinsons-disease-patients/

Melzer, T. R., Myall, D. J., MacAskill, M. R., Livingston, L., Pitcher, T. L., **Wood, K.,** Keenan, R. J., Dalrymple-Alford, J. C., & Anderson, T. J. (2016). Tracking Parkinson's disease over 2-6 years with MRI [abstract]. *Movement Disorders*, 31

(suppl. 2). http://www.mdsabstracts.org/abstract/tracking-parkinsons-disease-over-2-6-years-with-mri/

Almuqbel M., Melzer T. R., Myall D. J., MacAskill M. R., Livingston L., **Wood K.,** Pitcher T. L., Keenan R. J., Dalrymple-Alford J. C. & Anderson T. J. (2015) Longitudinal magnetic resonance spectroscopy and cognitive impairment in Parkinson's disease. *21st Meeting of The Organization for Human Brain Mapping,* Honolulu, HI, USA: 14-18 Jun

Melzer T. R., Myall D. J., Livingston L., **Wood K.,** Pitcher T. L., Watts R., Keenan R. J., MacAskill M. R., Dalrymple-Alford J. C. & Anderson T. J. (2015). White matter lesions contribute to future dementia in Parkinson's disease. *21st Meeting of The Organization for Human Brain Mapping,* Honolulu, HI, USA: 14-18 Jun

Myall, D. J., **Wood, K. L.,** Livingston, L., Pitcher, T. L., Melzer, T. R., MacAskill, M. R., Anderson, T. J., & Dalrymple-Alford, J. C. (2015). Individualised medicine using an abbreviated cognitive screen for dementia prediction in Parkinson's disease [abstract]. *Movement Disorders*, 30 (Suppl. 1: 893). http://www.mdsabstracts.com/abstract.asp?MeetingID=802&id=113429

Almuqbel, M., Melzer, T., Myall, D., MacAskill, M., Livingston, L., **Wood, K.,** Pitcher, T., Dalrymple-Alford, J., & Anderson, T. (2014). Cognitive status in Parkinson's disease characterised by magnetic resonance spectroscopy. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 32, 34

Melzer, T., Myall, D., Livingston L., **Wood, K.,** Pitcher, T., Keenan, R., MacAskill, M., Dalrymple-Alford, J., & Anderson, T. (2014). White matter lesions - a factor in developing dementia in patients with Parkinson's disease. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 32, Abstract 3.5

Myall, D., **Wood, K.,** Livingston, L., Pitcher, T., Melzer, T., MacAskill, M., Anderson, T., & Dalrymple-Alford, J. (2014). Individualised medicine: Predicting dementia in Parkinson's disease. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 32, Abstract 8.1.

Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease Assessment Scale – Cognitive
ADL	Activities of Daily Living
AUC	Area under the Curve
BG	Basal Ganglia
BRNZ	Brain Research New Zealand
CI	Confidence Interval
CDR	Clinical Dementia Rating Scale
CSC	Coeruleus-Subcoeruleus Complex
CVLT-II SF	California Verbal Language Test – Version 2 Short Form
D-KEFS	Delia-Kaplan Executive Function System
DRS-2	Dementia Rating Scale - 2
EMS	Enteric Motor System
FAST	Functional Activities Questionnaire
FAQ	Functional Assessment Staging
GDS	Geriatric Depression Score

GM   Grey Matter

GPe   Globus Pallidus pars externalis

GPi   Internal Globus Pallidus

Global Z Score   Mean derived from the average scores of the attention, executive,

visuospatial, and episodic memory domains.

HADS   Hospital Anxiety and Depression Scale

JLO   Judgement of Line Orientation

LASSSO   Least Absolute Shrinkage and Selector Operator

LB   Lewy Body

LR   Logistic Regression

MBF   Magnocellular nuclei of the Basal forebrain

MCI   Mild Cognitive Impairment

MDS-PD   Movement Disorder Society Clinical Diagnostic Criteria for

Parkinson's disease

MDS-TF   Movement Disorder Society-Task Force

MDS-UPDRS   Movement Disorder Society – Unified Parkinson's Disease Rating

Scale

MMSE   Mini Mental State Examination

MoCA	Montreal Cognitive Assessment
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NPI	Neuropsychiatric Inventory
NZBRI	New Zealand Brain Research Institute
OR	Odds Ratio
PD	Parkinson's Disease
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PD-N	Parkinson's disease with Normal cognition
PDD	Parkinson's disease with Dementia
PDQ	Parkinson's Disease Questionnaire
PET	Positron-Emission Tomography
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease
RBD	REM Sleep Behaviour Disorder
RCFT	Rey Complex Figure Test
ROC	Receiver Operator Curves
RR	Relative Risk

SD	Standard Deviation
SMA	Supplementary Motor Area
SNc	Substantia Nigra pas compacta
SNr	Substantia Nigra pas reticulata
S.O.	Significant Other
STN	Subthalamic Nucleus
TEA	Test of Everyday Attention
UKBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale
WM	White Matter
WTAR	Wechsler Test of Adult Reading

Chapter 1: Introduction and Orientation

Rates of Parkinson's disease (PD) are expected to double over the next 25 years in New Zealand (Myall et al., 2017). Dementia in Parkinson's disease (PDD) is common, with over 80-90% of patients expected to develop the condition (Gratwicke, Jahanshahi, & Foltynie, 2015). The time course to PDD, however, can vary anywhere from 2-25 years after diagnosis. This makes it difficult to determine the efficacy of potential treatments or interventions to slow or halt the progression to dementia. In 2011, the Movement Disorders Society sanctioned a Task Force (MDS-TF) to develop criteria for diagnosing PD patients with Mild Cognitive Impairment (PD-MCI; Litvan et al., 2012). The primary idea behind setting up this Task-Force was that patients who meet PD-MCI criteria may be at an intermediate stage of cognitive decline and are therefore more likely to develop PDD than PD patients who have 'normal' cognition. The last 20 years has shown a greater recognition that PD is far more than just a motor disorder and before the development of the MDS-TF PD-MCI criteria in 2011, there was little consensus on what level of impairment constituted to PD-MCI classification being made. This resulted in many different PD-MCI classifications being employed in the literature. The true frequency and nature of PD-MCI and its trajectory course towards progression to dementia is largely uncharted.

This thesis aims to validate the MDS-TF PD-MCI Level II criteria by specifically determining their relevance to progression to PDD over a four-year period. Several currently permitted PD-MCI criteria will be compared to assess which criterion captures patients who have a high risk of developing PDD within this period. Key variations between the different PD-MCI criteria are (1) cut-off scores used to define impairment, and (2) whether the impairments occur within or across different cognitive domains. Once optimal PD-MCI criterion has been determined, we will test its performance on a reduced Level II 10

neuropsychological test battery to assess whether the shortened battery captures at-risk patients. Finally, the predictive nature of neuropsychiatric symptoms over the same four-year period will be evaluated and compared to that of cognition.

1.1. Study overview

This Thesis will begin by discussing the PD literature with a focus on the cognitive and neuropsychiatric aspects of PD *(Chapter 2)* and then discuss the findings of four research chapters *(Chapters 3-6)*. This thesis looks to validate the MDS-TF PD-MCI Level II criteria in terms of their ability to capture patients at high risk of dementia, by applying different variants of the accepted PD-MCI criteria to a four-year longitudinal PD cohort who live in the Canterbury region of New Zealand. The research chapters will assess (1) the influence of different permitted impairment cut-off scores (1SD, 1.5SD or 2SD) on relative rates of dementia in patients classified as PD-MCI *(Chapter 3)*, (2) The difference in relative risk of PDD in PD-MCI patients who have their impairments falling in a single cognitive domain only or across multiple cognitive domains only *(Chapter 3)*, (3) whether a reduced 10 neuropsychological test battery can identify patients at a high risk of developing PDD *(Chapter 4 and 5)*, and (4) the relationship between neuropsychiatric symptoms and future progression to PDD *(Chapter 6)*. All aspects of this study will look at progression to PDD over a four-year period, which is a clinically relative period of time in terms of considering the utility of PD-MCI criteria in future clinical intervention or therapy trials (Eberling et al., 2014). Finally, the overall findings of this thesis will be discussed along with study limitations and the future direction of the work *(Chapter 7)*.

Chapter 2: Overview of the Parkinson's disease literature

2.1. PD diagnosis and differential diagnosis

Parkinson's disease (PD) is a complex, multisystem, neurodegenerative disorder that affects every aspect of an individual's life, physically, emotionally and cognitively. Diagnosing Parkinson's disease (PD) is not straight forward. Most clinicians agree that a combination of cardinal clinical signs must be present, but there are no definitive diagnostic tests to diagnose the disorder. Thus, an autopsy is required for a 'definite' PD diagnosis (Berg et al., 2014). This presents an issue, as (1) not all patients who experience the clinical symptoms of PD will receive an autopsy to confirm pathology, or (2) some will experience PD symptoms but at autopsy show no PD pathology. Diagnostic criteria, based only on clinical features of the disease, have however been developed to aid clinicians in making the correct diagnosis. These include the criteria developed by the United Kingdom Parkinson's Disease Society Brain Bank (UKBB; Hughes, Daniel, Kilford, & Lees, 1992), the diagnostic criteria proposed by Gelb, Oliver, and Gilman (1999) and more recently the revised Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease (MDS-PD; Postuma et al., 2015). A few differences exist across these three diagnostic PD criteria. For example, a probable PD diagnosis according to the UKBB guidelines is based on clinical criteria. Bradykinesia is the only required symptom, with at least one of either rigidity, rest tremor or postural instability, and three other supporting features, such as unilateral onset, progressive disorder or an excellent response to levodopa (Hughes et al., 1992). To meet a definite PD diagnosis using the Gelb et al. (1999) criteria, there must be pathological evidence (i.e. at autopsy) plus the patient must have met all of the criteria for probable PD during life. A probable diagnosis requires the presence of any three of the four cardinal PD symptoms (rest tremor, bradykinesia, rigidity, asymmetric onset) as well as a positive response to dopamine

treatment. For a possible PD diagnosis, there only needs to be two of the four cardinal PD symptoms present, with bradykinesia not necessary if a rest tremor is present. For the MDS-PD criteria bradykinesia must be present, with at least one other symptom of either rest tremor or rigidity. When these symptoms are present and there are no alternate 'red flags', such as rapid progression of gait impairment or a complete absence of progression of motor symptoms, then a clinically-established PD diagnosis can be made. If the 'red flags' that are present, can be counterbalanced with other supportive features (e.g. a dramatic beneficial response to dopaminergic therapy), then a clinically-probable PD diagnosis can be made (Postuma et al., 2012). This therefore means that bradykinesia for example is not an essential requirement when using the Gelb et al. (1999) PD criteria, but it is when using more-commonly-used MDS-PD and the UKBB PD criteria.

2.2. Epidemiology and pathophysiology

Of particular relevance to this thesis is that PD is the second most common neurodegenerative disease that causes dementia, after Alzheimer's disease (Sharma et al., 2013). Older age is the primary risk factor for developing PD (Lees, Hardy, & Revesz, 2009; Reeve, Simcox, & Turnbull, 2014; Sharma et al., 2013). A recent New Zealand Brain Research Institute study showed that the 2013 prevalence of PD was estimated as 191 per 100,000 population while the incidence rate was 29 per 100,000 person-years, with males being 1.7 times more likely to develop the disease than females (Myall et al., 2017). These rates were estimated by this study to double over the next 25 years as the baby-boomer population reach retirement age. Clearly, PD is becoming an increasing relevant burden for New Zealand.

2.2.1. PD - The pathology of the motor disorder

The principal pathology of PD was originally characterised in the late 1930's as the death of pigmented nigrostriatal dopaminergic neurons in the substantia nigra pars compacta (SNc; Bezard & Gross, 1998). After the death of dopaminergic cells in the SNc cells death extends into other areas of the brain, including the locus coeruleus, Meynert's nucleus basalis and the hypothalamus, as PD pathology progresses (Agid, 1991; Bezard & Gross, 1998). Bezard and Gross (1998) summarised the functional organisation of the motor circuit model for both the normal and parkinsonian state. The motor circuit links the cortex, basal ganglia (BG) and thalamus in (A) the normal brain and (B) the parkinsonian brain (Figure 2-1). In this model, there are two pathways to the output structures, one 'direct' and the other 'indirect', both of which are under the modulatory control of dopamine. In the direct pathway of a normal brain, outputs from the putamen inhibit the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr), which in turn inhibits the thalamus. The indirect pathway of the motor circuit also begins in the putamen which projects to output structures via a pathway which has an inhibitory effect on the globus pallidus pars externalis (GPe) which in turn inhibits the subthalamic nucleus (STN). The STN then has an excitatory effect on the GPi (and SNr) which has an inhibitory effect on the thalamus. Motor dysfunction in PD occurs over time due to the progressive death of dopaminergic neurons in the SNc. This upsets the balance in the 'direct' and 'indirect' pathways, causing the thalamus to become over-inhibited, which reduces the excitatory influence on the cortex (Bezard & Gross, 1998; Obeso et al., 2000).
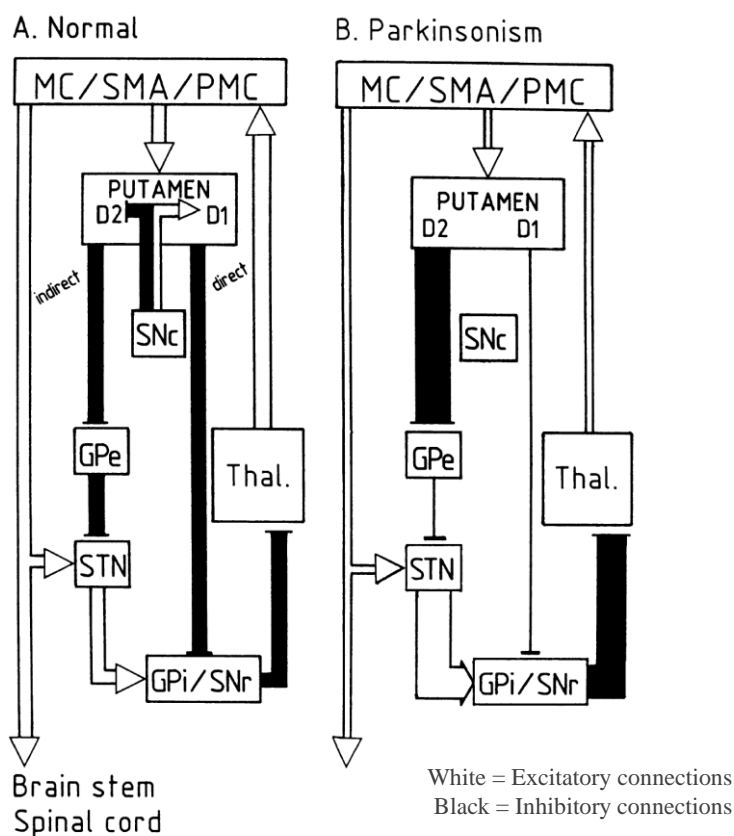
Figure 2-1. *The functional connectivity within the basal ganglia-thalamo-cortical of the motor circuit.(Bezard & Gross, 1998). (A) The normal circuit. (B) The parkinsonian circuit. White arrows are excitatory connections and black arrows are inhibitory Reproduced with permission from Elsevier.*

The progressive nigrostriatal death in PD is relentless, with the cardinal motor symptoms of PD beginning to appear once cell death exceeds the critical threshold of about 50-60% of SNc cell bodies and 70-80% of the striatal nerve terminals (Agid, 1991). Once motor symptoms are present, neuronal death continues to accelerate compared to the normal-age-related neuronal cell loss (Agid, 1991), which only exacerbates these symptoms. However, the gradual appearance of symptoms associated with PD suggests that the BG has inherent properties within these pathways that act as compensatory mechanisms to adapt to cell loss in the SNc (Agid, 1991; Obeso & Schapira, 2009). Furthermore, extensive dopamine loss in the caudate nucleus and putamen, as seen at autopsy, can be associated with relatively

few clinical symptoms (Agid, 1991; Bezard & Gross, 1998). Zigmond and Stricker (1989) suggest that compensatory mechanisms initially maintain a sufficient amount of dopamine in the striatum and then optimise supply from the remaining neurons. The first compensatory mechanism alters the discharge frequency of dopamine. This increases the amount of dopamine that is released per pulse and/or synthesises a greater quantity. The second compensatory mechanism increases the responsiveness of striatal neurons to dopamine and supplements the synthesis of tyrosine hydroxylase. In a healthy brain, there is a provision for dopamine 'redundancy' in the nigrostriatal pathway, thus allowing the circuit to tolerate some degree of damage to dopamine neurons before these compensatory mechanisms are needed.

The functional connectivity model (Figure 2-1) outlined by Bezard and Gross (1998) implies that the basal ganglia's role in the control of movement is a serial and hierarchical process. This suggests that movement control follows an arrangement of excitatory and inhibitory events, assuming that the motor system uses a procedural approach to facilitate the execution of movement. This model has been supported, as it explains the motor consequences of lesions in the SNc and GPi, but it fails to explain several other features of PD, including the cognitive and emotional aspects of the disorder (Obeso et al., 2000). This suggests that PD is more than just a disorder affecting motor circuitry, but more likely a disease that involves multiple brain circuits and systems.

The anatomy of the motor circuit is much more complex than first envisioned. Not only is it arranged in separate, parallel, loops, but each individual cortical motor area is somatotopically organised (Obeso et al., 2000). The cortical regions (Brodmann area 4 and 6, and supplementary motor area) and the primary somatosensory cortex project to the striatum in this same organised manner. The motor control area is located in the dorsolateral section of the basal ganglia, with the leg represented in the dorsal region, the face in the ventral region

and the arm in between the two on a coronal plane (Figure 2-2). Neural activity of the STN

and GPi has been observed during PD surgery to follow the same pattern of organisation,

with cortical projections from area 4 and the supplementary motor area (SMA) in the

putamen, STN and GPi (Hoover & Strick, 1993; Obeso et al., 2008; Rodriguez-Oroz et al.,

2001; Theodosopoulos, Marks, Christine, & Starr, 2003). However, no clear arrangement has

been found for the SNc and the dopaminergic projections of the nigrostriatum (Obeso et al.,

2008).
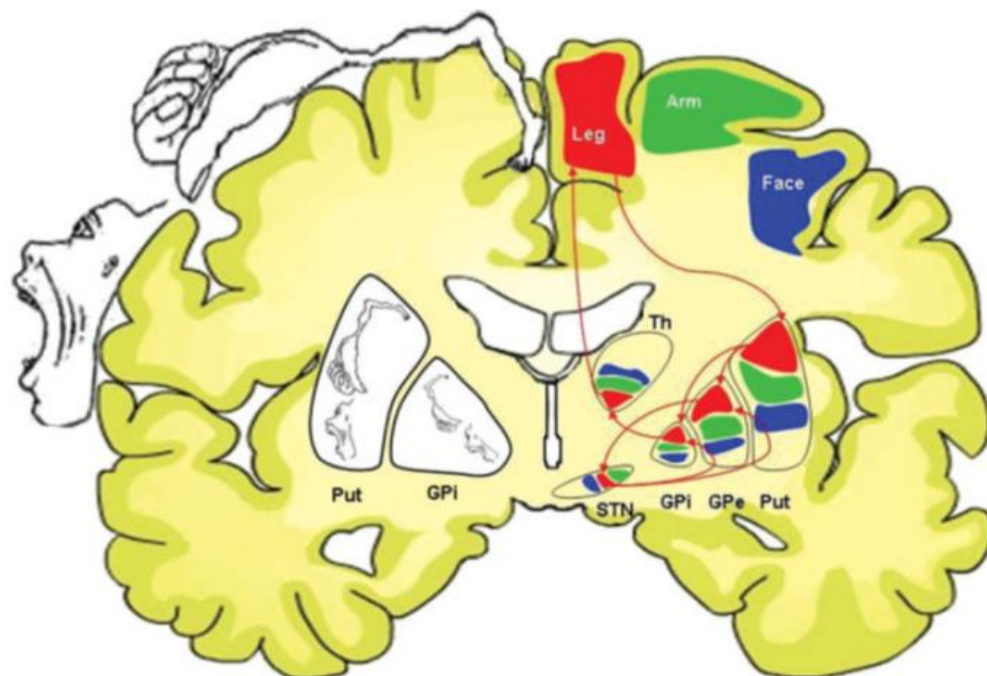
Figure 2-2. The somatotopically-organised basal ganglia tends to mimic the cortical representation of the body, with the leg represented dorsally, the face ventrally and the arm in-between (Obeso et al., 2008). Reproduced with permission from John Wiley and Sons.

The motor circuit of the basal ganglia is therefore regarded as a complex network,

connected by separate and hierarchically arranged cortico-basal ganglia-cortical parallel

circuits and 'internal' loops which project motor inputs to different areas of the motor cortex.

The cortico-basal ganglia-cortical parallel loops are regarded as positive feed-forward signals

to aid the preparation and execution of movement while the 'internal' circuits may primarily

serve a feedback-stabilisation function (Figure 2-3). Monkey studies suggest that the main

role of neurons in the direct pathway is the performance of complex oculomotor and manual

movements, whereas the indirect pathway's role has yet to be as clearly established (Obeso et

al., 2000). Obeso et al. (2000) surmised from animal studies that cortical activation of the

region do tend to have immediate and influential disynaptic effects on the GPi/SNr. These

effects are not driven by inhibitory pathways (i.e. direct) from the GPi/SNr nor excitatory

pathways (i.e. indirect) originating from the STN. This finding suggests the projections from

the cortico-STN may be involved with learned motor sequences and repetitive movement

control. The polysynaptic indirect pathway, in contrast, directly excites the GPi/SNr

suggesting this pathway is involved in complex motor-learning tasks. BG excitability is

controlled closed-loop 'internal' circuits along with the dopaminergic system, which also

plays a stabilising role. A depletion of dopamine would destabilise the network and would

lead to instability within these circuits, resulting in an increase in parkinsonian symptoms

(Obeso et al., 2000).
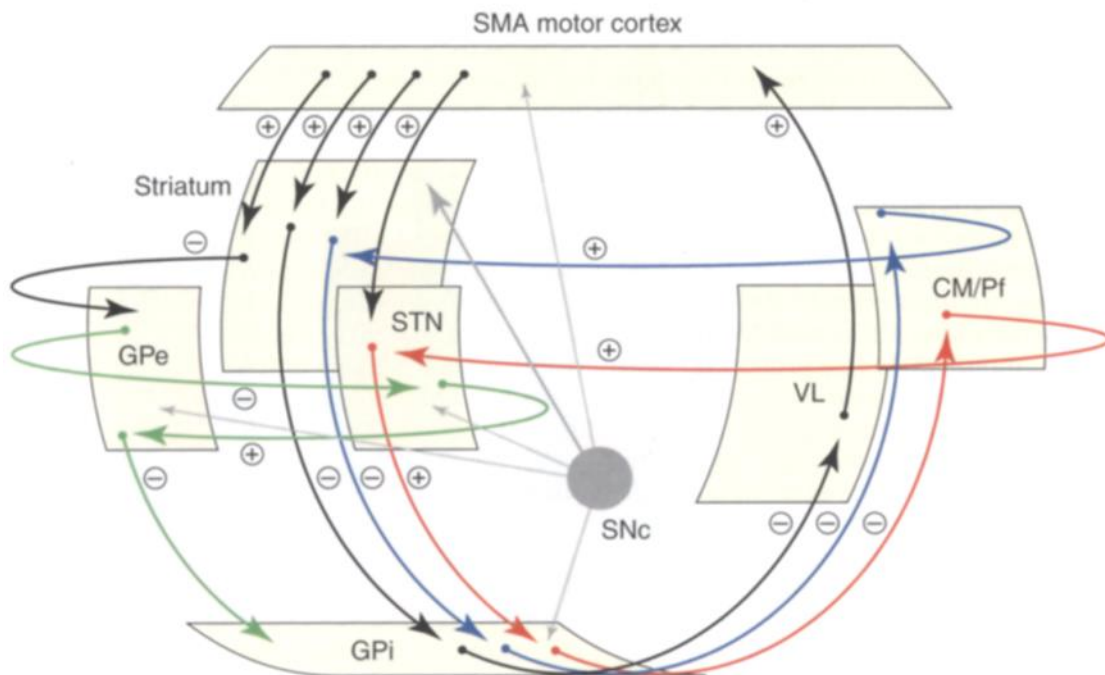
Figure 2-3. *The cortico-basal ganglia-cortical feedback loop of motor control. The black loops represent closed somatotopically-organised parallel projection circuits between the motor cortex, the basal ganglia and the motor circuit. The horizontal loops provide 'internal' stabilisation of basal ganglion activity. The blue loop represents the centromedian-parafascicular complex (CM/Pf) which is a CM/Pf-striatum-GPi-CM/Pf positive feedback circuit. The red loop is the CM/Pf-SNT-GPi-CM/Pf negative feedback loop. The green arrows represent the STN's control of GPi activity through a direct STN-GPi monosynaptic excitatory connection and STN-GPe-GPi excitatory-inhibitory loop. The GPe has a reciprocal inhibitory effect on the STN. The grey arrows represent the dopaminergic modulation of the striatum, SNT, GPi, GPe and SMA motor cortex (Obeso et al., 2000). Reproduced with permission from Elsevier.*

2.2.2. PD is more than just a dopaminergic disorder: It is a multisystem neurodegenerative disorder

Braak, Ghebremedhin, Rub, Bratzke, and Del Tredici (2004) developed a staging system of PD progression based on neuroanatomical changes that happen over time. The model consists of six sequential stages where α-synuclein deposits (Lewy body pathology; LB) aggregate and disperse throughout the brain (Braak et al., 2006; Braak & Del Tredici, 2008; Braak et al., 2004; Hawkes, Del Tredici, & Braak, 2010). Predictable changes of the disease progression drive the idea behind this staging system (Figure 2-4). LBs in the brain stem and

olfactory regions of individual's that do not yet experience any motor symptoms are the

characteristic features of the presymptomatic phase. When an individual has progressed to the

symptomatic phase LB pathology exceeds (Figure 2-4) the threshold and is particularly

evident in the SNc. Most neuropathologist's support the concepts underlying Braak's PD

staging model, but acknowledge that in about 10-20% of PD cases pathology differs from

what is outlined (Hawkes et al., 2010). Jellinger (2008, 2009) however has argued that in

retrospective PD studies, 6.3-43% of cases differ from the proposed stages of

neuroanatomical changes outline by Braak. Furthermore, Jellinger (2008, 2009) observes that

there is considerable overlap within each stage in terms of the LB pathology related to other

neurodegenerative multisystem disorders, especially the related condition known as dementia

with Lewy bodies (DLB).
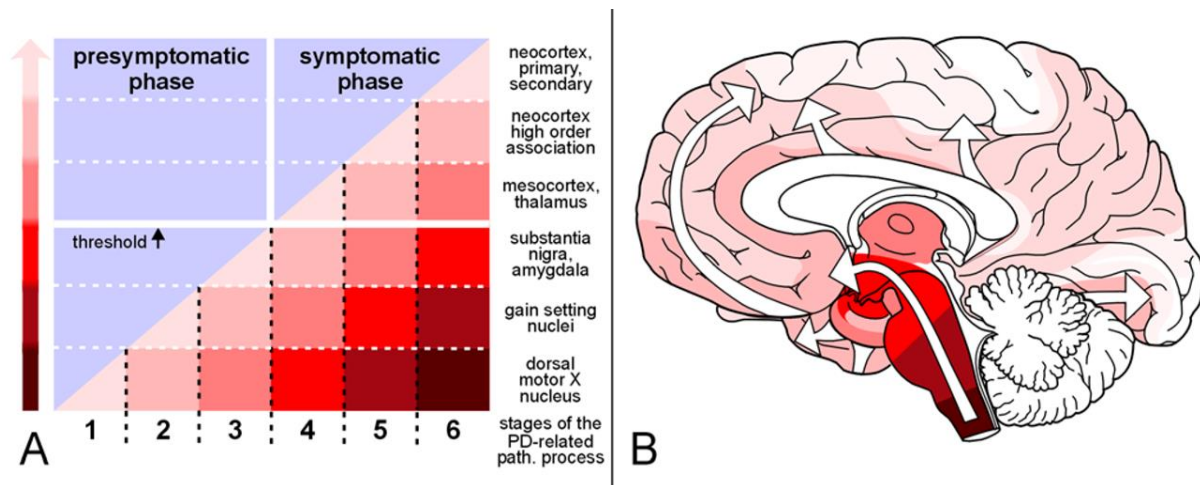
Figure 2-4. Braak's staging model of PD. (A) PD progression is divided into two phases, the presymptomatic and symptomatic phases. The increasing slope and the intensity of the coloured areas that are below the diagonal line show the growing severity of the Lewy pathology. The severity of Lewy pathology in different regions of the brain is shown by the degree of red shading and it's spread from the brain stem and olfactory bulb through to the cortical regions are illustrated by the coloured arrow. (B) This diagram shows the ascending pathological processes (white arrows) while the shading corresponds to Figure 2-4A (Braak et al., 2004). Reproduced with permission from Springer for the purposes of thesis submission and defence, but not for electronic or print use after thesis defence.

At stage one, LB pathology is sparse and isolated to the vagal nerve dorsal motor nucleus and olfactory structures of the anterior bulb (Figure 2-4; Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010). No other pathology is found anywhere else in the brain, suggesting these regions are where PD pathology begins before spreading to other areas of the brain. Signs of pathology in the enteric motor system (EMS) could include constipation. A study looking at the relationship between constipation and the development of PD found that men who had less than one bowel movement a day were at an increased risk (2.7 times) of later developing PD compared to those who had one bowel movement a day. The risk increased further (4.5 times) when compared to men who had more than two movements a day (Abbott et al., 2001). A follow-up study found additional evidence to support the relationship between constipation and an increased risk of developing PD with incidental LB pathology present in the SNc which was four time greater in men who had less than one bowel movement a day. This would suggest constipation may be early prodromal symptom of PD (Abbott et al., 2007). Olfactory dysfunction may also be present at this stage along with urinary, bladder and erectile problems. However, although these symptoms may indicate the initial phases of PD, they are not specific to PD and thus are not diagnostic features of the disorder (Hawkes et al., 2010).

At Braak's stage two of PD, there is increasing LB pathology in the areas already involved and the pathology has spread into the lower raphe nucleus, coeruleus-subcoeruleus complex (CSC) and reticular formation (Figure 2-4). The 'gain setting' system comprised of these structures, controls motor and pain function. The pathological changes as LBs aggregate in these regions could be the underpinnings of the painful symptoms which can develop during the course of PD. Depression is a common co-morbidity of PD, and if it is related to serotonergic pathways, CSC changes could be the basis of the depressive symptoms

experienced by the patient. The changes in the CSC could also be the underpinning of sleep disorders in PD (Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010). Stages one and two are both popular research areas surrounding the prediction of PD in the prodromal stage of the disorder (Morley & Hurtig, 2010; Postuma et al., 2012). Some risk factors include loss of smell, REM sleep behaviour disorder (RBD) and constipation (Postuma et al., 2012).

The classic characteristic motor-features of PD emerge during stage three of Braak's model. The spread of LB pathology has reached the upper limits of the pontine tegmentum and basal areas of the mid and forebrain (Figure 2-4), including the SNc, central subnucleus of the amygdala, the magnocellular nuclei of the basal forebrain (MBF) and nucleus basalis of Meynert. The loss of more than 50% of neurons in the SNc are the basis of the cardinal motor signs (bradykinesia, rigidity and rest tremor) seen in PD. Changes in the MBF are attributed to attention and sleep-wake cycle dysfunction. Disordered behaviour, poor memory and hallucinations are thought to relate to pathology within Meynert's nucleus among other regions (Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010).

By stage four of Braak's PD model, pathology is severe in the amygdala and the anteromedial temporal mesocortex. There is also evidence of pathology developing in the second sector of Ammon's horn, characteristic of advanced stage PD (Figure 2-4). At stage four, the pathology is wide-spread which makes it problematic to discern what pathological changes are the underpinnings of which specific symptoms/signs that the individual is experiencing clinically. Cognitive decline is one of the most noticeable clinical signs and could be related to pathological changes in thalamic intralaminar nuclei. The LB pathology may impede higher-order sensory information from reaching structures such as the entorhinal region, amygdala and hippocampal formation (Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010).

In stage five, the LB pathology invades the insular, anterior cingulate regions and subgenual mesocortex, while intensifying in regions where pathology had developed previously (Figure 2-4). Cortical areas are now involved which can be the cause of balance impairments and cognitive decline. Layers V-VI neocortical pyramidal cells now also exhibit pathology, chiefly in the secondary and tertiary association areas. The regions affected in stage five all have a role in viscerosensory and visceromotor function, meaning that heart rate, the regulations of breathing, blood pressure and even bowel motility can be affected (Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010).

In the sixth and final stage of Braak's PD model, the pre-existing damage to the limbic, autonomic and somatomotor systems is aggravated by the spread of LBs to centres of the superordinate limbic system. Pathology can now be seen in virtually every area of the brain, including primary motor and sensory areas, first-order sensory association regions and the premotor regions of the neocortex (Figure 2-4). If an individual was to progress to stage six of Braak's model, they would have severe dementia and be practically immobile due to the extent of this pathology (Braak et al., 2006; Braak et al., 2004; Hawkes et al., 2010).

Earlier models of PD, discussed previously, attributed the underlying neuropathology of PD to a dopaminergic deficiency in the dorsal striatum but failed to include other non-dopaminergic systems that are now known to be affected by PD as the disease progresses. An updated model illustrates the wider pathological changes that occur in PD (Figure 2-5). The amendments to the earlier models suggest that PD is not just a dopaminergic dysfunction but a multi-system neurodegenerative disorder (Braak & Del Tredici, 2008). This change in thinking has transformed PD research, as now the focus has shifted from purely motor-related studies to multi-system research. Parallel neurochemical models could further explain the cognitive and non-cognitive symptoms that are associated with dementia in PD and the

interaction between these neurochemical systems that could result in the parkinsonian

condition (Calabresi, Picconi, Parnetti, & Di Filippo, 2006).
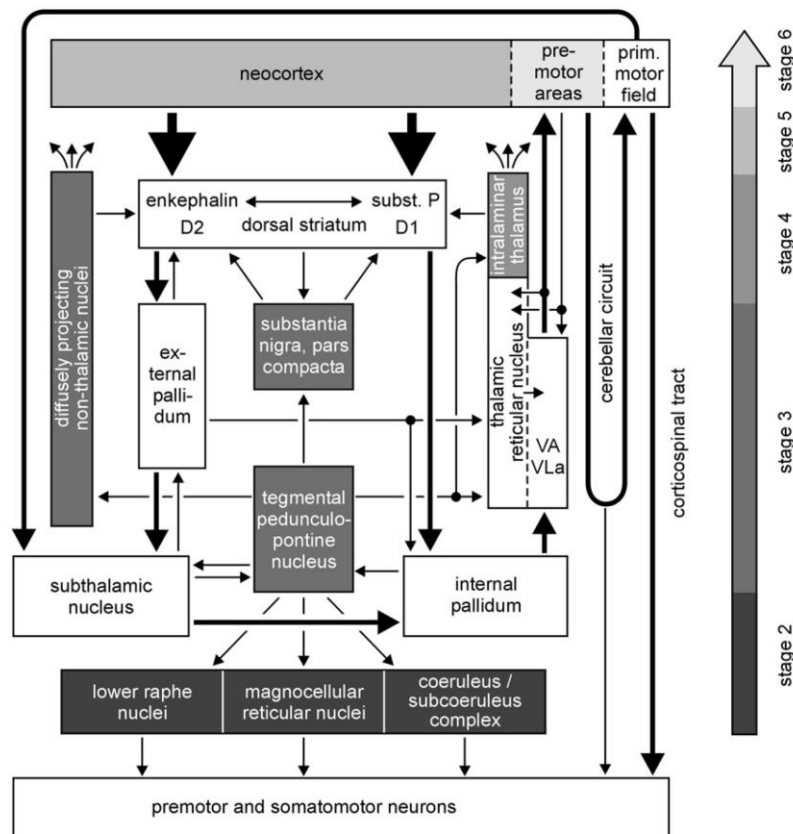
Figure 2-5. *Braak's updated model of dopamine depletion in PD. This includes the motor areas of the spinal cord through to the neocortex. It not only shows the consequences of dopamine depletion in the dorsal striatum but also the non-dopaminergic centres that become consecutively and severely impaired as PD progresses. The cortico-striatal projection is most probably impaired because of the cortical pathology while the cortico-subthalamic contention remains intact. The neuropathological stages are illustrated by the various degrees of shading (Braak & Del Tredici, 2008). Reproduced with permission from Elsevier.*

2.3. Signs and symptoms of PD

The non-motor symptoms associated with PD can have the biggest impact on an individual's

ability to function in everyday life (Lawson et al., 2014). The cardinal features of PD are

bradykinesia, tremor at rest and rigidity and some include the later development of loss of

postural reflexes which can result in falls and postural deformities (Jankovic, 2008). Some of

these secondary motor symptoms and non-motor symptoms are listed in Table 2-1.

Table 2-1. Common secondary motor and non-motor features of PD

Motor Symptoms	Description
Hypomimia	A paucity facial of expression.
Dysarthria	The poor articulation of phonemes.
Dysphagia	Difficulty swallowing.
Sialorrhoea	Excessive build-up of saliva.
Micrographia	Abnormally small, cramped handwriting and/or the progressives to smaller handwriting across the page.
Shuffling gait	Where the individual's feet skate across the ground because they make contact too early.
Festination	The involuntary quickening of gait of shortened stride length.
Akinesia/Freezing	Difficulties in the initiation of movement.
Dystonia	An abnormal tonicity of muscles characterised by prolonged, repetitive muscle contractions that may cause twisting or jerking movements.
Gabellar reflexes	The inability to resist blinking when the forehead (gabellar) is repetitively tapped.
Postural instability	This usually presents in the later stages of the disease and is the most common cause of fall related to PD.
Non-Motor Symptoms	**Description**
Orthostatic hypotension	Low blood pressure occurring when an individual stands up.
Sweating dysfunction	Excessive sweating (hyperhidrosis).
Sphincter dysfunction	This can lead to incontinence (the loss of regular control of bladder or bowel).
Cognitive decline	Studies have shown that that most patients diagnosed with PD have some degree of cognitive decline and are at a six-time increased risk of developing dementia.
Depression	There is a high comorbidity between PD and depression ($> 55\%$).
Apathy	A state of indifference (high prevalence in PD patients $> 50\%$)
Anxiety	About 50% of patients develop anxiety.
Hallucinations	About 40% of patients report hallucinations.
Impulse control disorders	Some patients develop behaviour that may manifest as pathological gambling, hypersexuality, or compulsive shopping and binge eating; these are related to dopamine agonist therapy in particular.
Excessive sleepiness	Some patients may exhibit excessive daytime sleepiness; this can be caused or aggravated by dopaminergic therapy.

Rapid eye movement sleep behavioural disorder (RDB)	Characterised by a tendency to talk or act out dreams. May be associated with an increase in violent dream content coupled with injurious motor activity. At least one third of patients exhibit this and it frequently presents in the pre-motor stages of PD.
Insomnia	About 50% of patients have fragmented sleep patterns.
Paraesthesias	A skin sensation, such as burning, prickling, itching, or tingling, with no apparent physical cause.
Olfactory dysfunction	Loss or altered sense of smell. Some individuals may experience olfactory hallucinations.

Note: Information adapted from Jankovic (2008).

2.3.1. Cognitive decline

Cognitive decline is the most common non-motor feature of Parkinson's disease. Cognitive impairments arguably have the greatest impact on a patient's quality of life, their family and the health care system (Lawson et al., 2014; Leroi, McDonald, Pantula, & Harbishettar, 2012). Parkinson's disease with dementia (PDD) has been associated with early mortality (Lawson et al., 2014; Oosterveld et al., 2015). The issue facing PD patients is that at least 80-90% of patients ultimately experience dementia (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Hobson & Meara, 2015), though an individual's time course to dementia is highly variable (2-25 years; Aarsland et al., 2003; Buter et al., 2008; Hely, Reid, Adena, Halliday, & Morris, 2008). Surprisingly, the recognition of cognitive impairment and its role within PD has only recently become center stage in the literature, primarily after longitudinal cohort studies were recently published. Another reason is that life span has increased, primarily due to more effective cardiovascular intervention. This has resulted in PD patient's living longer and thus more patients have experienced significant cognitive impairment and dementia.

The highest risk factors for cognitive decline in PD are older age and severity of motor symptoms. Early decline in cognition, Parkinson's disease with mild cognitive impairment (PD-MCI), is increasingly recognized as an important sign of future decline to PDD (Aarsland & Kurz, 2010; Dubois et al., 2007; Palavra, Naismith, & Lewis, 2013; Troster, 2011; Yarnall, Rochester, & Burn, 2013). Other risk factors include lower education, being male, REM sleep behaviour disorder (RBD), hallucinations, smoking and hypertension (Palavra et al., 2013; Xu, Yang, & Shang, 2016).

PD-MCI is believed to be present in approximately one-in-three newly diagnosed patients (Lewis et al., 2003; Litvan et al., 2012), despite being considered an intermediate stage of cognition between 'normal' cognition in PD (PD-N) and PDD. This observation underscores the prevalence of cognitive impairment in PD. Cognitive impairment in PD can include any of the classic cognitive domains – attention, working memory, executive functioning, memory, language and visuospatial functioning. Thus, all cognitive domains should be assessed when determining if a patient is cognitively impaired (Dubois et al., 2007; Emre et al., 2007; Litvan et al., 2012). Diagnostic criteria for both PDD and PD-MCI have been proposed by the Movement Disorder Society Task Force (MDS-TF) and are used in both clinical and research settings (Dubois et al., 2007; Emre et al., 2007; Litvan et al., 2012). PD patients who do not meet either of these cognitive status criteria are deemed by exclusion to have 'normal' cognition for PD (PD-N).

The CamPaIGN study was the first study to examine the evolution of PD from diagnosis in an unselected representative population of patients. They have consistently reported that impaired reproduction of the overlapping pentagons copy, age, poor semantic fluency performance, UPDRS motor scores 25 points or higher and the microtubule-associated protein tau gene were all baseline predictors of future dementia up to 10-years

later (Foltynie, Brayne, Robbins, & Barker, 2004; Goris et al., 2007; Williams-Gray et al., 2009; Williams-Gray et al., 2013). This group has also attempted to determine what the underlying processes are which result in the heterogeneity of cognitive impairment that is seen in PD patients. They suggest that there are two broad syndromes of cognitive impairment where (1) one syndrome results in frontal-striatal dysfunction causing cognitive impairments in planning, working memory and executive functioning and (2) the other syndrome is dominated by early deficits in semantic fluency and visuospatial functioning which rapidly declines to dementia (Kehagia, Barker, & Robbins, 2012).

Brain-related changes in PD have been shown to associate with cognitive decline in MRI studies. Hattori et al. (2012) found that decreases in fractional anisotropy (FA) – indicating white matter (WM) damage – related to MMSE scores. This decrease was particularly evident in the bilateral parietal WM. The authors claimed that the underlying cause of cognitive impairment in PD could be a result of the WM damage. They also suggest that as the degree of cognitive impairments worsens from PD-N to PD-MCI and finally to PDD, functional changes are seen in the early stages of cognitive decline and structural changes appear later. These changes preceded grey matter (GM) atrophy and the authors hope that these changes could be useful at identifying early PD, possibly during the prodromal phase. Melzer et al. (2012) reported that GM loss correlated with global cognitive scores, even after accounting for motor impairment, sex, age, education and intracranial volume. This atrophy was mostly limited to the cortex, with clustering around the lateral-frontal regions adjacent to the insula cortex and posterior regions of the brain. Changes in the cerebral metabolism have been found in positron-emission tomography (PET) studies which relate to cognition in PD. These include metabolic decreases in the dorsolateral prefrontal cortex, medial and superior parietal regions as well as the rostral supplementary motor area.

An increase was also found in the dentate nucleus region of the cerebellum (Eckert, Tang, &

Eidelberg, 2007; Huang et al., 2007).

2.3.1.1. PDD classification

In 2007, the Movement Disorder Society Task Force (MDS-TF) developed diagnostic criteria

for probable and possible PDD (Emre et al., 2007) and a two-level set of practical guidelines

for diagnosis (Table 2-2; Dubois et al., 2007). A PDD classification requires significant

cognitive impairment to be present in at least two cognitive domains, and can be supported by

behavioural features (i.e. hallucinations or depression) but requires that the cognitive

impairment, results in the individual's inability to cope with everyday tasks. These new PDD

criteria were found to be more sensitive than the diagnostic and statistical manual of mental

disorders-IV criteria for diagnosing PDD (Martinez-Martin et al., 2011). A Level I PDD

classification can be made on patients who would not cope with the cognitive demands of

comprehensive testing required by Level II criteria or in a clinical setting where resources can

restrict testing times (Dubois et al., 2007). Like the diagnostic criteria for PD itself, criteria

for PDD classification mirror the same structure (i.e. probable PDD or possible PDD). The

two different Levels of PDD diagnosis are outlined in Table 2-2. Both PDD criteria require

an established PD diagnosis, cognitive deficits severe enough to interfere with daily life, and

the presence of behavioural symptoms such as depression or anxiety. Furthermore, the Level

I Dubois et al. (2007) criteria need evidence of motor symptom onset before the cognitive

decline began. This is to rule out the existence of Dementia with Lewy bodies, where the

cognitive impairment usually occurs around the same time as motor symptom onset. The

abbreviated Level I criteria require a global cognitive measure, such as the MMSE, to show

cognitive impairment (i.e. score <26) and evidence of cognitive impairment on at least two

other brief cognitive assessments (i.e. MMSE pentagons or 3-word recall; Dubois et al.,

2007). For a Level II diagnosis of PDD the dementia type symptoms need to have slowly developed, impairments must be severe, affecting at least one cognitive domain, and there needs to be evidence of premorbid decline in the individual's functioning. In addition to these features, a probable PDD classification requires that both core features are present (established PD and progressive decline), at least one behavioural symptom, and cognitive impairment, when formally assessed and in everyday life. A possible PDD classification, however, only needs the two core symptoms, atypical cognitive impairment (i.e. storage-failure type amnesia where cueing does not improve memory ability), but does not require the presence of behavioural symptoms (Emre et al., 2007). The Level I and Level II probable PDD criteria are very similar as both require cognitive and behavioural impairments, although the cognitive testing is much more robust when the Level II criteria are used, while the Level II possible PDD criteria do not require the presence of behavioural symptoms.

Table 2-2. Criteria to classify PDD (Dubois et al., 2007; Emre et al., 2007)

Diagnosis and features of Parkinson's disease associated with dementia (Emre et al., 2007)	<u>Core features</u>
	− Diagnosis of PD
	− A dementia syndrome with an insidious onset and a slow progression that develops within an established context of PD, where:
	    o Impairments need to be present in at least one cognitive domain.
	    o There is evidence of a decline from premorbid functioning
	    o Deficits are severe enough to affect daily life (social, occupational or personal), but cannot be attributed to the patient's motor impairments.
	<u>Associated clinical features</u>
	− Cognitive features of PDD include impaired performance on attentional, executive functional, visuospatial, memory and language-based tasks (both when formally assessed and in everyday life).
	− Behavioural features include apathy, changes in mood and personality, hallucinations, delusions and even excessive daytime sleepiness.
	<u>Probable PDD classification</u>
	− Both core features present
	− Associated clinical features including:
	    o Cognitive decline where there is a presence of impairment in at least two cognitive domains
	    o At least one behavioural symptom present
	<u>Possible PDD classification</u>
	− Both core features present
	− Associated clinical features:
	    o Atypical cognitive impairment in one or more domains.
	    o Behavioural symptoms may or may not be present

Criteria for diagnosing Level I PDD (Dubois et al., 2007)	− A diagnosis of PD
	− PD developed prior to onset of dementia
	− MMSE < 26
	− Cognitive deficits severe enough to affect everyday living
	− Impairments in at least two of these scales:
	    o Months reversed or sevens backwards
	    o Lexical fluency or clock drawing
	    o MMSE pentagons
	    o 3-word recall
	− The presence of one or more of the following behavioural symptoms:
	    o Apathy
	    o Depression
	    o Delusions
	    o Excessive daytime sleepiness

Note: These PDD diagnostic criteria were taken from Emre et al. (2007) and Dubois et al. (2007)

2.3.1.2. PD-MCI classification

The concept of mild cognitive impairment (MCI) began in the Alzheimer's disease (AD) literature, where it was initially used to indicate a measure of decline beyond an age-expected norm and in particular a decline in episodic memory. Today, it has evolved into a more general cognitive syndrome, in part due to the emphasis on biomarkers, which is used as both a clinical and a research diagnostic classification (Albert et al., 2011; Petersen et al., 2009). Most early studies reported that individuals who have amnestic MCI are more likely to develop AD than those with other sub-types of MCI (Petersen et al., 1999). Not every individual who is classified as MCI will progress to dementia, but the MCI construct does suggest that a continuum exists from normal age-related cognition through to dementia, such as AD or PDD. The MCI state therefore represents an intermediate or pre-clinical stage of cognitive decline. This MCI framework has since been applied to PD research, where PD-MCI is defined as the transitional state between PD-N and PDD. Cognitive impairment is present but, unlike PDD, individuals experience no significant impact from this cognitive impairment on their ability to function in everyday life (Litvan et al., 2012). Studies have found that there is a higher, albeit variable, rate of progression to PDD in PD-MCI than non-PD-MCI patients (19-62% vs 0-20%, respectively) when patients were followed for two to five years (Broeders, de Bie, et al., 2013; Janvin, Larsen, Aarsland, & Hugdahl, 2006; Pedersen, Larsen, Tysnes, & Alves, 2013). In a group of PD patients followed for 16 years, 91% of those identified as PD-MCI eventually reached PDD. This was over four times the proportion of non-PD-MCI who progressed to PDD (Hobson & Meara, 2015). It is, however, difficult to directly compare these studies as each one used different diagnostic criteria to define their group of PD-MCI patients.

The heterogeneous methods employed to define the cognitive status of "PD-MCI"

have led to substantial variation in the percentage of patients so classified (Aarsland et al., 2010; Dalrymple-Alford et al., 2011; Goldman et al., 2013; Janvin et al., 2006; Liepelt-Scarfone et al., 2011), where anywhere from 10-90% of patients in a given sample can be classified as PD-MCI, simply by applying different PD-MCI criteria to the same group of patients. Using non-dementing PD patients from the NZBRI cohort, I extended the dot plot from Dalrymple-Alford et al. (2011) where parameters of the PD-MCI criteria were varied to illustrate theses diagnostic problems (Figure 2-6) by separating the patients within each group who developed PDD within the four-year follow-up period from those who did not develop PDD. Clearly, not all PD-MCI criteria are sensitive to capturing patients at risk of progression to PDD. This issue forms the basis for the study described in Chapter 3.
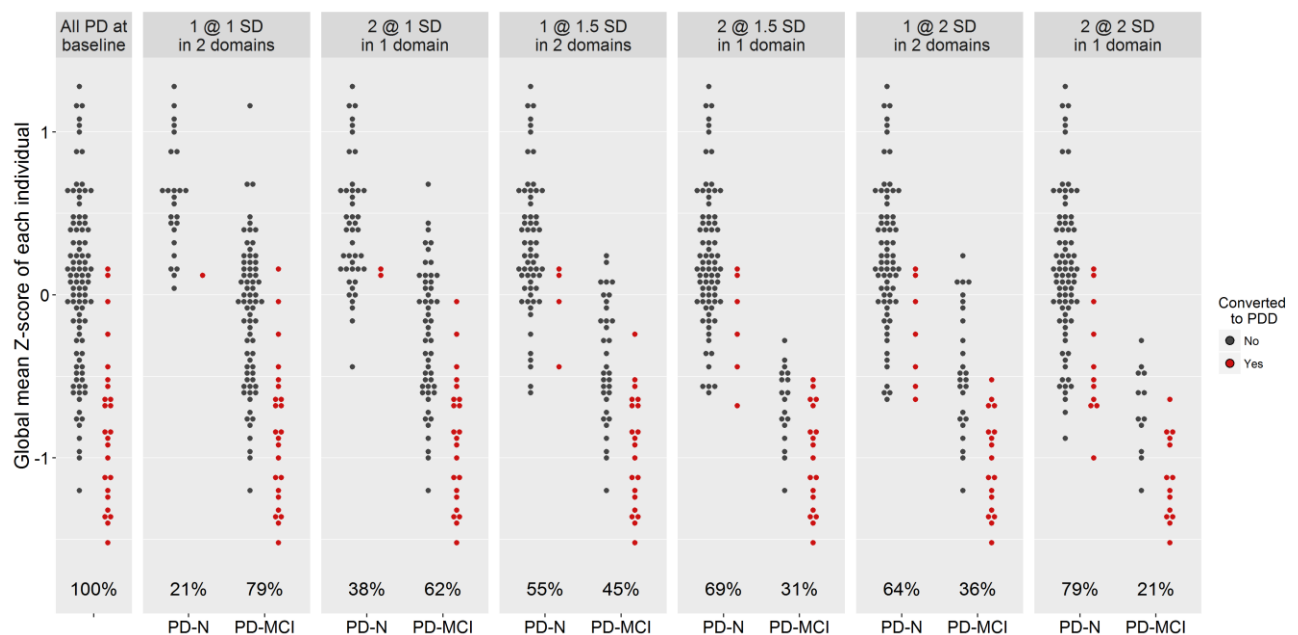
Figure 2-6. *Global cognitive scores of PD patients who have been classified as PD-MCI or PD-N based on different allowable parameters of MDS-TF PD-MCI Level II criteria. All non-dementing patients at study entry are shown on the left panel (converters to PDD are shown as red dots). Baseline scores as a function of the six PD-MCI criteria are displayed on the subsequent panels along the x-axis, with the percentage of patients classified as PD-MCI varying markedly (79% to 21%). We see that as the cut-off score become more stringent (i.e. 2SD) fewer patients classify as PD-MCI, whereas when the cut-off is more lenient (i.e.1SD) more patients are classified as PD-MCI. The similar pattern emerges when the location of tests impairments is restricted to two or more impairments only within a cognitive domain (fewer patients meet the PD-MCI criterion) vs. one impairment in each of two or more*

cognitive domains (larger proportions of patients meet the PD-MCI criterion) across cut-off variants. When progression to PDD within the next four-years is considered (red dots represent patients who convert) when criterions require more stringent cut-off scores and restrict impairments to both occur in the same cognitive domain (i.e. '2 @ 2SD in 1 domain'), there is a high proportion of patients who convert to PDD in the PD-MCI group, but a large number of converts are not captured by this criterion. The opposite occurs when a criterion with more lenient cut-off scores is employed (i.e. '1 @ 1SD in 2 domains'), here almost all of the converters to PDD are captured by the criterion, but there is a very high false positive rate.
PD-N, normal cognition, not meeting the relevant MCI criteria;
PD-MCI, mild cognitive impairment for the relevant MCI criteria. For example, "1 @ 1SD in 2 domains" represents a deficit score of -1SD in at least 1 test in each of two cognitive domains.

To guide the research field, standardised diagnostic criteria were proposed by the Movement Disorder Society PD-MCI Task Force (MDS-TF; Litvan et al., 2012). The Task Force's Level I criteria permit the use of global cognition scales or an abbreviated neuropsychological assessment that includes fewer than two tests in each of five cognitive domains (attention/working memory; executive function; episodic memory; visuoperceptual/ visuospatial function; language) or assessment of less than five cognitive domains (Table 2-3). The more comprehensive (Level II) criteria require the application of at least two tests in each of the five cognitive domains. PD-MCI is established when any two (or more) impaired neuropsychological test scores are present, but everyday function is generally preserved. Nonetheless, the Level II PD-MCI recommendations still allow for variations within the permitted PD-MCI criteria, such as cut-off scores to define an impaired score being free to range from 1SD to 2SD below normative data, in part to account for the interpretation of a decline from premorbid levels. Additionally, the maximum number of tests permitted per cognitive domain is not defined. Lastly, both test impairments are permitted to occur within a single cognitive domain, or can occur across two or more cognitive domains (**Figure 2-7**; Litvan et al., 2012). This variation can result in differences as PD-MCI criterions which require that more than one test be impaired within a single cognitive domain

have a stricter statistical threshold. This stricter threshold reduces the likelihood of false

alarms (i.e. patients who are not declining towards PDD to be classified as PD-MCI) but the

trade-off is lower sensitivity to impairments. The MDS-TF found that about 27% of PD

patients met their criteria for PD-MCI. Both the Level I and Level II PD-MCI criteria

outlined in Table 2-3 require a clinically-established PD diagnosis and gradual cognitive

decline that is attributed to the underlying disease processes rather than to any other cause.

The cognitive decline can be reported by the patient, their significant other or a clinician and

must not be severe enough to interfere with the patient's functional independence.

Table 2-3. MDS-TF PD-MCI criteria guidelines (Litvan et al., 2012)

Level I PD-MCI Criteria (abbreviated)	Level I PD-MCI classification requires ONE of the below: − Impairment on a global cognitive scale validated for use in PD (i.e. MoCA). − Impairment on at least two tests, when a limited test battery is preformed (i.e. fewer than five cognitive domains assessed or when there are fewer than two tests assessed within each of the five cognitive domains).

Level II PD-MCI Criteria (Comprehensive)	− At least two tests assessed within each of five cognitive domains (attention, executive function, visuospatial, memory and language).
	− Impairment on at least two of these tests (can be two tests within a single cognitive domain or across more than one cognitive domain).
	− Impairments on neuropsychological testing is demonstrated via ONE of the below:
	    o Performance between 1SD – 2SD below normative data
	    o Significant decline on serial cognitive testing
	    o Significant decline from estimated premorbid levels

Subtype classification of PD-MCI (suggested for research)	− PD-MCI-single-domain: at least two impaired test scores that occur within a single cognitive domain, with other cognitive domains remaining unimpaired (specify the domain). − PD-MCI-multiple-domains: the two impaired test scores occur on at least one test in two or more cognitive domains (specify the domains).

Note: Information adapted from Litvan et al. (2012)
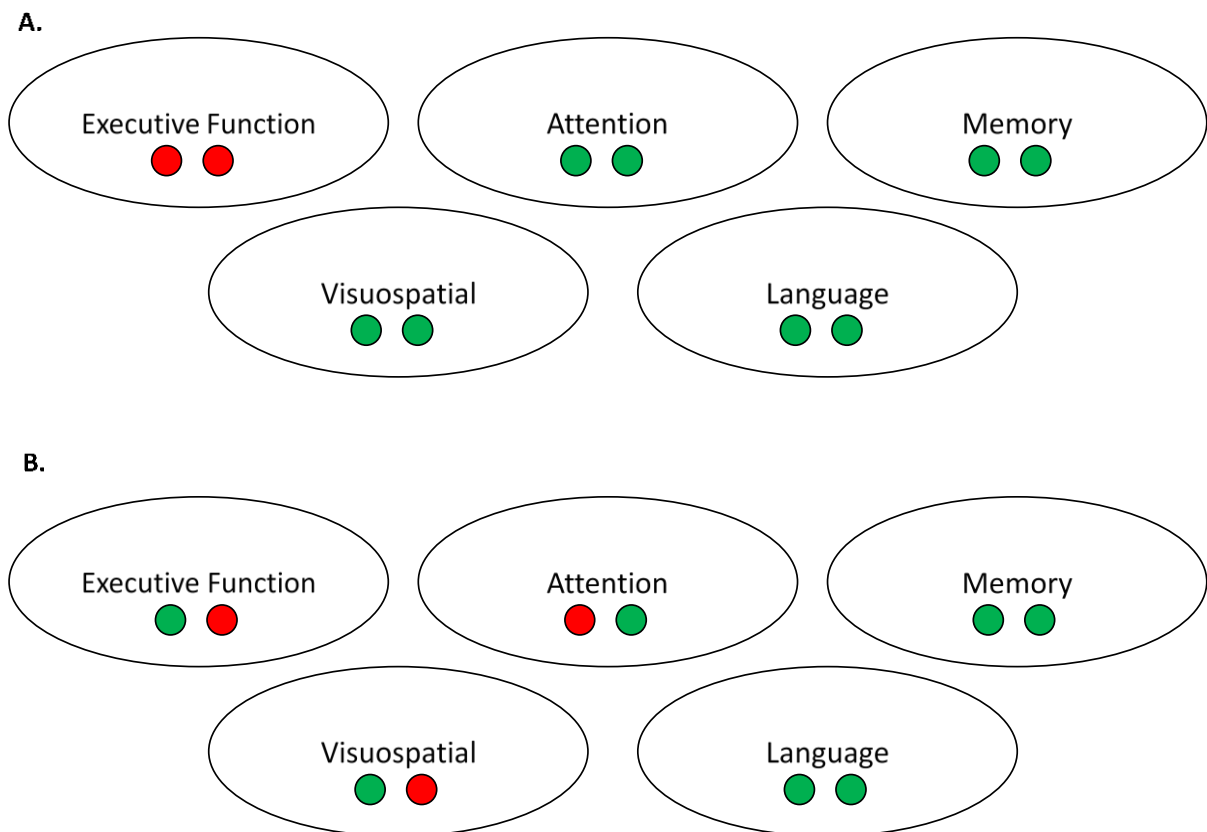
Figure 2-7. Illustration of where impairments can occur within MDS-TF PD-MCI Level II criteria. (A) Two or more test impairments must occur within one or more cognitive domain. (B) Two or more test impairments can occur, across any number of cognitive domains.

2.3.2. Neuropsychiatric symptoms

PD has an extremely high comorbidity with neuropsychiatric conditions, with up to 90% of patients experiencing at least one symptom such as depression, apathy or hallucinations during their disease course (Aarsland et al., 1999; Brown & MacCarthy, 1990; Chaudhuri & Schapira, 2009; Emre et al., 2007; Kulisevsky, Pagonabarraga, Pascual-Sedano, García-Sánchez, & Gironell, 2008; Lee & Weintraub, 2012; Marsh, 2000; Pedersen, Alves, Aarsland, & Larsen, 2009; Poewe et al., 2008; Riedel et al., 2010). Those with PDD experience the highest rates of neuropsychiatric symptoms (Aarsland et al., 2007; Bronnick, Aarsland, & Larsen, 2005). Major depression, anxiety, emotionalism, apathy, and psychosis

with hallucinations and delusions are all prevalent in PDD (Emre et al., 2007; Marsh, 2000; Poewe et al., 2008). Neuropsychiatric symptoms have been identified as one of the precipitating factors for nursing home placement, as it is often too difficult and upsetting for family members to adequately care for such unpredictable individuals at home (Aarsland et al., 2010). The relationship between neuropsychiatric symptoms and progression to PDD will be further discussed in Chapter 6.

2.4. Management and treatment of PD

PD is difficult to manage because of its extremely variable presentation and progressive nature. Consequently, patient management is not standardised but tailored to individual patients and their needs (Guttman, Kish, & Furukawa, 2003). There is no cure and symptoms have to be managed as they occur, so as to provide the individual with the best possible quality of life. Treatment is thus symptomatic and varies between patients, depending on their disease progression and its interference with their daily life. It is best managed in a multidisciplinary setting, where all aspects of the disorder can be addressed together, including both motor and non-motor complications (Massano & Bhatia, 2012). Management is aimed at maximising an individual's quality of life so as to function as normally as possible, but at the same time minimising side-effects from treatment (Guttman et al., 2003; Massano & Bhatia, 2012). There are a variety of medications – including levodopa and dopamine agonists available for managing the motor symptoms, as well as physiotherapy and, in appropriate cases, surgical therapies such as deep brain stimulation (Fox et al., 2011). Clinicians must continually re-evaluate patients to assess whether the treatment goals are being met and to monitor side-effects. Changes are therefore made when needed to enable the patient to function as normally as possible (Guttman et al., 2003). Treatment-related events include wearing-off, dyskinesia, on-off fluctuations and psychiatric manifestations. Levodopa

is still the most effective medication for controlling motor symptoms of PD and these positive effects on movement have been proven to last years (Schapira, Emre, Jenner, & Poewe, 2009). Dopaminergic treatments (levodopa and dopamine agonists) are useful for treating some non-motor symptoms of PD, but in specific cases can exacerbate other symptoms, such as cognitive impairment, excessive daytime sleepiness, as well as precipitating impulse control disorders (Antonini, Tolosa, Mizuno, Yamamoto, & Poewe, 2009). Dementia in PD is frequently treated with cholinesterase inhibitors (Emre et al., 2010; Truong, Bhidayasiri, & Wolters, 2008), such as donepezil or rivastigmine (both are funded medications in New Zealand) or memantine which is unavailable in New Zealand, as cholinergic deficits are thought to be more pronounced in PDD than in Alzheimer's disease (Emre et al., 2004; Leroi et al., 2004). However mild cognitive impairment prior to dementia in PD is usually not treated (Emre, Ford, Bilgic, & Uc, 2014).

2.5. Summary

PD is a complex, multisystem neurodegenerative disorder that over time affects nearly every brain region. Symptoms experienced can be both motor and non-motor, which together can have a crippling effect on a patient's quality of life. There is no cure, so treatments are symptomatic and need to be continually re-assessed due to the evolving nature of PD. Psychiatric symptoms such as anxiety, hallucinations, depression and especially cognitive decline are common. Dementia (PDD) ultimately occurs in nearly 90% of patients and is a source of considerable burden to patients, families and the health system. It is therefore pertinent to have early indicators of imminent progression to PDD, particularly if/when a preventative therapy because available. In this thesis, I will (1) validate whether the several allowable variation in the PD-MCI Level II criteria permitted by the MDS-TF have the ability to capture patients at high risk of developing dementia (PDD) within a four-year follow-up

period, (2) determine whether a reduced neuropsychological test battery, but one which still meets Level II PD-MCI criteria, can be effective for identifying patients who have a high risk of developing PDD and (3) examine the relationship between neuropsychiatric symptoms and progression to PDD. The overall aim is to provide markers of early cognitive decline which can be applied not only in the selection of enriched patient samples for future intervention studies developed in the future but also in the clinic.

2.6. Study aims and hypotheses

This thesis looks to validate the MDS-TF PD-MCI criteria in terms of their ability to capture patients at high risk of dementia, by applying different variants of the accepted PD-MCI criteria to a four-year longitudinal PD cohort who live in the Canterbury region of New Zealand. It is expected that when different cut-off thresholds (SD) are applied to a cohort of patients each specific PD-MCI criterion will capture a different proportion of patients. Criterion's which require more stringent impairment cut-off (i.e. 2SD) will capture fewer patients where as more lenient impairment cut-off scores (i.e. 1SD) will capture the majority of patients (Figure 2-6). When considering the PD-MCI criteria in terms of their ability to identify patient's at-risk of developing PDD within the next four-years, it is a balance of trading sensitivity of the specific criterion (i.e. ensuring patients who develop PDD are classified as PD-MCI) for sensitivity to progression to PDD (i.e. minimising the number of false positives). Furthermore, additional variance will occur when the location of the two required impairments for PD-MCI classification are restricted to only occur with a cognitive domain or across two or more cognitive domains.

The Thesis chapters will assess:

1. The influence of different permitted impairment cut-off scores on relative rates of dementia in patients classified as PD-MCI at each cut-off level (i.e. the two impaired scores falling at -1SD, -1.5SD or -2SD below normative data). We hypothesised that the risk of PDD will differ across the three impairment level cut-off scores in PD-MCI (-1SD, -1.5SD and -2 SD) permitted by the MDS-TF recommendations within a defined four-year follow-up period (*Chapter 3*).

2. Whether there is a difference in relative risk of PDD in PD-MCI patients who have their impairments falling in a single cognitive domain or across multiple cognitive domains (but never in the same domain). We hypothesised that when the two impaired test scores occur <u>within</u> a single cognitive domain there would be a higher risk of PDD in this PD-MCI group compared to the PD-MCI group defined by two impaired test scores which are instead spread <u>across</u> different cognitive domains (but never occur within the same domain; *Chapter 3*).

3. Whether the neuropsychological test battery can be reduced to 10 neuropsychological tests and determine if this abbreviated test battery is still able to identify patients at a high risk of developing PDD. We hypotheses that when a reduced 10 neuropsychological test battery consisting of tests sensitive to progression to PDD, patients classified as PD-MCI will be at-risk of developing PDD four-years later. We expect that a relaxed PD-MCI where impairments are not restricted to occur only within or across cognitive domains could now be employed when a 10 neuropsychological test battery is used (Chapter 4+5).

4. The relationship the relationship between neuropsychiatric symptoms and future progression to PDD. We hypotheses that some neuropsychiatric symptoms, particularly hallucinations and depression, will have a strong relationship to progression to PDD,

while others will not. We also anticipate that when compared to know predictors of future

PDD, neuropsychiatric symptoms will not be as informative (*Chapter 6*).

All aspects of this study will look at progression to PDD over a four-year period, which is a

clinically relative period of time, when considering utility of PD-MCI criteria in future

clinical intervention or therapy trials (Eberling et al., 2014).

The studies in this thesis utilise a sub-sample of patients from the New Zealand Brain

Research Institute's Parkinson's disease cohort. In Chapters 3 and 4 a sub-sample of 121 non-

dementing PD patients are analysed. In Chapter 5, the same sub-sample of 121PD patients are

assessed plus an additional 17 PD patients, who have now been followed-up for four-years. In

Chapter 6, 77 PD-N, 46 PD-MCI and 35 PDD patients were included in this study, with the

majority of the non-demented PD patients having been included in the analysis of the

previous 3 Chapters.

Chapter 3: Cognitive criteria and progression to PDD

3.1. Background

In Parkinson's disease (PD), cognitive impairment and other non-motor symptoms have a greater impact on quality of life than do motor symptoms and are associated with early mortality (Lawson et al., 2014; Oosterveld et al., 2015). Some 60% of patients may develop dementia (PDD) within 12 years of their motor symptoms and over 80% ultimately reach PDD, although an individual's time course to dementia is highly variable (Aarsland et al., 2003; Buter et al., 2008; Hely et al., 2008). Risk factors include older age and severity of motor symptoms, but recognition of early cognitive impairment is particularly important (Aarsland & Kurz, 2010; Palavra et al., 2013; Troster, 2011; Yarnall et al., 2013). Recently, studies have examined the progression to PDD from mild cognitive impairment (PD-MCI). While specific findings are variable, more PD-MCI patients than non-PD-MCI patients progress to PDD (19-62% vs 0-20%, respectively) when followed two to five years after showing PD-MCI (Broeders, de Bie, et al., 2013; Janvin et al., 2006; Pedersen et al., 2013). In a cohort that was followed for 16 years, 91% of PD-MCI patients reached PDD, over four times that of the non-PD-MCI patients (Hobson & Meara, 2015). It is difficult to compare these studies however, as each used different diagnostic criteria to define PD-MCI.

The heterogeneous methods to ascertain PD-MCI has led to substantial variation in the percentage of patients classified as PD-MCI (Aarsland et al., 2010; Dalrymple-Alford et al., 2011; Goldman et al., 2013; Janvin et al., 2006; Liepelt-Scarfone et al., 2011). To address this situation, standardized diagnostic criteria were proposed by the Movement Disorder Society PD-MCI Task Force (MDS-TF) (Litvan et al., 2012). The Task Force's Level I criteria permit the use of global cognition scales or an abbreviated neuropsychological

assessment that includes fewer than two tests in each of five cognitive domains (attention/working memory; executive function; episodic memory; visuoperceptual/visuospatial function; language) or less than five cognitive domains assessed. More specific, comprehensive (Level II) criteria require the use of more than one test in each of the cognitive domains and PD-MCI is confirmed when any two (or more) impaired neuropsychological test scores are present but everyday function is generally preserved. Nonetheless, the Level II recommendations still permit several alternative criteria, for example, cut-offs ranging 1SD-2SD below normative data to define an impaired score (Litvan et al., 2012).

We hypothesized that the risk of progression to PDD differs across three common cut-off variants for PD-MCI (1SD, 1.5SD and 2 SD) permitted by the MDS-TF recommendations. Moreover, the high probability of eventual PDD for all patients means that the validity of PD-MCI criteria should be determined by whether they detect patients at increased risk of PDD within a defined period of time. Here, we specified a four-year window as a suitable period of time because we considered this relevant for the use of PD-MCI in both clinical practice and potential therapeutic interventions (Eberling et al., 2014). There is, however, a second important issue that has also not been addressed: does the distribution of impaired scores across cognitive domains influence the risk of conversion to dementia? On the basis of evidence from the non-PD literature on MCI (Jak et al., 2009; Teng, Tingus, Lu, & Cummings, 2009), we hypothesized that having the minimum of two impaired test scores *within* a single cognitive domain would result in a higher risk of PDD compared to having a minimum of two impaired test scores instead spread *across* different cognitive domains.

3.2. Methods

3.2.1. Participants

A convenience sample of 184 PD patients was recruited from our research institute and movement disorders clinic. Comparison of the rate of progression to PDD in this sample was made by recruiting 54 age-, sex-, and education-similar healthy controls who volunteered in response to community advertisements and did not report subjective cognitive complaints. Figure 3-1 shows recruitment, exclusions, and retention of participants (Bossuyt et al., 2003), which resulted in a final followed-up sample of 121 PD patients, none of whom met PDD criteria (Emre et al., 2007) at baseline, and 36 controls. Patients were diagnosed using the UK Parkinson's Society criteria (Hughes et al., 1992) and had motor symptoms present for at least 1 year at study entry (mean symptom duration = 6 years, SD = 4 years) to minimize the inclusion of those with dementia with Lewy bodies. Atypical parkinsonian disorder, other medical conditions (e.g. history of moderate/severe head injury, stroke, early-life learning disability, major psychiatric or medical illness in the previous six months), poor English (precluding testing) were exclusion criteria. Patients were also excluded at baseline if they had Parkinson's disease with dementia (Emre et al., 2007). A PDD diagnosis at any point in the study required the presence of significant impairments (2SD below normative data) in at least two of five cognitive domains, plus evidence of significant impairment in everyday functional activities, not attributed to motor impairments. Everyday function was assessed from interviews with a significant other, based on evidence obtained from the Reisberg IADL-scale, Clinical Dementia Rating and Global Deterioration Scale to attribute non-dementia status or PDD (Morris, 1993; Reisberg et al., 2008). Direct evidence from a significant other was not available, at baseline only, in 39 PD patients. However, we confirmed baseline non-dementia status in these cases from contemporaneous clinical notes

and from detailed patient interview by an experienced examiner, followed by consensus

discussion.
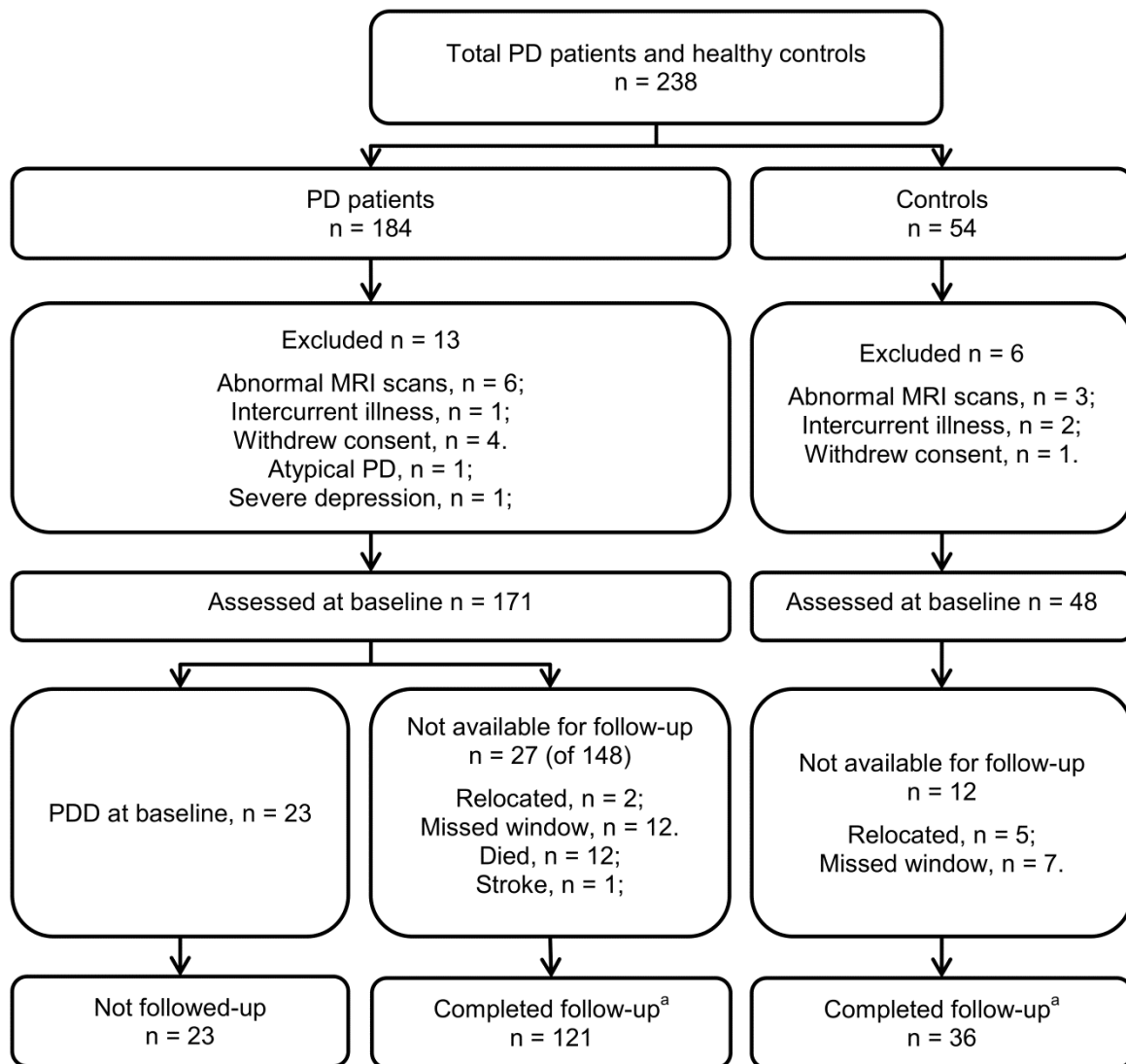
Figure 3-1. *Participant recruitment, exclusions and total followed over 4 years.*
PD = Parkinson's disease; PDD = Parkinson's disease with dementia.
[a] Assessments were conducted at baseline and every one to two years; patients with dementia
were not followed further.

Comprehensive neuropsychological assessments fulfilling the MDS-TF Level II

requirements for PD-MCI (for tests see below) (Litvan et al., 2012) were undertaken at study

entry and subsequently every one to two years, for up to 3.5–4.5 years later (mean = 46

months, SD = 8 months). Progression to PDD before the end of the 4.5-year period was treated as an a priori end-point, with no further follow-up. All participants took their usual medications on the day of testing to allow optimal performance during the morning test sessions. The study was approved by a local ethics committee of the New Zealand Ministry of Health, with informed consent provided by all participants.

3.2.2. Neuropsychological assessment

Five cognitive domains were examined, with tests conducted over two sessions (Dalrymple-Alford et al., 2011; Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006). Executive function was assessed using Stroop interference, letter fluency, category fluency and category switching (from the Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001a)), and action fluency and Trails B. Attention, working memory and processing speed was evaluated using digits forwards/backwards, digit ordering, map search task (from the Test of Everyday Attention), Stroop color reading, Stroop word reading, and Trails A. Episodic memory was measured with the California Verbal Language Test-II Short Form (CVLT-II SF; acquisition, short and long delays), and the Rey Complex Figure Test (RCF test; short and long delays); impairment in either or both delay components of each episodic memory test counted as one impairment. Visuoperceptual/visuospatial performance was determined using judgment of line orientation (JLO), fragmented letters test, the picture completion test and the RCF-Copy. Language was assessed using the Boston Naming Test, Dementia Rating Scale-2 (DRS-2) similarities sub-test, and the language component of the Alzheimer's Dementia Assessment Cognitive Scale (ADAS-Cog; object and finger naming, commands, comprehension, spoken language and word finding difficulties). Scoring of the neuropsychological tests was conducted using age- and education-adjusted normative data. Participants also completed the Montreal Cognitive Assessment (MoCA).

3.2.3. **Application of PD-MCI criteria**

There were two phases to the analysis. In Part One, we applied three commonly used and

accepted PD-MCI cut-off criteria to examine their association with risk of progression to

PDD, irrespective of whether the minimum of two impairments occurred within a cognitive

domain or across different cognitive domains. In Part Two, we examined the additional issue

of the distribution of impairments across cognitive domains, focusing on the optimal cut-off

criterion resulting from the analysis in Part One. That is, we again determined risk of

progression with a minimum requirement of two impairments, but first with both

impairments within a single cognitive domain and then when there was only one impairment

in each of two or more cognitive domains.

3.2.3.1. Part One: Application of PD-MCI criteria

In order to test the unique contribution of each PD-MCI criterion, we generated three

mutually exclusive groups of PD-MCI patients using a step-wise process. The three primary

SD cut-off scores were applied sequentially to signify impairment on any test measure

(Figure 3-2A). First, we identified patients who had two scores that were 2SD or more below

normative data, then we identified from the remainder those with two scores that were 1.5SD

but better than 2SD below normative data, and lastly those with two scores that were 1SD but

better than 1.5SD below normative data. Thus, each PD-MCI group in Part One consisted of

an independent and discrete sample of patients for analysis purposes. In clinical practice, any

patient who met a 2SD criterion would also by definition meet the 1.5SD or 1SD criterion

(and similarly those meeting 1.5SD also exceed the 1SD criterion). It is important for the

purpose of comparing the effectiveness of the cut-offs, however, that groups of patients

classified under each criterion be mutually exclusive. For example, the effectiveness of the

1.5SD criterion cannot be meaningfully compared to the 2SD criterion if both capture overlapping groups of subjects. Thus, once a patient was identified as PD-MCI (for example under the 2SD criterion), they were excluded from the next step in the analysis so that effectiveness of a criterion was not influenced by the more severely impaired patients who would also be captured by a more stringent criterion. That is, we began by applying the 2SD criterion at baseline to all of the 121 non-dementing patients. The risk of progression to PDD was evaluated in this PD-MCI group relative to the remainder of the PD patients. This 2SD PD-MCI group was then excluded and, using only the remaining patients, the risk of PDD in patients who met the 1.5SD PD-MCI cut-off relative to those not meeting the 1.5SD criterion was determined. This 1.5SD PD-MCI group was in turn also excluded and the remaining sample reassessed. This final sample was used to assess the risk of PDD in patients now meeting only the 1SD cut-off relative to the risk in the remaining patients who did not meet any of the PD-MCI criteria at baseline. Following the MDS-TF recommendations, the minimum of two impairments at the cut-off required for any given criterion could appear anywhere within, or across, the five cognitive domains assessed.

3.2.3.2. Part Two: Application of PD-MCI criteria

The second part of the analysis was different in that it examined the influence of whether the minimum of two impaired scores occurred either within one cognitive domain or across two different cognitive domains. Impairments beyond two deficits did not change these allocations. This approach was used only for the optimal cut-off score (1.5SD), as determined by Part One (Figure 3-2). Here, we once more began with the entire followed-up sample and again followed a stepwise approach so that each PD-MCI group consisted of a discrete (independent) sample of patients. We first identified all patients with a minimum of two impairments at 1.5SD within a single cognitive domain at baseline (that is, all patients from

the entire sample of 121 patients who had two or more scores at or worse than the 1.5SD cut-off score) and determined the risk of dementia within this group of PD-MCI patients relative to those who did not meet this criterion. Those meeting that criterion were then discarded. The remaining patients were then assessed by comparing risk in those patients who had the minimum of two impairments at the cut-off score of 1.5SD but the two impairments never occurred within a single cognitive domain (i.e. at least two cognitive domains each had a maximum of one impaired score) relative to the remaining patients who did not meet either of these two PD-MCI criteria. As any patient with multiple impairments within a single cognitive domain had been excluded in the previous stage, by definition this latter PD-MCI group all had only one impaired score within any one cognitive domain. In clinical practice, this second more relaxed 1.5SD criterion would also capture those with multiple impairments within a cognitive domain, but for analysis purposes we kept the samples independent.

Part One

Baseline (n = 121)

Two impairments at 2SD?

No → n = 75 remaining

Two impairments at 1.5SD?

Yes → PD-MCI: 2SD group (n = 46)

No → n = 65 remaining

Two impairments at 1SD?

Yes → PD-MCI: 1.5SD group (n = 10)

No → n = 25 remaining

Not meeting any PD-MCI criteria

Yes → PD-MCI: 1SD Group (n = 40)

Part Two

Baseline (n = 121)

Two impairments at 1.5SD within a single domain?

No → n = 84 remaining

Impairments at 1.5SD across multiple domains?

Yes → PD-MCI: 2 impairments in 1 domain (n = 37)

No → n = 65 remaining

Not meeting any PD-MCI criteria

Yes → PD-MCI: 1 impairment in each of 2 domains (n = 19)
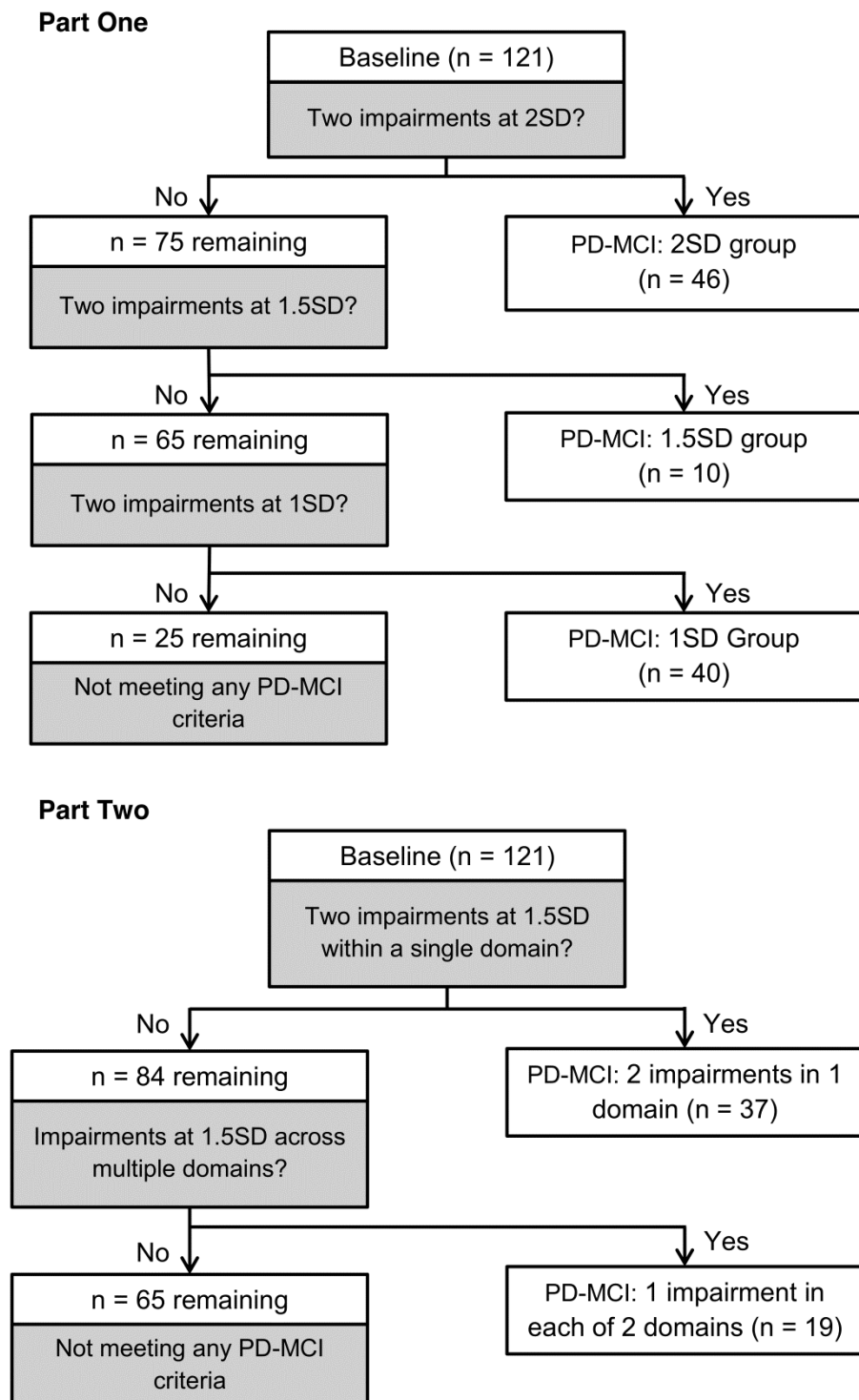
Figure 3-2. *Allocation of non-dementing PD patients at baseline to different PD-MCI groups in Part One (using 2SD, 1.5SD and 1SD cut-off scores, respectively) and Part Two (alternative PD-MCI criteria for 1.5SD).*
PD-MCI = Parkinson's disease patients with mild cognitive impairment.

3.2.4. Statistical analysis

Confidence intervals for relative risk of PDD in each comparison were determined using bootstrap methods (Efron, 1979). In this procedure, statistical samples were generated by resampling with replacement from the parent sample under study and a relative risk calculated. This resampling was repeated 5000 times, resulting in an empirical distribution for the relative risk for the comparison in question. Permutation tests were used to derive exact p-values. The code and data used in this analysis is available upon request.

3.3. Results

3.3.1. Participants

The mean patient age at baseline was 66 years (SD = 8 years). Table 3-1 summarizes the demographics and neuropsychological data of the patients and healthy control group at baseline. There was a 21% conversion rate to dementia for the PD patients in the four-year period (14 men and 11 women; 25 out of 121 patients). As expected, patients who later converted to PDD were older, had longer symptom duration, and worse motor symptoms, neuropsychological and functional measures at baseline than patients who did not convert to PDD. At baseline, 26 out of the 121 non-demented patients experienced hallucinations. A greater proportion of converters (13 vs. 12; 52%) relative to non-converters (13 vs. 83; 14%) experienced hallucinations at baseline (chi-square = 17.39, $p < 0.0001$; Table 3-1). Fifteen of the 25 patients (60%) who converted to PDD experienced hallucinations at the time of conversion, whereas only 24 of the 96 non-converters experienced hallucination at their last assessment (chi-square = 11.12, $p < 0.001$). Relatively few patients (9 out of 121) received medication that may affect their cognitive performance during the study. At baseline, only one patient who did not convert to PDD at follow-up was on antipsychotic medication and

one that did convert to PDD was receiving rivastigmine. Neither of these patients remained on these medications at their follow-up assessments. At follow-up, seven patients were on medication that could affect their cognition. Six of these seven patients were on antipsychotic medication (three of whom had progressed to PDD), and three were receiving donepezil (one of whom had progressed to PDD).

Table 3-1. Demographics and neuropsychological data at study entry [mean (SD)]

	Controls	Non-converters to PDD	Converted to PDD
Sample size	36	96	25
Sex, M:F	25:11	63:33	14:11
Age	67.5 (8.6)	64.3 (8.2)	70.2 (5.7)[c]
Education (y)	13.7 (2.7)	13.1 (2.7)	12.5 (2.8)
Premorbid IQ (WTAR)	112 (10.0)	111 (8.0)	109 (8.2)
CDR	0.0 (0.0)	0.2 (0.2)[b]	0.5 (0.2)[b,c]
Reisberg IADL	0.2 (0.2)	0.4 (0.4)	1.1 (0.6)[b,c]
DRS-2 (AESS)	12.8 (2.1)	11.7 (2.0)	10.7 (2.1)[b]
ADAS-Cog	5.1 (2.1)	6.6 (2.9)	10.0 (2.5)[b]
Symptom duration (y)		5.3 (4.0)	7.8 (5.0)[c]
Hoehn and Yahr stage		1.9 (0.6)	2.5 (0.7)[c]
UPDRS (Motor)		31.4 (16.2)	40.7 (15.4)[c]
MoCA	26.9 (2.0)	26.1 (2.5)	23.6 (2.5)[b,c]
Global Z score	0.64 (0.42)	0.06 (0.53)[b]	-0.81 (0.47)[b,c]
1. Executive function	0.73 (0.56)	0.12 (0.71)[b]	-0.81 (0.64)[b,c]
2. Attention, working memory & processing speed	0.37 (0.55)	-0.06 (0.55)[b]	-0.77 (0.51)[b,c]
3. Episodic memory	0.95 (0.81)	0.06 (0.88)[b]	-1.05 (0.69)[b,c]
4. Visuoperceptual/ visuospatial	0.52 (0.51)	0.11 (0.60)[b]	-0.62 (0.67)[b,c]
5. Language[a]	-0.07 (0.44)	0.12 (0.45)	-0.36 (0.50)[c]

Abbreviations: PDD = Patients who met Level II criteria for Parkinson disease with dementia; 1-5 = mean Z scores in each cognitive domain; Global Z score = mean derived from domains 1-4; ADAS-Cog = Alzheimer's Dementia Assessment Scale-Cognitive; CDR = Clinical Dementia Rating; DRS-2 (AESS) = Dementia Rating Scale-2 (Age and Education Scaled Score); IADL = Instrumental Activities of Daily Living; MoCA = Montreal Cognitive Assessment; UPDRS (Motor) = Unified Parkinson's Disease Rating Scale (Motor Component); WTAR = Wechsler Test of Adult Reading for premorbid IQ.
[a] eight controls and 37 PD patients did not have language measures at baseline.
[b] significantly different to controls, Tukey post hoc tests, $p<0.05$;
[c] significantly different from non-converters, Tukey post hoc tests, $p<0.05$.

3.3.2. Part One: Comparison of progression to PDD from PD-MCI defined by three cut-offs

3.3.2.1. Risk of PDD

The first stage of analysis showed that the 46 patients classified as PD-MCI using the 2SD cut-off had a significantly higher risk of progression to PDD than the remaining 75 PD patients (Relative Risk, RR = 4.2, CI 2.2-10.1, $p < 0.0001$; Table 3-2). A similar finding was evident in the 10 patients missed by the 2SD classification but defined as PD-MCI using the 1.5SD cut-off (RR = 4.9, CI 1.4-15.1, $p = 0.005$). By contrast, the additional group of 40 patients classified as PD-MCI using the 1SD cut-off criterion did not show a significantly greater risk of PDD progression than the remaining 25 patients not classified as PD-MCI under any of these three initial criteria (RR = 1.9, CI 0.3-4.3, $p = 0.13$).

3.3.2.2. Reversions from PD-MCI

Under each criterion, there were individuals who at their latest follow-up were classified as reverting to a non-PD-MCI status (i.e. to relatively "normal" cognition under that criterion). For the 2SD cut-off, 20% (9/46) of patients had reverted to a non-PD-MCI status at their last assessment (i.e. no longer having two impairments below 2SD). Of these nine reverters, seven had scores that also remained below a 1.5SD cut-off, but no longer met the 2SD cut-off. There was just one reversion in the extra 10 patients identified as PD-MCI under the 1.5SD criterion (i.e. in the group whose baseline scores reached the 1.5SD cut-off but not the 2SD cut-off). The reversion rate in the group of patients who met only the 1SD criterion was 20% (8/40).

Table 3-2. Conversion to PDD and reversion to non-PD-MCI status

Criteria	Three primary PD-MCI criteria			Two alternative 1.5SD PD-MCI criteria	
	2SD	1.5SD	1SD	2 in 1 domain	1 in each of 2 domains
PD-MCI (n/remaining sample)	46/121	10/75[a]	40/65[b]	37/121[c]	19/84[d]
Relative Risk (95% CI)[e]	4.2 (2.2-10.1)	4.9 (1.4-15.1)[a]	1.9 (0.3-4.3)[b]	7.2 (3.4-16.6)[c]	1.7 (0.5-7.4)[d]
PDD conversions from PD-MCI group	18/46 (39%)	3/10 (30%)[a]	3/40 (8%)[b]	19/37 (51%)[c]	2/19 (11%)[d]
Proportion of all PDD conversions	18/25 (72%)	3/25 (12%)[a]	3/25 (12%)[b]	19/25 (76%)[c]	2/25 (8%)[d]
Sex of PDD converters (M:F)	10:8	2:1[a]	1:2[b]	10:9[c]	2:0[d]
Reverted to non-PD-MCI[f]	9/46 (20%)	1/10 (10%)[a]	8/40 (20%)[b]	1/37 (3%)[c]	3/19 (16%)[d]

Abbreviations: 95% CI = Confidence interval of relative risk; PDD = Parkinson disease patients who met Level II criteria for Parkinson disease with dementia at follow-up; PD-MCI = Parkinson disease patients with mild cognitive impairment at baseline; non-PD-MCI = patients not meeting the PD-MCI criterion.
[a] Additional PD-MCI patients captured by the 1.5SD cut-off score, excluding the 46 who had already met the more stringent 2SD cut-off.
[b] Additional PD-MCI patients captured by the 1SD cut-off score, excluding the 56 who had already met the more stringent 2SD and 1.5SD cut-offs.
[c] PD-MCI patients, within the whole sample of 121 at baseline, who met the criterion of having two impairments at 1.5SD within a single cognitive domain.
[d] Additional PD-MCI patients captured by this cut-off score excluding those who had already met the two impairments in one cognitive domain criterion.
[e] Incidence rate in PD-MCI group divided by the incidence rate in the non-PD-MCI group, which is statistically significant when the lower bound of the CI is greater than 1.
[f] The number of PD patients reverting back to normal cognition rather than remaining PD-MCI or progressing to PDD, according to the PD-MCI cut-off criterion being examined.

3.3.2.3. Healthy control group Unlike the PD sample, none of the matched control group converted to dementia during the follow-up period. Only one control participant met the 2SD criterion at baseline (showing one impairment within each of two cognitive domains), two met the 1.5SD criterion (each showing one impairment within each of two cognitive domains) and 12 met the 1SD criterion for MCI. By the end of the four-year follow-up, however, the first control was no longer classified as MCI under the 2SD criterion (having one impairment within each of two cognitive domains, but now at 1.5SD) while the two who had met the 1.5SD criterion and six of those who had met the 1SD criterion no longer met any MCI criterion.

3.3.3. Part Two: Influence of the distribution of impaired scores within or across cognitive domains

 The analysis in Part One led us to select the 1.5SD cut-off as optimal for the second phase of analysis. The reason for this selection was that (1) the 1SD criterion failed to identify an increased risk of progression to PDD, (2) a similar RR of conversion to PDD was found for both the 2SD and 1.5SD criteria, (3) the reversion rate was lower in the 1.5SD criterion, and (4) combining the 2SD and 1.5 SD groups captured a greater percent of converters to PDD. We therefore re-examined the entire sample of followed patients to look at the influence of the distribution of impaired scores at baseline (that is, using all patients meeting a 1.5SD criterion, including those meeting a 2SD cut-off at baseline). The focus here was first to determine the relative risk of PDD when two (or more) impairments at 1.5SD were present within a single cognitive domain. We then examined risk when only a single impairment at 1.5SD was evident across at least two cognitive domains (that is, never two impairments within any one cognitive domain, but rather just one impairment at 1.5SD in each of two or more cognitive domains). Of course, all of the PD-MCI patients classified using the 2SD

criterion by definition also met one of these 1.5SD criteria.

3.3.3.1. PD-MCI at 1.5SD with two impairments within a single cognitive domain

The group of 37 patients classified as PD-MCI at baseline using the criterion of two impairments at 1.5SD in one cognitive domain (of whom 51% converted to PDD), had a high relative risk of progression to PDD compared to 84 patients (of whom 7% converted to PDD) who did not meet this criterion (RR = 7.2, CI 3.4-16.6, $p < 0.0001$; Table 3-2; 76% of all conversions to PDD). This risk was not influenced solely by the subgroup of patients (n = 26; 54% converted to PDD) who showed two impairments at 2SD within a single cognitive domain (RR = 4.7, CI 2.4-8.7, $p < 0.0001$), because the relative risk of the remaining subgroup of patients (n = 11; 45% converted to PDD) with two impairments at 1.5SD (but not 2SD) in one cognitive domain was also high (RR = 6.4, CI 2.2-15.6, $p = 0.0001$).

3.3.3.2. PD-MCI at 1.5SD with a maximum of one impairment in each of two cognitive domains

The additional group of 19 patients classified as PD-MCI using the criterion of only one impairment at 1.5SD in each of two (or more) cognitive domains (of whom 11% converted to PDD) did not show a significantly increased risk of progressing to PDD compared to the remainder of PD patients (RR = 1.7, CI 0.5-7.4, $p = 0.13$).

3.3.3.3. Reversions from PD-MCI at 1.5SD

The proportion of patients reverting to a non-PD-MCI status was only 3% with the 1.5SD criterion of two impairments in a single-domain, but was 16% with the 1.5SD criterion of one impairment in two cognitive domains. Combined across these two 1.5SD criteria, the

reversion rate was 5% (that is, including scores below either the 2SD or 1.5SD cut-off; 3 of 56 patients).

3.3.3.4. Progression over time and pattern of cognitive domain impairments

Support for the conclusion that two impairments within a single cognitive domain was effective in identifying PD-MCI patients at risk of PDD over a four-year period was found when the progression of cognitive status was assessed in three groups of patients that were characterized differently at baseline using 1.5SD criteria. More than half of the patients who did not meet either of the 1.5SD criteria at baseline remained non-PD-MCI over the four-year period (Figure 3-3A.). It is pertinent that patients who met the PD-MCI criterion (at baseline) of a maximum of one impairment in each of two cognitive domains tended to progress to meet the alternative PD-MCI criterion of two impairments in one cognitive domain, rather than to PDD (Figure 3-3B.). In contrast those who met the PD-MCI criterion (at baseline) of two impairments in one cognitive domain tended either to remain stable at this criterion or progress to PDD (Figure 3-3C.).

A. Non-PD-MCI.

B. PD-MCI criterion, one impairment at 1.5SD in each of two domains.

C. PD-MCI criterion, two impairments at 1.5SD in one domain.
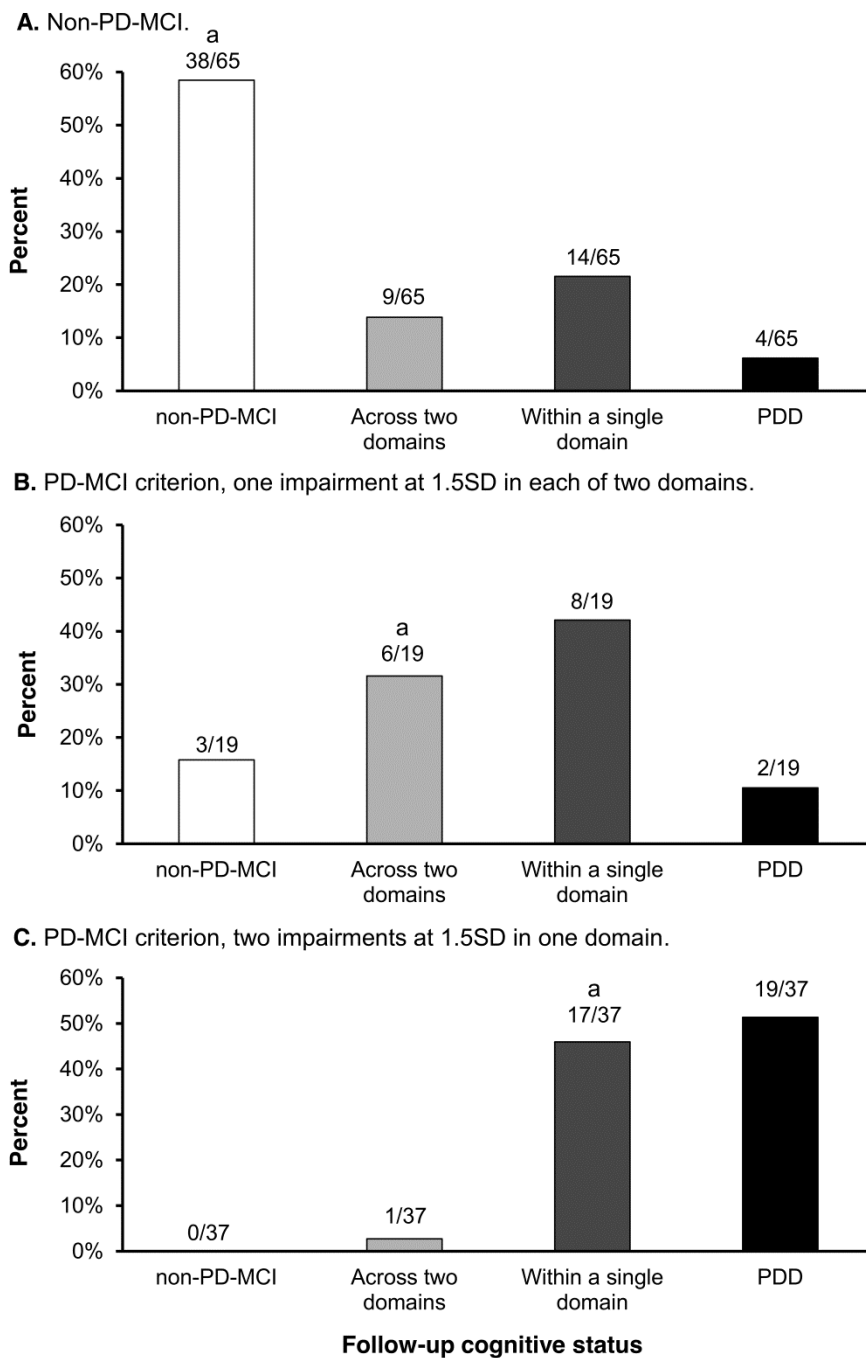
Figure 3-3. *Follow-up cognitive status in the non-PD-MCI group at baseline (A) and the PD-MCI subgroups meeting the criterion of one impairment at 1.5SD in each of two cognitive domains (B) and the criterion of two impairments at 1.5SD in one cognitive domain (C).*

Figure 3-4 shows the pattern of domain impairments at baseline in the PD-MCI group

who had at least two impairments at 1.5SD within at least one of the five cognitive domains.

Note that multiple domain impairments therefore meant that they had two impairments in each domain of two or more cognitive domains. Most of these PD-MCI patients (25 of 37) had multiple cognitive domain impairments (thus defined). Sixty-four percent of the patients with multiple cognitive domain impairments converted to PDD (16 of 19) whereas only 25% of those with single cognitive domain impairments (3 of 12) converted to PDD. All PD-MCI patients who had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not, had a mixture of other cognitive domains involved (episodic memory and executive, n = 5; episodic memory and visuospatial, n = 3; episodic memory, executive and attention, n= 4; episodic memory, executive and visuospatial, n = 1; episodic memory, executive, attention and visuospatial, n = 1. Multiple cognitive domain impairments that did not include episodic memory were: executive and attention, n = 5; executive and visuospatial, n = 3; and attention and visuospatial, n = 3. No PD-MCI patients had single cognitive domain impairments in visuospatial function or language. There was no obvious pattern to the cognitive domains impaired and conversion to PDD.
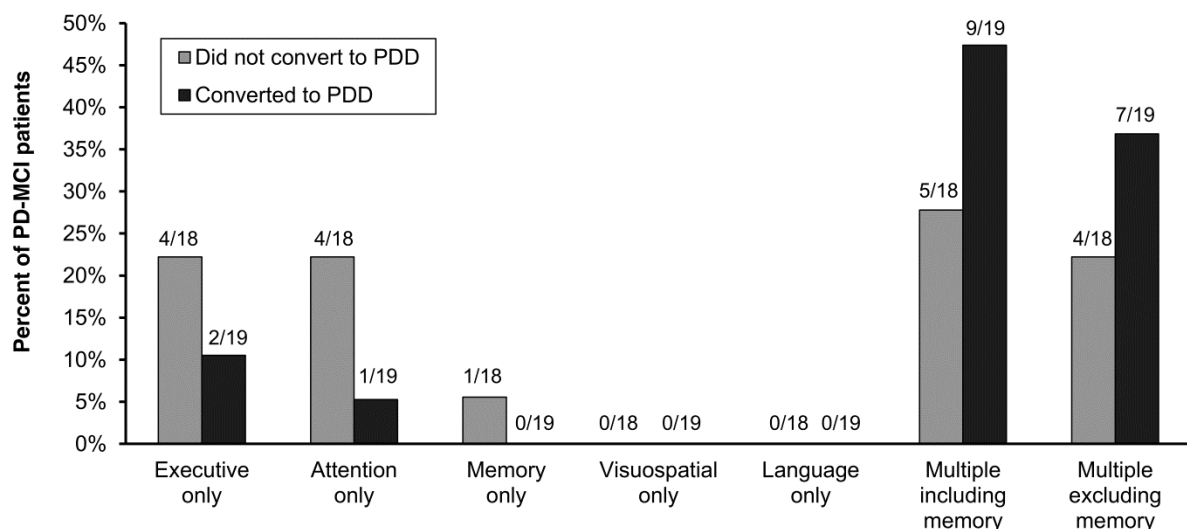
Figure 3-4. *Pattern of domain impairments at baseline in PD patients meeting the criterion of at least two impairments at 1.5SD in one* cognitive *domain.*
PDD = Patients who met Level II criteria for Parkinson's disease with dementia; PD-MCI = Parkinson's disease patients with mild cognitive impairment.

3.4. Discussion

The diagnosis of PD-MCI is important in facilitating patient management, prognosis and especially opportunities for novel therapeutic interventions (Eberling et al., 2014; Litvan et al., 2012; Palavra et al., 2013; Troster, 2011; Yarnall et al., 2013). The explicit intent of a PD-MCI diagnosis is to identify patients who are at risk of PDD, and this can only be determined by longitudinal follow-up of patients. Dementia is an outcome facing most PD patients as the disease unfolds and multiple brain networks become increasingly disrupted (Beach et al., 2009; Jellinger, 2012; Melzer et al., 2011; Melzer et al., 2013). The validity of a PD-MCI diagnosis is, therefore, most relevant in the context of the window of time when risk is evaluated. Our longitudinal study evaluated this risk over a four-year period, a pertinent medium-term time-frame from the patient and their carer's perspective.

In a typically-aged group of patients (42 to 80 years, mean of 66 years; mean disease duration of 6 years at the start of the study), we found that the 1SD cut-off did not identify patients who were at higher risk of PDD over the next four years than patients who did not meet any PD-MCI criterion at baseline. By contrast, the criterion of impairments at 1.5SD below normative data, when at least two such deficits occurred within one cognitive domain, has high validity for PDD risk in a four-year period. This criterion classified a group with a 51% progression rate to PDD, the highest proportion of conversions for the criteria we examined. The literature on MCI in non-PD populations has established that poor performance on multiple tests within a cognitive domain is likely to identify worsening cognition over time (Jak et al., 2009; Teng et al., 2009). The alternative 1.5SD criterion, which did not require two impairments within a single cognitive domain, was similar to the 1SD criterion in that it did not identify patients with a significantly increased risk of PDD progression over a four-year period. Indeed, this alternative 1.5SD criterion instead may

identify patients who were at an earlier stage of cognitive decline because many of these patients were more likely to convert to having two impairments within a single cognitive domain than to PDD. The option of 2SD as a cut-off criterion had good concordance with a consensus clinical diagnosis of PD-MCI when neuropsychological data were available for assessment (Goldman et al., 2013). However, the 2SD criterion applied to our sample produced a lower relative risk estimate because it missed the additional conversions to PDD captured by the 1.5SD cut-off, especially when two impairments occurred within one cognitive domain. The 2SD criterion also produced an apparent higher rate of reversion to a non-PD-MCI status at follow-up than did the specific 1.5SD criterion requiring two impaired scores within a single cognitive domain (20% vs. 3% respectively). A recent proposal suggested the use of 2SD cut-offs for PD-MCI criteria (Goldman et al., 2013; Goldman et al., 2015), but that study used a cross-sectional design and thus did not assess progression over time to PDD. The longitudinal design of the present study suggests instead that a 1.5SD cut-off is sufficient to maximize risk of progression to PDD.

PD-MCI criteria using different cut-off values resulted in a percentage of patients classified as impaired at a given point in time that can vary from as high as 92% to as low as 10% (Aarsland et al., 2010; Dalrymple-Alford et al., 2011; Goldman et al., 2013; Liepelt-Scarfone et al., 2011). The current consensus based on non-standardized PD-MCI criteria is that 25-30% of PD patients at any given time will demonstrate PD-MCI when the most common cut-off of 1.5SD is administered, but even then significant variation is found across centers (Aarsland et al., 2010). Similarly, within our study 46% of patients at baseline were PD-MCI when a 1.5SD cut-off with only a single impairment in each of two cognitive domains was applied across the entire sample, but 31% were PD-MCI when the minimum of two impairments within a single cognitive domain was met. The proportions differed again if

the entire sample was evaluated using 2SD or 1SD cut-offs (38% and 79%, respectively). Hence, different permissible MDS-TF cut-offs (1SD, 1.5SD or 2SD) contribute to considerable variation in the proportion of PD-MCI identified within a given sample of patients. More importantly, our four-year study illustrates that different cut-off variants identify groups of patients with markedly different relative risks of progression to PDD, and different rates of reversion to non-PD-MCI.

Several factors could influence conversion or not to PDD within any group of patients. The small proportion of PD patients who do not to progress to PDD until very old age may be protected by genetics and/or lifestyle factors that confer resilience to brain pathology (Hindle et al., 2013; Sebastiani et al., 2013). Some patients may be misdiagnosed as PD-MCI because either their depleted dopaminergic function or their treatment regimens may induce various fronto-striatal dysfunctions that cause cognitive impairment that does not necessarily portend progression to PDD (Barker & Williams-Gray, 2014). There are also contributions to risk from general factors such as age, presence of REM sleep disorder, and additional neuropathology (Aarsland & Kurz, 2010; Anang et al., 2014; Irwin, Lee, & Trojanowski, 2013; Jellinger, 2012; Yarnall et al., 2013). In some patients, the extent of decline from premorbid level of intellectual function may be more relevant than rigid cut-offs (Marras et al., 2013). Hence, consideration of age or other variables may improve the predictive value of the specific criterion suggested by our study. Like other studies of conversion to PDD from PD-MCI, we found similar rates of conversion to PDD between the sexes when the 1.5SD criterion was used (10 men and 9 women) (Janvin et al., 2006; Pedersen et al., 2013).

The pattern of cognitive domain impairments observed in the patients who met the criterion of two impairments at 1.5SD in a single cognitive domain showed no obvious

association with conversion to PDD, which is consistent with the heterogeneity of failing cognition in PD (Broeders, de Bie, et al., 2013; Jacobs et al., 1995; Janvin et al., 2006; Mahieux et al., 1998; Woods & Troster, 2003). Like other studies, multiple-domain impairments may be more common in PD-MCI (Goldman et al., 2013) and more likely to be associated with conversion to dementia (Broeders, de Bie, et al., 2013). However, the frequency of multiple cognitive domain impairments will vary with the specific PD-MCI criteria that are applied. In some studies, most PD-MCI patients showed multiple impairments, often as high as four cognitive domains impaired, when only a single impairment per cognitive domain was required (Goldman et al., 2013; Marras et al., 2013). The present study had only one patient with 4 impaired cognitive domains, when using two impairments necessary for any cognitive domain to be considered deficient. Multiple deficit scores within a single cognitive domain, however, appear to be optimal to identify conversion to PDD within 4.5 years. Neither the language nor visuospatial domains showed single impairments using our criteria, so it is possible that worsening attention, executive function and memory may reflect the earlier signs of global cognitive decline in PD, similar to that reported by Pedersen et al. (2013).

The strength of the current study is its longitudinal design and the use of Level II assessments for both PD-MCI and PDD diagnoses. It evaluated for the first time the validity of different recommended PD-MCI criteria in relation to PDD progression. The use of a specified medium-term window for progression is highly relevant because the high rate of eventual progression PDD means that virtually all PD-MCI criteria will identify conversion to PDD if the follow-up period is sufficiently long. The four-year window is particularly relevant for patients and their families, as it meets their expectations for clinical management while also allowing for the assessment of potential therapeutic outcomes.

One limitation to our study, like similar studies, that is the sample size was modest (n = 121) and there was potential for bias due to an attrition rate of 18%. Our sample size was twice that of three studies that examined PDD progression over three-five years (n = 51-64) (Broeders, de Bie, et al., 2013; Hobson & Meara, 2015; Janvin et al., 2006), but smaller than one study that followed patients over three years (n = 167; Pedersen et al., 2013). Our attrition rate (18%) was half that of two of these studies (41% and 48%; Broeders, de Bie, et al., 2013; Hobson & Meara, 2015), equivalent to one study (18%; Janvin et al., 2006) and larger than another (8%; (Pedersen et al., 2013). The current data will, however, contribute to an international consortium to enable better statistical precision for determining relative risk of PDD from different cut-off options, and the ability to assess the influence of potential modifiers such as age and education (Geurtsen et al., 2014).

A second limitation is that the identification of PD-MCI may depend on the number of tests we used per cognitive domain, and especially the sensitivity and psychometric qualities of our individual tests. The uneven number of tests per cognitive domain in our study could mean that the attention and executive functioning domains, which each consisted of six tests, may be more likely to detect impairment than, say, the visuospatial domain for which four tests were used. However, Goldman et al. (2015) found that having more than two tests in the attention and/or executive function domains did not increase the probability of detecting an impairment and that having more tests in memory, visuospatial functioning and language only increased by 5% the chance of finding more cognitive domain impairments. In terms of the sensitivity of tests, there is mixed evidence whether "frontal" or "posterior" cortical tests provide good predictors of decline to PDD (Barker & Williams-Gray, 2014; Jacobs et al., 1995; Janvin et al., 2006; Mahieux et al., 1998; Woods & Troster, 2003). Indeed, the allocation of tests to cognitive domains may also differ across experts because

tests vary in their domain purity. This issue is relevant to the current findings in which multiple impairments within a cognitive domain better identified those PD-MCI patients at risk of conversion to PDD, at least over a four-year period. For example, executive function tests can vary in their domain allocation (Goldman et al., 2013; Pedersen et al., 2013) and visuospatial tests range from specific measures through to more complex tasks that also involve orientation, attention, memory and executive function (Lezak et al., 2012). That is, the selection of tests and their domain purity may contribute to variation in the frequency of impairments reported across studies. These limitations emphasize the need for further evaluation of cognitive impairments and progression to PDD.

3.5. Conclusions

The conclusion from the current study is to adopt a specific PD-MCI criterion when the intent is to identify a medium-term (up to four years) risk of progression to PDD. For this purpose, the requirement of at least two deficits at 1.5SD below normative data within any single cognitive domain provides a valid PD-MCI diagnosis that optimizes the relative risk of progression to dementia. Deciding upon the selection and number of tests required remains as a major task facing the Parkinson's disease research community.

Chapter 4: Optimisation of tests to predict dementia

4.1. Background

Cognitive testing has been the most reliable and researched method of identifying PD patients who are at the greatest risk of future PDD. Recently, it has been confirmed that meeting PD-MCI criteria is a significant risk factor for future PDD (Chapter 3; Broeders, Velseboer, et al., 2013; Hobson & Meara, 2015; Hoogland et al., 2017; Pedersen et al., 2013). The early identification of patients, who will later progress to PDD within a relatively short period after assessment (i.e. within four years) is a clinically-relevant issue for PD patients (Svenningsson, Westman, Ballard, & Aarsland, 2012; Yarnall et al., 2013). For example, early identification of those at imminent risk of developing PDD may facilitate selection of appropriate participants for novel disease-modifying interventions (Eberling et al., 2014). However, neuropsychological testing can be very time consuming and the value of different tests remains uncertain.

As discussed in earlier chapters, the specific PD-MCI criteria guidelines that have been developed by the MDS-TF (Litvan et al., 2012) allow a degree of ambiguity in terms of the number and specific tests required to classify an individual as PD-MCI. There is a minimum requirement of two tests in each of the five cognitive domains needed to meet Level II PD-MCI criteria, but no maximum number of tests allowed. Hence there can be variation between study sites in meeting Level II criteria. In Chapter 3, we determined that the PD-MCI criterion of 'two impairments at 1.5SD in a single domain' was the most suited criterion for identifying patients at the highest risk of PDD four-years later. This conclusion was based on a large battery of neuropsychological tests, with 24 measures, employed by the NZBRI to capture a range of potentially heterogeneous deficits in non-dementia patients

(Dalrymple-Alford et al., 2011). While this approach has been extremely useful, it is possible that errors in prediction are inflated by false positives due to tests that are insensitive to progression. Conversely, PD-MCI patients may be missed if a restricted test battery consisted of tests that produced impairments in some patients but which were not sensitive for future PDD.

Few studies have looked at identifying an optimal trade-off in terms of a reduced number of tests that are sufficiently sensitive in identifying patients at a high risk of developing PDD. An initial study by Goldman et al. (2015) used a least absolute shrinkage and selection operator (LASSO) logistic regression model to select the two most sensitive tests to PD-MCI within each cognitive domain for the five MDS-required cognitive domains. When using the full test battery of 19 tests over five cognitive domains, they determined that 48 of their 76 patients had PD-MCI, with PD-MCI being determined by "expert consensus". The restricted test battery of 10 tests captures 83% of PD-MCI patients from their original classification. A second study also used the LASSO approach to generate a reduced test battery of 10 tests, and reported a sensitivity of 73% and a specificity of 100% for classifying patients as PD-MCI, when compared to the PD-MCI patients classified using the original 23-item test battery (Federico et al., 2017). Our NZBRI data contributed one of four sites in a recent MDS consortium study (Hoogland et al., 2017), which was the first study to examine progression to PDD using a neuropsychological test battery of only 10 neuropsychological tests. "Expert consensus" across the sites was used to select the 10 measures (two from each of the five cognitive domains) within each of the four different PD cohorts and then the risk of PDD in PD-MCI patients was examined. They reported that PD-MCI patients who were classified using a 10 neuropsychological test battery were at a greater risk of PDD, which suggests that even when applied to a 10 neuropsychological Level II test battery, PD-MCI

criteria can identify patients at a high risk of developing PDD. Cross-sectional studies, such as Biundo et al. (2014), have identified specific individual neuropsychological tests which are good at distinguishing between PD-MCI or PDD patients when compared to PD-N patients, but the merits of these tests have not been directly compared when they are part of cognitive domains consisting of multiple tests, unlike the Goldman et al. (2015) and Federico et al. (2017) studies. Longitudinal studies, however, have shown that specific cognitive tests can perform poorly when tracking progression to PDD over time (Jacobs et al., 1995; Janvin et al., 2006; Levy et al., 2002; Mahieux et al., 1998; Williams-Gray et al., 2013; Woods & Troster, 2003). In saying this, the PD-MCI classification used in these studies was not determined using currently accepted Level II criteria.

The aim of this study was to determine the value of a reduced test battery, of 15 and 10 neuropsychological tests, when compared to the original 24 neuropsychological test battery, (1) in terms of their ability to identify patients as PD-MCI and (2) evaluate the risk of developing PDD four-years later in these PD-MCI groups. A reduced test battery would be less demanding on patients, particularly those who are showing signs of cognitive decline. It would also reduce the resources needed to assess patients' risk of PDD. The test battery was reduced by selecting the two or three tests per cognitive domain which identify the most impairment (i.e. the tests which show the most scores of -1.5SD or below). PD-MCI patients will be classified using these reduced 15- or 10 neuropsychological test batteries to determine the relative risk of PDD for two different PD-MCI groups compared to patients who do not meet the PD-MCI criteria. These relative risk scores will then be compared to the PD-MCI group risk scores when the original 24 neuropsychological test battery was used to determine whether the PD-MCI patients who develop dementia (PDD) were still able to be distinguished from those who did not progress to PDD four-years later.

4.2. Methods

4.2.1. **Participants**

A convenience sample of 121 non-dementing PD patients was recruited from our research institute and movement disorders clinic. This is the same sample described in Chapter 3 (Figure 3-1). The comprehensive neuropsychological assessment, *PD diagnostic procedure and exclusion criteria were the same as detailed in Chapter 3.* As in chapter 3, progression to PDD before the end of the 4.5-year follow-up period was treated as an a priori end-point, with no subsequent follow-up.

4.2.2. Neuropsychological battery

The same comprehensive neuropsychological assessment was administered as described in Chapter 3. A full description of each test used in the comprehensive neuropsychological test battery is in Appendix A.

4.2.3. Test selection for the reduced cognitive test battery

4.2.3.1. Part One: Test selection for the reduced cognitive test battery

Each individual test was tallied to identify how many impairments were present across the entire sample, and were rank-ordered within each cognitive domain. An impairment was defined as a score of -1.5SD or more below the normative data for each specific test. The top three tests within each cognitive domain were selected and the two PD-MCI criteria were applied to this reduced test battery (three tests per domain, 15 tests total). Although this procedure confounds test selection with the subsequent identification of PD-MCI, it provided a preliminary approach towards test reduction in the absence of a separate validation cohort.

It is also recognised that we cannot ascertain whether the selected tests would outperform other test options that were not included in the original battery.

4.2.3.2. Part Two: Test selection for the reduced cognitive test battery

To further optimise the test battery, only two tests were then selected per cognitive domain using the same test selection method as Part One. This optimised test battery of two tests in each cognitive domain is the minimum number of tests that must be included to meet Level II PD-MCI criteria as advised by Litvan et al. (2012). The two PD-MCI criterions were then applied to the reduced test battery (two tests per domain, 10 tests total).

4.2.4. Application of PD-MCI criteria

In this study, we used two different PD-MCI criteria, based on the findings of Chapter 3. The PD-MCI criteria were applied to both the full and reduced test batteries (Figure 4-1). We tested two reduced test batteries: (1) three tests per domain, and (2) two tests per domain. Like Chapter 3, a stepwise approach was used so that each PD-MCI group consisted of a discrete (non-overlapping) sample of patients. Firstly, we identified all patients with a minimum of two impairments at -1.5SD within at least one cognitive domain at baseline (that is, all patients from the entire sample of 121 patients who had two or more scores at or worse than the -1.5SD cut-off score) using the full test battery. The risk of dementia within this group of PD-MCI patient's relative to those who did not meet this criterion was then determined using relative risk. The remaining patients who did not meet the previous criterion (two or more scores at or worse than -1.5SD) were then assessed by comparing relative risk in those patients who had the minimum of two impairments at the cut-off score of -1.5SD but in whom the two impairments did not occur within a single cognitive domain (i.e. at least two domains each had a maximum of one impaired score) relative to the

remaining patients, who did not meet either of these two PD-MCI criteria. As any patient with multiple impairments within a single cognitive domain had been excluded in the previous stage, by definition this latter PD-MCI group all had only one impaired score within any one cognitive domain. In clinical practice, this second, more relaxed 1.5SD criterion would also capture those with multiple impairments within a cognitive domain, but for analysis purposes we kept the samples independent. This two-step process of identifying patients as PD-MCI for both criteria was repeated using (1) three tests per domain, and then again for the (2) two tests per domain comparison. The risk of PDD conversion was then compared between PD-MCI groups who had been determined using the full and each of the reduced test batteries (i.e. three tests per domains and then two tests per domain) to evaluate the efficacy of using a shortened test battery for risk of developing PDD within the next four-years.

A.

B.

C.
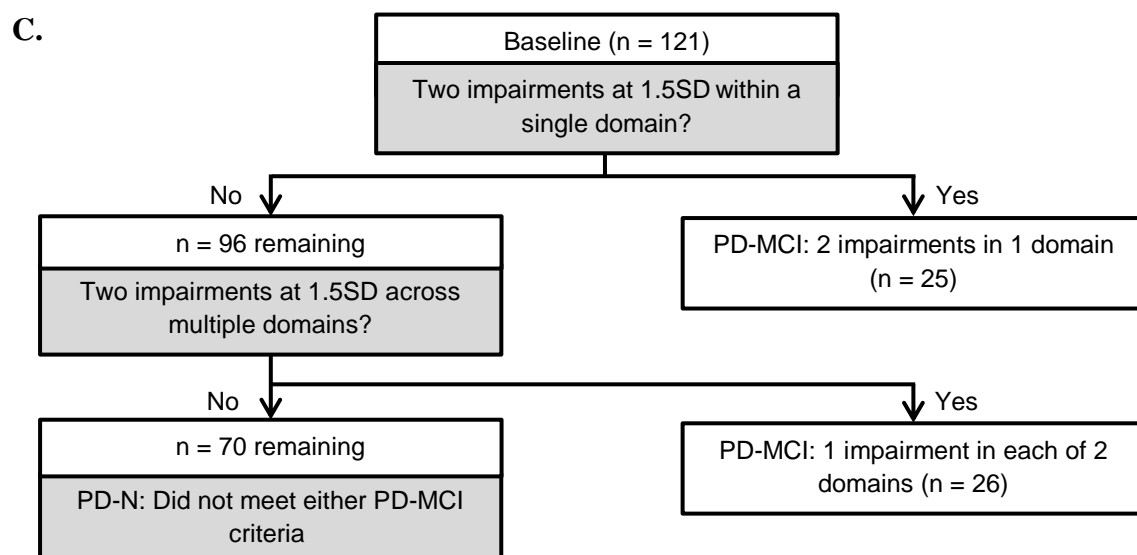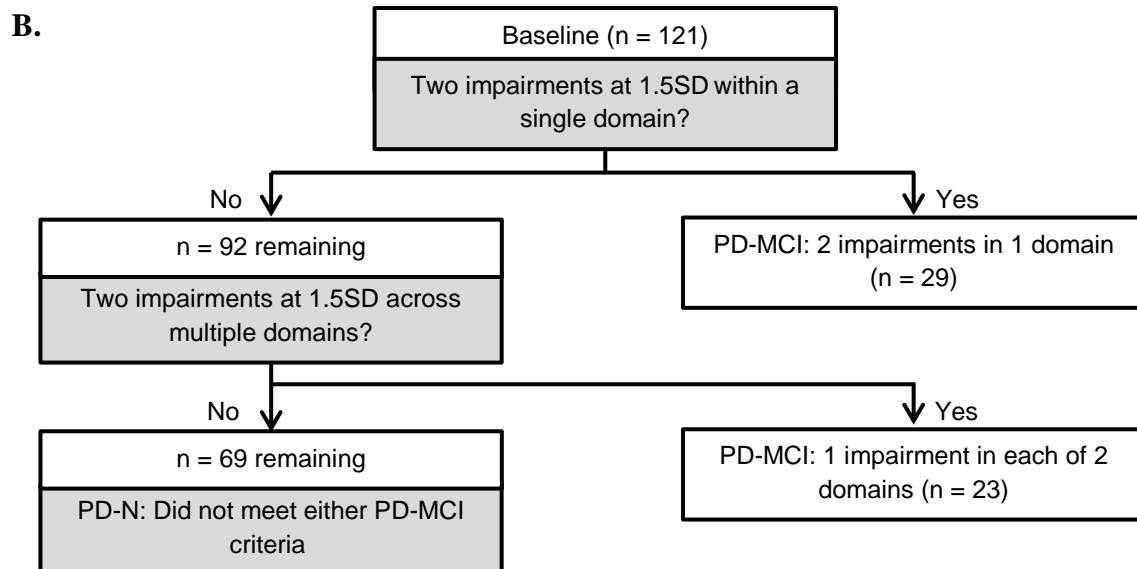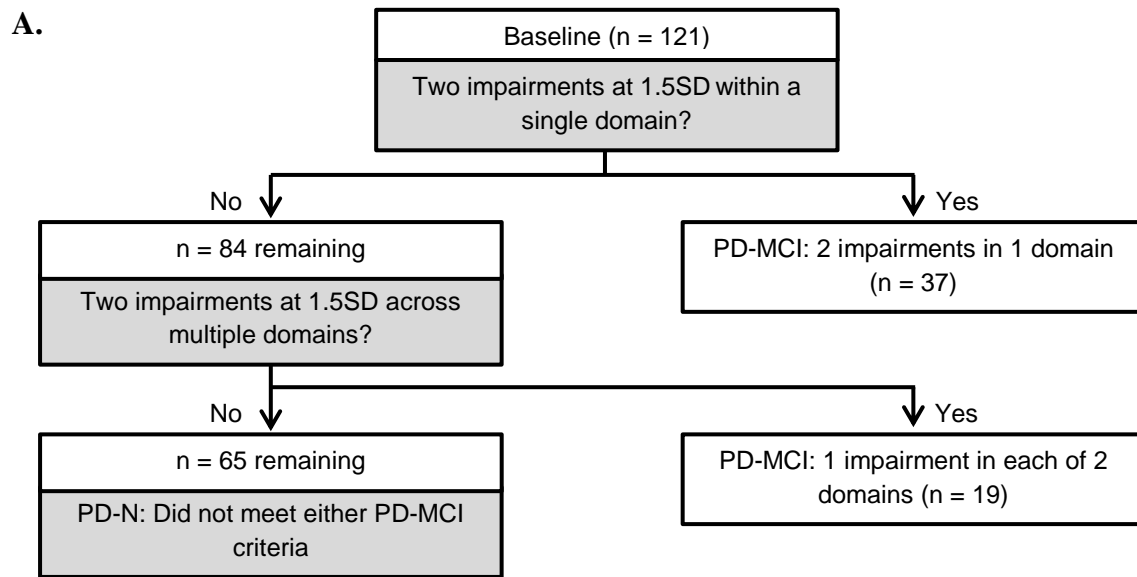
Figure 4-1. *PD-MCI criterion application. (A) PD-MCI selection when applied to the full neuropsychological test battery. (B) PD-MCI selection when applied to the reduced three tests per cognitive domain neuropsychological test battery. (C) PD-MCI selection when applied to the reduced two tests per cognitive domain neuropsychological test battery.*

4.2.5. Assessing the efficacy of the reduced test battery

Baseline demographic and cognitive differences were compared between the PD-N, PD-MCI 'one impairment in each of two domains' and the PD-MCI 'two impairments in one domain' groups using ANOVA, with Tukey post hoc tests. Relative Risk (RR) was used to determine whether the group of patients classified using each of the PD-MCI criterions when applied to the reduced 15 or 10 neuropsychological test batteries were able to capture patients who were at a greater risk of PDD compared to those who did not meet the PD-MCI group criteria. The RR scores from the restricted test batteries were then compared to the RR scores of the full test battery to evaluate how well the restricted test battery could capture the at-risk PD-MCI patients. This analysis was conducted using R (v3.3.2). Patient groups (i.e. PD-MCI 'one impairment in each of two domains' versus the remaining PD-N patients) were deemed as being at significantly more risk of developing PDD if the lower boundary of the 95% confidence interval (CI) was above 1.0.

4.3. Results

4.3.1. Participants

Table 4-1 summarizes the demographic and neuropsychological data of the patients used in this study at baseline. The average patient's age at study entry was 65.5 years (SD = 8.1 years). There was a 21% conversion rate to dementia for all PD patients in the four-year follow-up period (25 out of 121 patients; 14 men and 11 women). There were no significant

differences between age, level of education, premorbid IQ (WTAR) and symptom duration across the PD-N, PD-MCI 'one impairment in each of two domains' and the PD-MCI 'two impairments in one domain' groups.

Full neuropsychological battery. The PD-MCI 'two impairments in one domain' group had significantly higher ADL, DRS-2, Hoehn and Yahr and UPDRS (Motor) scores than the PD-N group. They also had worse CDR, ADAS-Cog and MoCA scores than both the PD-MCI 'one impairment in each of two domains' and the PD-N groups. The PD-MCI 'one impairment in each of two domains' group had significantly higher CDR scores than the PD-N group. Regarding cognitive performance, the PD-MCI 'two impairments in one domain' group had significantly lower global cognition scores than the PD-MCI 'one impairment in each of two domains' and the PD-N groups, as well as some poorer scores in the executive function, attention, episodic memory and visuospatial domains. In the language domain, the PD-MCI 'two impairments in one domain' group had significantly lower scores than the PD-N, but not the PD-MCI 'one in each of two domains' group. The PD-MCI 'one in each of two domains' group had poorer global cognition than the PD-N groups and had lower scores in the executive, memory and visuospatial domains.

Table 4-1. Demographics and neuropsychological data at study entry [mean (SD)]

	PD-N	PD-MCI: 'One impairment in each of two domains'	PD-MCI: 'Two impairments in one domain'
Sample size (n)	65	19	37
Convert to PDD (n)	4	2	19
Sex, M:F	41:24	11:8	25:12
Age	64(8)	66(7)	68(8)
Education (y)	13(3)	13(3)	13(3)
Premorbid IQ (WTAR)	112.1(7.4)	108.5(8.0)	109.0(8.7)
CDR	0.1(0.2)	0.2(0.3)[b]	0.4(0.2)[b,c]
Reisberg IADL	0.3(0.4)	0.6(0.7)	0.7(0.6)[b]
DRS-2 (AESS)	12.4(1.9)	11.6(2.1)	10.2(1.8)[b]
ADAS-Cog	5.7(2.4)	7.0(2.5)	10.0(2.7)[b,c]
Symptom duration (y)	4.8(4.0)	7.2(4.6)	6.7(4.5)
Hoehn and Yahr stage	1.9(0.7)	2.0(0.5)	2.4(0.6)[b]
UPDRS (Motor)	30.0(16.4)	31.0(12.1)	40.5(16.5)[b]
MoCA	26.7(2.3)	26.1(2.0)	23.5(2.5)[b,c]
Global Z score	+0.27(0.40)	-0.18(0.26)[b]	-0.88(0.33)[b,c]
1. Executive function	+0.25(0.59)	-0.14(0.47)[b]	-1.00(0.63)[b,c]
2. Attention, working memory & processing speed	+0.12(0.47)	-0.17(0.38)	-0.78(0.51)[b,c]
3. Episodic memory	+0.36(0.75)	-0.21(0.73)[b]	-1.08(0.67)[b,c]
4. Visuoperceptual/ visuospatial	+0.36(0.45)	-0.18(0.42)[b]	-0.68(0.61)[b,c]
5. Language[a]	+0.57(0.98)	+0.17(0.70)	-0.08(0.77)[b]

Abbreviations: PDD = Patients who met Level II criteria for Parkinson disease with dementia; Global Z score = mean derived from attention, executive function, visuospatial and episodic memory domains; ADAS-Cog = Alzheimer's Dementia Assessment Scale-Cognitive; CDR = Clinical Dementia Rating; DRS-2 (AESS) = Dementia Rating Scale-2 (Age and Education Scaled Score); IADL = Instrumental Activities of Daily Living; MoCA = Montreal Cognitive Assessment; N/A = Not Applicable; NPI = Neuropsychiatric Inventory; UPDRS (Motor) = Unified Parkinson's Disease Rating Scale (Motor Component); WTAR = Wechsler Test of Adult Reading for premorbid IQ.
[a] Thirty-seven PD patients did not have two language measures at study entry.
[b] Significantly different from PD-N, Tukey post hoc tests, p<0.05.
[c] Significantly different from PD-MCI: 'One impairment in each of two domains', Tukey post hoc tests, p<0.05.

4.3.2. Selecting tests

The rank-ordered tests, based on each measure's ability to identify impairment (i.e. the number of scores below -1.5SD) per cognitive domain is displayed in Table 4-2.

4.3.2.1. Part One: three tests per cognitive domain

In the Attention domain, Map Search identified an impairment most frequently, followed by Digit Ordering, and Trails A. In the Executive domain, Action Fluency identified the most frequent impairments, followed by Trails B and Stroop Interference. Rey Copy was the test which most frequently identified an impairment in the Visuospatial domain, followed by JLO and then Picture Completion. In the Memory domain, Rey Short Delay identified impairment most frequently, followed by CVLT-II SF Short Delay and then CVLT-II SF Free Recall. The short delay versions of the CVLT-II SF and Rey were selected because impairments in either the short or long delay components in each of these tests were counted as one impairment. Furthermore, patients who were impaired after only a short delay generally were impaired to the same degree or more during the long delay component of the test. Finally, in the language domain the DRS-2 Similarities test identified the most impairment, followed by the ADAS-Cog Language measures, and then the Boston Naming Test.

4.3.2.2. Part Two: Two tests per cognitive domain

Table 4-2 has the tests rank-ordered per cognitive domain that identify the most impairments. When the test battery was restricted to two tests per cognitive domain, we find that Trails A drops out of the Attention domain. In the executive functioning domain, Stroop Interference is no longer included. Picture Completion drops out of the visuospatial domain and CVLT-II

SF Free Recall in the Memory domain. Finally, in the Language domain the Boston Naming

Test is no longer included in the 10 neuropsychological test battery.

Table 4-2. Ranking of tests per domain and the number of impairments identified

Domain	Test	Number of participants with scores $\leq$ -1.5SD
Attention	TEA Map Search	28
	Digit Ordering	26
	Trails A	16
	Stroop colour	8
	Stroop word	2
	Digits Forwards and Backwards	0
Executive Function	Action Fluency	36
	Trails B	21
	Stroop Interference	15
	Category Switching	14
	Letter Fluency	6
	Category Fluency	2
Visuospatial	Rey Copy	27
	JLO	13
	Picture Completion	3
	VOSP	2
Episodic Memory	Rey Short delay	32
	CVLT-II SF Short delay	16
	CVLT-II SF Free recall	10
	Rey Long delay	25
	CVLT-II SF Long delay	14
Language	Language ADAS-Cog Z-score	4
	Language DRS-2 Similarities Z-score	3
	Boston Naming Test	0 (only 21 received test)

Abbreviations: ADAS-Cog = Alzheimer's Dementia Assessment Scale-Cognition; CVLT-II SF = California Verbal Learning Test – Second Edition, Short Form; DRS-2 = Dementia Rating Scale-2; JLO, Judgement of Line Orientation; TEA Map Search, Test of Everyday Attention: Map Search; VOSP, Visual Object and Space Perception test battery.
NB. The short delay versions of the CVLT-II SF and the Rey were selected because impairments in either the short or long delay components in each of these tests were counted as one impairment.

4.3.3. Effect of reduced test battery on selection of PD-MCI groups

4.3.3.1. Part One: Reducing the test battery to three tests per cognitive domain

Having three neuropsychological tests in each of the five cognitive domains had a small effect on the number of patients classified as PD-MCI, across both criteria used, when compared to the full 24 neuropsychological test battery. When the test battery was reduced to three tests per cognitive domain, the group selected by the PD-MCI 'two in one domain' criterion changed from 37 patients (19 converted to dementia; 51%), to 29 patients, 17 of whom converted to PDD (59%; Figure 4-1A and Figure 4-1B). The number of patients in the PD-MCI 'one in each of two domains' group increased from 19 (2 of who converted to PDD; 11%), to 23 patients (4 of whom converted to PDD; 17%) when the criterion was applied to the reduced 15 neuropsychological test battery (Figure 4-1A and Figure 4-1B).

4.3.3.2. Part Two: Reducing the test battery to two tests per cognitive domain

Having only two neuropsychological tests per cognitive domain in the cognitive battery again reduced the number of patients classified as PD-MCI using the 'two in one domain' criterion when compared to the full cognitive test battery (Full 24 neuropsychological test battery = 37 patients, Reduced 10 neuropsychological test battery = 25 patients; Figure 4-1A and Figure 4-1C). The proportion of patients who developed dementia during the follow-up period remained stable however (Full 24 neuropsychological test battery, 19 patients develop PDD at follow-up, Reduced 10 neuropsychological test battery, 13 patients develop PDD at follow-up). The number of patients classified as PD-MCI using the 'one in each of two domains' criterion increased when a reduced test battery consisting of two tests per cognitive domain was used (Full 24 neuropsychological test battery = 19 patients, Reduced 10 neuropsychological test battery = 26 patients; Figure 4-1A and Figure 4-1C). The PD-MCI

criterion of 'one in each of two domains' when applied to the reduced test battery (two tests per cognitive domain) was able to capture substantially more patients who develop PDD during the study compared to when it was applied to the full test battery (Full 24 neuropsychological test battery = 2 patients develop PDD at follow-up, Reduced 10 neuropsychological test battery = 8 patients develop PDD at follow-up).

4.3.4. Risk of PDD progression

4.3.4.1. Part One: Progression to PDD and three tests per cognitive domain

The relative risk (RR) of progressing to PDD in the PD-MCI 'two impairments in one domain' group was similar to the full test battery (RR of full 24 neuropsychological test battery = 7.2, 95% CI = 3.3-15.8; RR of reduced 15 neuropsychological test battery = 6.7, 95% CI = 3.3-13.5). There was no evidence to suggest that the patients classified as PD-MCI using the 'one in each of two domains' criterion were more at-risk of developing PDD four-years later than the PD-N group when using the 3 tests per cognitive domain battery (RR of full 24 neuropsychological test battery = 1.7, 95% CI = 0.5-6.8; RR of reduced 15 neuropsychological test battery = 3.0, 95% CI = 0.9-9.8).

4.3.4.2. Part Two: Progression to PDD and two tests per cognitive domain

When the test battery was reduced to two tests per cognitive domain, both PD-MCI criteria captured patients who were at significant risk of developing dementia. There was no evidence of a difference in RR of progression to PDD in the PD-MCI 'two in one domain' group classified using the full 24 neuropsychological test battery compared to when this criterion was applied to the reduced 10 neuropsychological test battery as the CI's are overlapping (95% CI of full 24 neuropsychological test battery = 3.3-15.8; RR of reduced 10

neuropsychological test battery = 4.2, 95% CI = 2.2-7.8). This criterion was able to significantly identify at risk patients (i.e. a higher rate of patients who were classified using this criterion progressed to PDD four-years later than the remaining patients who did not meet this criterion) when applied to both the full 24- and reduced 10 neuropsychological test batteries. When the PD-MCI criterion of 'one in each of two domains' was applied to the reduced 10 neuropsychological test battery, it captured patients at a higher risk of dementia progression within four-years than the PD-N group (RR = 5.4, 95% CI = 1.9-15.0), as the CI no longer intercepts one. This was not the case when the PD-MCI criterion of 'one in each of two domains' was applied to the full 24 neuropsychological test battery (RR = 1.7, 95% CI = 0.5-6.8).

When using a reduced 10 neuropsychological test battery, both PD-MCI criteria are able to identify patients who had a greater risk of developing PDD four-years later. We therefore decided to combine these two groups of patients into one PD-MCI group. This meant that we were no longer restricting the PD-MCI group to either (1) having both of their impairments solely <u>within</u> a cognitive domain or (2) having the two impairments only <u>across</u> two or more of the five cognitive domains, but never both in a single cognitive domain. The new PD-MCI group was comprised of all of the patients who had 'two impairments anywhere across the five domains' (n = 51; 21 patients develop PDD at follow-up). This new group of patients had a high risk of developing PDD than the PD-N patients (RR = 7.2, 95% CI = 2.9-18.5) when this criterion was applied to the two tests per cognitive domain reduced test battery.

4.3.5. Pattern of domain impairments when the test battery is reduced to two tests per cognitive domain

Figure 4-2 shows the pattern of domain impairments at baseline in the PD-MCI group who

(A) had at least 'two impairments at -1.5SD within a <u>single</u> cognitive domains' (Figure 4-2A), (B) had 'one impairment at -1.5SD in each of two and domains' (never two in the same cognitive domain; Figure 4-2B) and (C) had at least 'two impairments at -1.5SD <u>anywhere</u>' (Figure 4-2C) when applied to a reduced 10 neuropsychological battery (Part Two analysis). Note that multiple cognitive domain impairments are therefore different due to the criterions. In Figure 4-2A, multiple cognitive domain impairments are defined as two impairments in each of two or more domains, while in Figure 4-2B and Figure 4-2C multiple cognitive domain impairments are defined as two impairments across two or more cognitive domains.

4.3.5.1. PD-MCI group defined as having at least 'two impairments at -1.5SD within a <u>single</u> cognitive domain'

Figure 4-2A shows the pattern of domain impairments at baseline in the PD-MCI group who had at least two impairments at 1.5SD within at least one of the five cognitive domains, when a reduced battery of two tests per cognitive domains was used (Part Two analysis). Note that multiple cognitive domain impairments therefore meant that they had two impairments in each of two or more cognitive domains. Nine of the 25 PD-MCI patients had multiple cognitive domain impairments (defined above). Eighty-nine percent of the patients with multiple cognitive domain impairments converted to PDD (8 of 9), whereas 31% of those with single cognitive domain impairments (5 of 16) converted to PDD. All PD-MCI patients who had multiple cognitive domain impairments that included memory, irrespective of conversion or not, had a mixture of other cognitive domains involved (episodic memory and executive, n = 1; episodic memory and visuospatial, n = 2; episodic memory and attention, n= 1; episodic memory, executive, attention and visuospatial, n = 1). Multiple cognitive domain impairments that did not include memory were: executive and attention, n = 2; executive and

visuospatial, n = 1; and attention and visuospatial, n = 1. None of the PD-MCI patients had single cognitive domain impairments in the language domain. The rest of the single cognitive domain impairments were spread over the other four cognitive domains (memory, n = 3; executive, n = 6; visuospatial, n = 3; and attention, n = 4). There was no obvious pattern to the cognitive domains impaired and conversion to PDD, but over half of the patients who later converted to PDD had impairments in multiple cognitive domains.

4.3.5.2. PD-MCI group defined as having 'one impairment at -1.5SD in <u>each of two cognitive domains</u>' (but never two in the same domain)

In Figure 4-2B, all 26 PD-MCI patients in this category had multiple cognitive domain impairments due to this definition of the PD-MCI. The PD-MCI patients who had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not, had a mixture of other cognitive domains involved (episodic memory and executive, n = 3; episodic memory and attention, n = 2; episodic memory, executive and attention, n = 3; episodic memory, attention and visuospatial, n = 1; episodic memory, executive, attention and visuospatial, n = 2; episodic memory, attention, executive, and language, n = 3; episodic memory, attention and visuospatial, n = 2; episodic memory and language, n = 1; episodic memory and visuospatial, n = 3; and episodic memory, visuospatial and language, n = 1). Multiple cognitive domain impairments that did not include episodic memory were: executive and attention, n = 3; executive and visuospatial, n = 1; and attention, executive, visuospatial, n = 1. There was no obvious pattern to the cognitive domains impaired and conversion to PDD.

4.3.5.3. PD-MCI group defined as having at least 'two impairments at -1.5SD on <u>any</u> of the restricted set of tests

In Figure 4-2C, only one patient out of 51 who met this PD-MCI criterion had a single cognitive domain impairment (Executive domain: Figure 4-2C) and this patient was not a converter to PDD four-years later. Again, most patients who met this PD-MCI criterion had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not. Alongside the episodic memory impairment there were a mixture of other cognitive domains involved (episodic memory and attention, n = 3; episodic memory, attention and executive, n = 5; episodic memory, attention, executive and language, n = 3; episodic memory, attention and visuospatial, n = 5; episodic memory, attention, executive and visuospatial, n = 9; episodic memory and executive, n = 5; episodic memory, executive and visuospatial, n = 4; episodic memory, executive, visuospatial and language, n =1; episodic memory and language n = 1; episodic memory and visuospatial, n = 3; episodic memory, visuospatial and language, n = 1; and episodic memory, executive, visuospatial and language, n = 1). Multiple cognitive domain impairments that did not include episodic memory were: attention and executive, n = 4; attention, executive and language, n = 1; attention, executive and visuospatial, n = 3; and attention and visuospatial, n = 1. Again, there was no obvious pattern to the cognitive domains impaired and conversion to PDD.
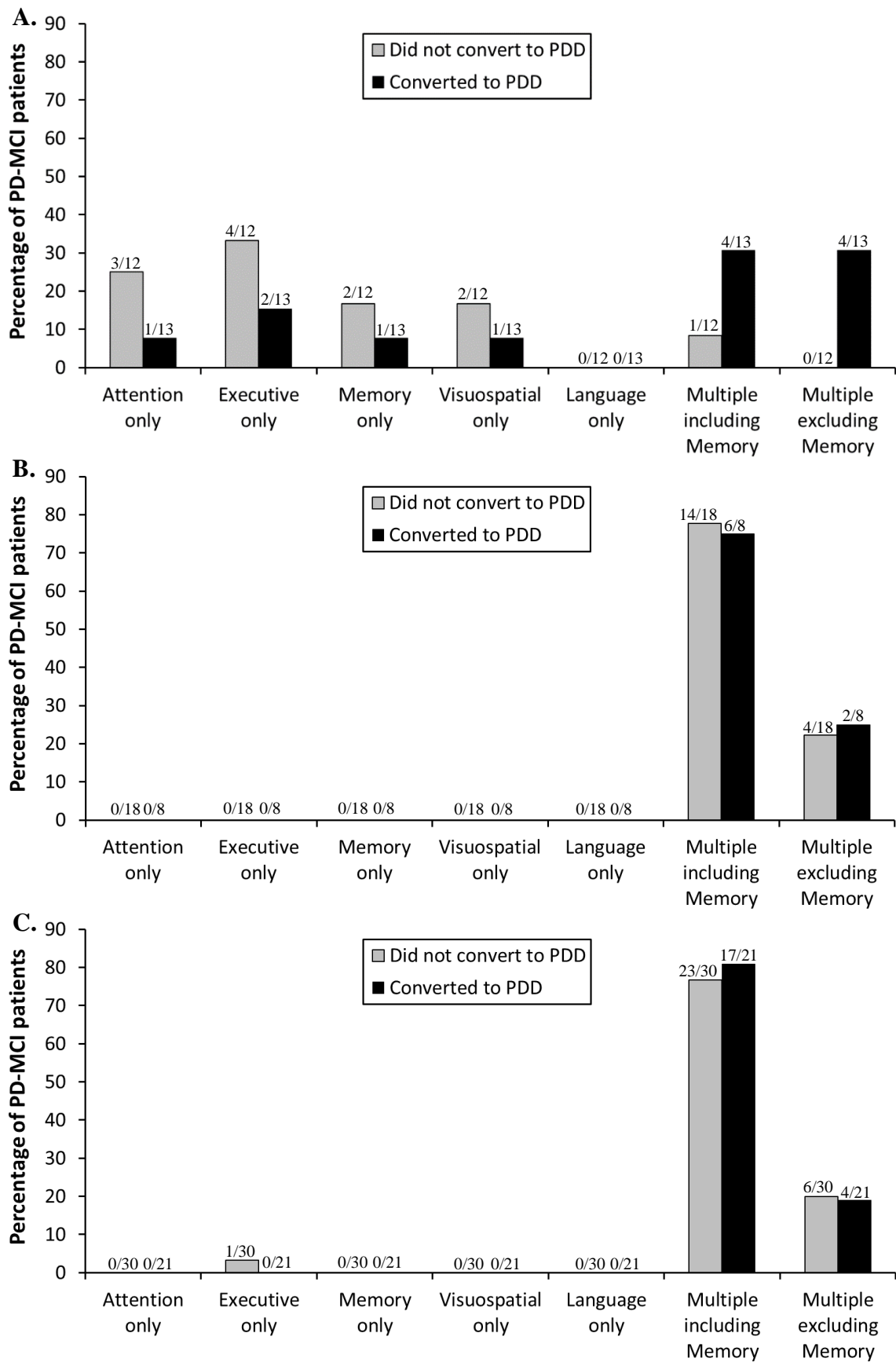
Figure 4-2. *Pattern of Domain Impairments using a reduced 10 neuropsychological test battery. (A) PD-MCI 'two impairments at -1.5SD in a single cognitive domain'. (B) PD-MCI*

'one impairment in each of two domains'. (C) PD-MCI 'two impairments at -1.5SD anywhere'. The grey bars represent the percentage of patients who had two or more impairments in a simple cognitive domain only or two or more impairment in each of two or more cognitive domains and did not develop PDD. The black bars represent the percentage of patients who had two or more impairments in a simple cognitive domain only or two or more impairment in each of two or more cognitive domains and did develop PDD four-years later. The numbers above the bars show the number of patients who have that impairment out of the sub-group.
NB. Multiple cognitive domain impairments are not equivalent in A, B and C. In A, a multiple cognitive domain impairment is defined as two impairments in each of (or more) domains, while in B and C, a multiple domain impairment is defined as two or more tests impaired across two (or more) domains. This is due to the PD-MCI criteria being different.

4.4. Limitations and Conclusions

In this study, we used a simple method for reducing the number of tests within each cognitive domain to the minimum number required to still meet Level II criteria. We found that when using the reduced test battery, it is still possible to identify PD-MCI patients at high risk of imminent dementia (i.e. within 4 years). However, the PD-MCI criterion of 'two impairments at -1.5SD occurring in a single domain', which classified the highest at-risk proportion of patients who would later progress to PDD as PD-MCI in Chapter 3, was likely not as effective at identifying at-risk patients when a reduced battery was used. Rather a combined PD-MCI criterion of 'two impairments in any domain at -1.5SD' was likely more effective at identifying at-risk PD-MCI when using the reduced test battery.

The difference in the specific PD-MCI criteria which identified the patients with the highest risk of progression to PDD in this Chapter compared to Chapter 3, is a direct result of applying each criterion to the reduced neuropsychological test battery. When there are only two or three tests in a cognitive domain compared to four-six tests, the possibility of 'failing' a test by chance reduces. Goldman et al. (2015) found that the probability of detecting an impairment increased when a cognitive domain consisted of more than two tests, but in the attention and executive domains, this chance of detecting impairment did not increase when

there were three or four tests in these cognitive domains. In the other cognitive domains (memory, visuospatial and language) there was only a five percent increased chance of finding an impairment when the cognitive domains consisted of more than two tests (Goldman et al., 2015). Furthermore, it is much more difficult to fail two tests within a single cognitive domain when there are only two or three possible tests. We saw in the present study that the total number of PD-MCI patient classified using the alternative PD-MCI criteria did not drastically change compared to Chapter three, but those that originally met the PD-MCI criterion of 'two impairments in a single cognitive domain' when a comprehensive test battery was employed now meet the PD-MCI criterion of 'one impairment in each of two domains'. Additionally, we found when the combined PD-MCI criterion, which did not restrict the impairments to occur within or across cognitive domains ('two impairments in any of the 10 tests'), captured the patients who had the highest risk of PDD. This differed from what we found when this combined criterion was applied to the comprehensive 24 neuropsychological test battery. This is clearly evident in the literature as more patients are identified as being PD-MCI when a PD-MCI criterion is used which does not restrict the impairments only to a single cognitive domain or across multiple cognitive domains but allows them to occur in any two tests in any of the cognitive domains (i.e. they can occur in any of the tests which are assessed; Dalrymple-Alford et al., 2011; Liepelt-Scarfone et al., 2011).

Despite this finding, the methodology used to select the 'best' tests per domain in this present study was not the optimal approach. I have developed another approach which is discussed in the next chapter (Chapter 5). The evaluation of the usefulness of a test based solely on the number of patients who receive a score of -1.5SD or below could bias which tests are selected as not all neuropsychological tests are of equal importance. Some tests are

more stringent than others, due to the poor normative data used for the generation of z-scores (Crawford & Howell, 1998), floor and ceiling effects and as well as the overall difficulty of the task being assessed. Issues surrounding the normalisation of data have been long argued, with some studies commenting that age- and education-corrected neuropsychological data is not necessary in brain-injured populations (Reitan & Wolfson, 1995), because it can lead toad to a loss predictive power when looking for cognitive impairment or dementia (M Sliwinski, Lipton, Buschke, & Wasylyshyn, 2003; Martin Sliwinski, Buschke, Stewart, Masur, & Lipton, 1997), and the over-correction of the data can lead to an increase in false positives being identified (M. E. O'Connell, Tuokko, Graves, & Kadlec, 2004). However, in the context of a neuropsychological test battery, which includes multiple measures to assess across multiple cognitive domains, this loss in sensitivity is not as important, as any loss would likely be offset by the use multiple test measures (Megan E. O'Connell & Tuokko, 2010). There is still the danger that when selecting only two or three tests per cognitive domain, using the approach described in this chapter, we are selecting tests which have inflated levels of impairment (i.e. scores below -1.5SD).

Despite normalised scores potentially having an effect when not used within a comprehensive test effect, there is consistent evidence for their use. Younger and/or more educated individuals consistently perform better than individuals who are older in age and/ or less educated (Lezak, 2004; Strauss et al., 2006; Vanderploeg, Axelrod, Sherer, Scott, & Adams, 1997). In saying this, the value of data normalisation does lie within the population with which the normalisation is based upon and this is better in some neuropsychological test than others (Crawford & Howell, 1998). This evidence strongly suggests that it is important to use normalised scores, but the methodology used to select tests in this study could have been influenced as normalised scores were the basis of test selection.

Due to this limitation, we subsequently developed a different method to reduce the test battery, using logistic regression (Chapter 5). Logistic regression was selected since it enables selection of tests in relation to progression to PDD four-years later. Thus, we can create a logistic regression model which is sensitive to progression to PDD within each cognitive domain and then find the two tests per cognitive domain which fit the progression to PDD model the most robustly. This approach is fully discussed in the next chapter (Chapter 5)

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Chapter 5: Optimising the test battery to 10 neuropsychological tests sensitive to future Dementia

5.1. Aims

The previous chapter looked to reduce the test battery to 15 and 10 neuropsychological tests using the frequency of PD-MCI level impairments (i.e. scores of -1.5SD or below) in any given test to rank-order the tests based on sensitivity of identifying an impairment. From this we then selected the two or three tests per cognitive domain to form our 10 and 15 neuropsychological reduced test batteries. Here, we used logistic regression models to instead select two sensitive tests within each cognitive domain that are associated with progression to dementia. Baseline scores were used to assess a specific test's ability to distinguish between patients who progressed to PDD four-years later from those that did not. We then evaluated whether the PD-MCI criterion recommended in Chapter 3 ('two impairments at -1.5SD in a single domain') was still able to identify patients who were at a high risk of developing PDD four-years later, once applied to the resulting reduced 10 neuropsychological test battery.

5.2. Methods

5.2.1. Participants

A convenience sample of 138 non-demented PD patients was recruited from our research institute and movement disorders clinic. There were 17 additional patients included in this study, compared to the sample discussed in Chapters 3 and 4. During or after the studies in Chapter 3 and 4 were completed, an additional 27 PD patients were recruited to the study. Nine of these patients were excluded before baseline testing, while 18 received baseline assessments. Seven patients were found to have PDD and were not included in this analysis

and a further two patients were not available for follow-up assessments as they were not assessed during the follow-up window of 3.5-4.5 years after baseline testing. This left nine patients who completed their four-year follow-up assessments or progressed to PDD during the follow-up period and were therefore included in this study. An additional eight patients (seven PD-N and one PD-MCI 'two impairments in one domain') were also included in the study, even though they were assessed beyond the 3.5-4.5 year follow-up window. They were included as they had not progressed to PDD when they were next assessed (1-13 months after the 3.5-4.5 year follow-up window) and thus they would not have progressed to dementia during the 3.5-4.5 year follow-up window. This resulted in 138 patients being included in this study.

The comprehensive neuropsychological assessment, PD diagnostic procedure and exclusion criteria were the same as detailed in Chapter 3. At study entry, the average duration of motor symptoms was 5.8 years (SD = 4.3 years) and the average follow-up period was 46.6 months (SD = 9.7 months). As in chapter 3, progression to PDD before the end of the 4.5-year follow-up period was treated as an a priori end-point, with no subsequent follow-up. All participants took their usual medications on the day of testing to allow optimal performance during the morning test sessions. The study was approved by a local ethics committee of the New Zealand Ministry of Health, with informed consent provided by all participants.

5.2.2. Neuropsychological assessment

The same comprehensive neuropsychological assessment outlined in Chapter 3, which fulfils the MDS-TF Level II PD-MCI criteria (Litvan et al., 2012). A full description of each test use is in Appendix A.

5.2.3. est selection for the reduced cognitive test battery

Logistic regression was used to select two tests sensitive to progression to dementia within each of the five cognitive domains, based on whether each test could distinguish between patients who developed PDD and those who did not at follow-up. Baseline scores from all tests within a single cognitive domain were entered into a logistic regression (LR) model, with PDD status at follow up as the outcome variable (PDD or non-PDD). A new LR model was created for the four cognitive domains tested to determine which two tests would be included in the reduced test battery. The odds ratios generated from each LR model were rank-ordered according the tests association with progression to PDD. The Language domain was not examined as there were only two tests in any case that could be included in this analysis. If a test score was missing, the individual was excluded from that domain's logistic regression analysis. In any instances where there were fewer than two tests in a cognitive domain which were significantly associated with future progression to PDD, neuropsychological assessment expertise was used by my primary supervisor, Prof. John Dalrymple-Alford, and I to select additional tests included in the reduced 10 neuropsychological test battery. Considerations such as the composition of tests included within a cognitive domain (i.e. in the Episodic Memory domain including a measure of verbal as well visual memory impairments) and unpublished observations on the suitability of tests to identify the progression to PDD. If there were more than two significant tests associated with progression to PDD within a cognitive domain, that same neuropsychological assessment expertise procedure was used to select the two tests. This analysis was conducted in R (v3.3.2.) using the glm command (with family= "binomial" and link= "logit").

5.2.4. Application of PD-MCI criteria

Based on the findings of Chapter 3, we used the same two PD-MCI criterions here (as in Chapter 4). Each of the PD-MCI criteria was applied to the full 24 neuropsychological and reduced 10 neuropsychological test batteries. As in Chapters 3 and 4, a stepwise approach was used so that each PD-MCI group consisted of a discrete (non-overlapping) sample of patients (see Chapter 4.2.4. for methodology of PD-MCI criteria application).

5.2.5. Assessing baseline group differences, when grouped using the 24 neuropsychological test battery

Baseline demographic and cognitive differences were compared between the three groups (PD-N, PD-MCI 'one impairment in each of two domains' and the PD-MCI 'two impairments in one domain') using ANOVA, with pairwise Tukey post hoc tests. The cognitive groups shown on Table 5-1 were determined using the original 24 neuropsychological test battery.

5.2.6. Assessing the efficacy of the reduced test battery

Like in Chapter 3, confidence intervals for relative risk of PDD in each comparison were determined using bootstrap methods (Efron, 1979). Relative Risk (RR) was used to evaluate whether the different PD-MCI criteria applied to the reduced 10 neuropsychological test battery captured patients who converted to dementia over 3.5-4.5 years. The RR scores between the PD-MCI criteria when applied to both the full 24 neuropsychological and reduced 10 neuropsychological test batteries will be observed. The RR analysis was conducted in R (3.3.2.), with a statistic deemed significant when the 95% confidence intervals (CI) did not intersect one.

5.3. Results

5.3.1. Participants

The average patient age at study entry was 65.7 years (SD = 8.0 years). Table 5-1 summarizes the baseline demographic and neuropsychological data used in this study, with the cognitive groupings determined using the original 24 neuropsychological test battery. There was a 20% conversion rate to dementia for the PD patients in the four-year follow-up period (28 out of 138 patients; 16 men and 12 women). There were no significant differences between the level of education or premorbid IQ (WTAR) across the groups (PD-N, PD-MCI 'one impairment in each of two domains' and the PD-MCI 'two impairments in one domain').

The PD-MCI 'one impairment in each of two domains' group and PD-N group showed no evidence of a difference in age or symptom duration at study entry. When the PD-MCI 'one impairment in each of two domains' group were compared to the PD-N group we found that they had significantly higher CDR and ADAS-Cog scores. They also performed significantly worse than PD-N's in the executive, attention, episodic memory and visuospatial domains, and as a result also had worse global cognition.

The PD-MCI 'two impairments in one domain' group however were significantly older, had longer symptom duration than the PD-N group. The PD-MCI 'two impairments in one domain' group also had higher ADL's, Hoehn and Yahr and UPDRS (motor) scores than PD-N's. They also had significantly higher CDR, DRS-2, ADAS-Cog and MoCA scores than PD-N's and preformed significantly worse across all the five cognitive domains. In addition to this, the PD-MCI 'two impairments in one domain' group also had significantly lower global cognitive Z score than the PD-N group.

When the two PD-MCI groups were compared at study entry, there was no evidence of differences in age or symptom duration at study entry. The PD-MCI 'two impairments in one domain' group did however have significantly higher CDR, DRS-2, ADAS-Cog and MoCA scores than the PD-MCI 'one impairment in each of two domains' group. They also preformed significantly worse across all five cognitive domains and had a significantly lower global cognitive Z scores than the PD-MCI 'one impairment in each of two domains' group.

Table 5-1. Demographics and neuropsychological data at study entry [mean (SD)]

	PD-N	PD-MCI: 'One impairment in each of two domains'	PD-MCI: 'Two impairments in one domain'
Sample size (n)	74	22	42
Convert to PDD (n)	4	3	21
Sex, M:F	49:25	13:9	27:15
Age	64 (8)	67 (7)	68 (8)[b]
Education (y)	13.1(2.8)	12.4(2.7)	12.8(3.0)
Premorbid IQ (WTAR)	111.9(8.3)	107.7(8.1)	108.1(9.2)
CDR	0.0(0.1)	0.3(0.3)[b]	0.4(0.2)[b,c]
Reisberg IADL	0.4(0.4)	0.6(0.7)	0.8(0.6)[b]
DRS-2 (AESS)	12.4(1.9)	11.5(2.1)	9.9(2.0)[b,c]
ADAS-Cog	5.8(2.3)	7.7(3.3)[b]	10.3(3.1)[b,c]
Symptom duration (y)	4.7(3.9)	6.6(4.6)	6.7(4.4)[b]
Hoehn and Yahr stage	1.9(0.7)	2.0(0.5)	2.3(0.7)[b]
UPDRS (Motor)	29.2(16.1)	32.0(11.6)	38.9(17.0)[b]
MoCA	26.7(2.4)	26.3(2.1)	23.3(2.8)[b,c]
Global Z score	+0.32(0.41)	-0.16(0.25)[b]	-0.86(0.38)[b,c]
6. Executive function	+0.39(0.61)	-0.06(0.42)[b]	-0.84(0.70)[b,c]
7. Attention, working memory & processing speed	+0.14(0.48)	-0.19(0.37)[b]	-0.85(0.58)[b,c]
8. Episodic memory	+0.39(0.73)	-0.20(0.68)[b]	-1.07(0.64)[b,c]
9. Visuoperceptual/ visuospatial	+0.38(0.42)	-0.17(0.39)[b]	-0.68(0.60)[b,c]
10. Language[a]	+0.22(0.35)	-0.03(0.58)	-0.37(0.55)[b,c]

Abbreviations: PDD = Patients who met Level II criteria for Parkinson disease with dementia; Global Z score = mean derived from attention, executive function, visuospatial and episodic memory domains; ADAS-Cog = Alzheimer's Dementia Assessment Scale-Cognitive; CDR = Clinical Dementia Rating; DRS-2 (AESS) = Dementia Rating Scale-2 (Age and Education Scaled Score); IADL = Instrumental Activities of Daily Living; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; UPDRS (Motor) = Unified Parkinson's Disease Rating Scale (Motor Component); WTAR = Wechsler Test of Adult Reading for premorbid IQ.
[a] forty-two PD patients did not have two language measures at study entry.
[b] Significantly different from PD-N, Tukey post hoc tests, p <0.05.
[c] Significantly different from PD-MCI: 'One impairment in each of two domains', Tukey post hoc tests, p <0.05.

5.3.2. Selecting the most sensitive tests

Table 5-2 outlines the odds ratios and rankings of each test from the Attention, Executive Function, Episodic Memory, and Visuospatial domains. Both the tests that were selected in the Attention and Visuospatial domains, respectively, were significantly related to progression to PDD. However, in the episodic memory domain only CVLT-II SF Free recall was significantly associated with future progression to PDD. Rey Short Delay was selected, as from a practical standpoint, I suggested it was better to have two different types of episodic memory tests within the cognitive domain to ensure that patients who have both language-based and spatial-based memory deficits can be assessed using this reduced test battery. In the Executive Functioning domain, Trails B was selected as second test based on the test's ability to predict progression to PDD from an unpublished observation made by Dr Daniel Myall, it also should be noted that Trails B was only marginally non-significant in this analysis. This resulted in a 10 neuropsychological test battery consisting of the Map Search Test and Digit Ordering (Attention), Stroop Interference and Trails B (Executive), Picture Completion and Rey Copy (Visuospatial), and CVLT-II SF Free Recall and Rey Short Delay (Episodic Memory). In the Language domain, no odds ratios were calculated as too few patients received the Boston Naming Test at baseline, leaving only two tests in the cognitive domain (DRS-2 similarities sub-test, and ADAS-Cog language components).

Table 5-2. Ranking and odds ratio of each neuropsychological test assessed per cognitive domain (excluding the language domain)

Domain	Test	Odds ratio
Attention	TEA (Map Search)	0.19 (0.08-0.38)[a]
	Digit Ordering	0.53 (0.28-0.90)[a]
	Stroop word	0.64 (0.21-1.83)
	Trails A	0.85 (0.44-1.62)
	Stroop colour	1.02 (0.39-2.86)
	Digits Forwards and Backwards	1.61 (0.68-4.06)
Executive Function	Stroop Interference	0.38 (0.21-0.64)[a]
	Trails B	0.61 (0.35-1.04)
	Category Fluency	0.65 (0.34-1.20)
	Category Switching	0.73 (0.39-1.32)
	Action Fluency	0.99 (0.58-1.69)
	Letter Fluency	1.18 (0.72-1.95)
Visuospatial	Picture Completion	0.51 (0.26-0.93)[a]
	Rey Copy	0.64 (0.41-0.96)[a]
	JLO	0.69 (0.41-1.15)
	VOSP	0.73 (0.40-1.32)
Episodic Memory	CVLT-II SF Free recall	0.44 (0.19-0.91)[a]
	CVLT-II SF Short delay	0.72 (0.32-1.54)
	Rey Short delay	0.74 (0.22-2.32)
	Rey Long delay	0.84 (0.24-2.92)
	CVLT-II SF Long delay	1.24 (0.53-3.09)

Abbreviations: CVLT-II SF, Californian Verbal Learning Test - Second Edition, Short Form; JLO, Judgement of Line Orientation; TEA, Test of Everyday Attention; VOSP, Visual Object and Space Perception Battery.
[a]*Significant, $p < 0.05$. Here, odds ratio refers to the odds of a patient who develop PDD four-years later performing poorly on a specific neuropsychological test compared to the odds of a patient who does not progress to PDD performing poorly on the same test.*

5.3.3. Effect of reduced test battery on selection of PD-MCI groups

When the restricted 10 neuropsychological test battery was used (two tests per cognitive domain, ten in total), the number of patients in each PD-MCI group changed, relative to the full 24 neuropsychological battery. Using the PD-MCI 'two in one domain' criterion, the size of the group reduced from 42 patients to only 22 patients, whereas using the PD-MCI 'one in each of two domains' criterion the group grew from 22 patients to 25 patients (Figure 5-1A

and Figure 5-1B). The percentage of patients captured by each of the PD-MCI groups, respectively, who later converted to PDD increased when a restricted 10 neuropsychological test battery was employed increased for both PD-MCI criteria (PD-MCI 'two impairments in one domain', Full 24 neuropsychological test battery: 50% converted, n = 21; Reduced 10 neuropsychological test battery: 73% converted, n = 16; PD-MCI 'one in each of two domains' Full 24neuropsychological test battery: 14% converted, n = 3; Reduced 10 neuropsychological test battery: 24% converted, n = 6). An increase in the proportion of patients who converted to PDD at follow-up within each PD-MCI group was due to patients who did not progress to PDD no longer meeting PD-MCI criteria when applied to a 10 neuropsychological test battery. This was expected as when more sensitive tests are used, a smaller number of patients will meet each PD-MCI criterion, but the proportion of patients who late develop PDD within each group should increase as there are fewer false positives.

A.

B.
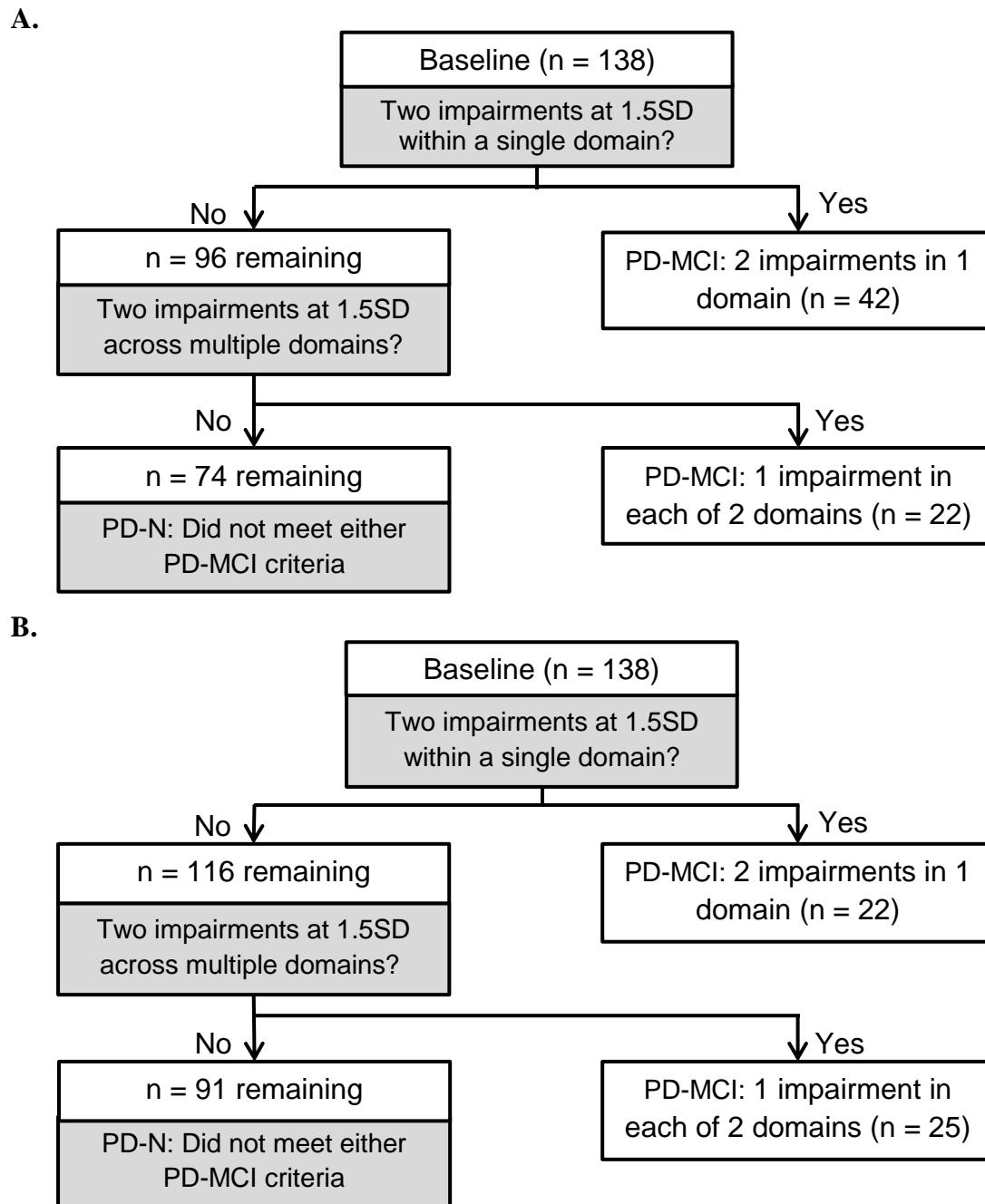
Figure 5-1. PD-MCI criterion application. (A) PD-MCI selection when applied to the full 24 neuropsychological test battery. (B) PD-MCI selection when applied to the reduced 10 neuropsychological test battery.

5.3.4. Risk of PDD progression

There was no evidence of a difference in relative risk (RR) of developing PDD between the groups classified using the PD-MCI 'two impairments in one cognitive domain' criterion, when applied to the reduced 10 neuropsychological test battery or the full 24 neuropsychological test battery (Full 24 neuropsychological test battery RR = 6.9, 95% CI 3.3-14.6; Reduced 10 neuropsychological test battery RR = 7.0, 95% CI 3.8-12.6). Both were also able to identify patients at significantly higher risk of developing PDD four-years later then the group of patients did not meet each of these criterions, respectively. Unlike when applied to the full 24 neuropsychological test battery, the PD-MCI 'one impairment in each of two domains' (but never both within a single cognitive domain) group identified using the reduced 10 neuropsychological test battery group had an increased risk of PDD compared to the remaining PD-N patients, unlike when this criterion was applied to the full 24 neuropsychological test battery (Full 24 neuropsychological test battery RR = 2.5, 95% CI 0.7-8.8; Reduced 10 neuropsychological test battery RR = 3.6, 95% CI 1.3-9.5).

As both PD-MCI criteria identified patients who were at an increased risk of future PDD, we decided to combine them. This means that we are no longer restricting the PD-MCI patient's impairments to being within or across cognitive domains. This new combined PD-MCI criterion of 'two impairments at -1.5SD anywhere' identified patients who were at a greater risk of imminent PDD (n = 47; 47% converted to PDD; RR = 7.1, 95% CI 3.2-16.1). There was no evidence, however, of a difference when the RR was compared to the PD-MCI group who had 'two impairments in one cognitive domain' using the reduced 10 neuropsychological test battery, even though all the patients who met the criterion for PD-MCI 'one impairment in each of two domains' are captured by this combined criterion. This suggests that when a restricted 10 neuropsychological test battery that consists of sensitive

tests is used, it can identify at risk PD-MCI patients who have impairments <u>within</u> a single cognitive domain and <u>across</u> multiple cognitive domains.

5.3.5. Pattern of domain impairments when the test battery is reduced 10 neuropsychological test battery

Figure 5-2 shows the pattern of domain impairments at baseline in the PD-MCI group who (A) had at least 'two impairments at -1.5SD within a <u>single</u> cognitive domain' (Figure 5-2A), (B) had 'one impairment at -1.5SD in each of two domains' (never two in the same cognitive domain; Figure 5-2B) and (C) had at least 'two impairments at -1.5SD <u>anywhere</u>' (Figure 5-2C) when applied to a reduced 10 neuropsychological battery. Note that multiple cognitive domain impairments are therefore different due to the criterions. In Figure 5-2A, multiple cognitive domain impairments are defined as two impairments in each of two or more cognitive domains (i.e. at least four impairments), while in Figure 5-2B and Figure 5-2C, multiple cognitive domain impairments are defined as two impairments across two or more cognitive domains (i.e. only two or more impairments).

5.3.5.1. PD-MCI group defined as having at least 'two impairments at -1.5SD within a <u>single</u> cognitive domain'

In Figure 5-2A, nine of the 22 patients who met the PD-MCI criterion of 'two impairments in a single domain' had multiple cognitive domain impairments (defined above). Eighty-nine percent of these patients converted to PDD at follow-up (8 of 9). Sixty-two percent of those with single cognitive domain impairments (8 of 13) converted to PDD. The PD-MCI patients who had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not, had a mixture of other cognitive domains involved (episodic memory and executive, n = 2; episodic memory and attention, n = 1; and episodic memory, executive

and attention, n = 1). Multiple cognitive domain impairments that did not include episodic memory were: executive and attention, n = 3; attention and visuospatial, n = 1; and executive, attention and language, n = 1. None of the PD-MCI patients had single cognitive domain impairments in the language domain. The rest of the single cognitive domain impairments were spread over the other four cognitive domains (episodic memory, n = 4; executive, n = 4; visuospatial, n = 1; and attention, n = 4). Again, there was no obvious pattern to the cognitive domains impaired and conversion to PDD, but about half of the patients who later converted to PDD had impairments in multiple cognitive domains.

5.3.5.2. PD-MCI group defined as having 'one impairment at -1.5SD in <u>each of two domains</u>' (but never two in the same cognitive domain)

In Figure 5-2B, all 25 PD-MCI patients in this category had multiple cognitive domain impairments due to this definition of the PD-MCI. The PD-MCI patients who had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not, had a mixture of other cognitive domains involved (episodic memory and executive, n = 1; episodic memory and attention, n = 5; episodic memory, executive, attention and visuospatial, n = 3; episodic memory, attention, executive, and language, n = 4; episodic memory, attention and visuospatial, n = 1; episodic memory, executive and visuospatial, n = 1; episodic memory and language, n = 1; episodic memory and visuospatial, n = 3; and episodic memory, visuospatial and language, n = 1). Multiple cognitive domain impairments that did not include episodic memory were: executive and attention, n = 1; attention and visuospatial, n = 2; executive, attention and language, n = 1, and attention, executive, visuospatial and language, n = 1. There was no obvious pattern to the cognitive domains impaired and conversion to PDD, as everyone had multiple cognitive domain impairments.

5.3.5.3. PD-MCI group defined as having at least 'two impairments at -1.5SD on <u>any</u> of the restricted set of 10 tests'

In Figure 5-2C, only one patient out of 47 who met this PD-MCI criterion had a single cognitive domain impairment (Executive domain: Figure 5-2C) and this patient was not a converter to PDD four-years later. Most patients who met this PD-MCI criterion had multiple cognitive domain impairments that included episodic memory, irrespective of conversion or not. Alongside the episodic memory impairment there were a mixture of other cognitive domains involved (episodic memory and attention, n = 6; episodic memory, attention and executive, n = 4; episodic memory, attention, executive and language, n = 4; episodic memory, attention and visuospatial, n = 3; episodic memory, attention, executive and visuospatial, n = 9; episodic memory, attention, executive, language and visuospatial, n =1; episodic memory and executive, n = 2; episodic memory, executive and visuospatial, n = 4; episodic memory, executive, visuospatial and language, n =1; episodic memory and language n = 1; episodic memory and visuospatial, n = 3; and episodic memory, visuospatial and language, n = 1). Multiple cognitive domain impairments that did not include episodic memory were: attention and executive, n = 1; attention, executive and language, n = 1; attention, executive and visuospatial, n = 1; attention and visuospatial, n = 4, and attention, executive, visuospatial and language, n = 1. Again, there was no obvious pattern to the cognitive domains impaired and conversion to PDD.
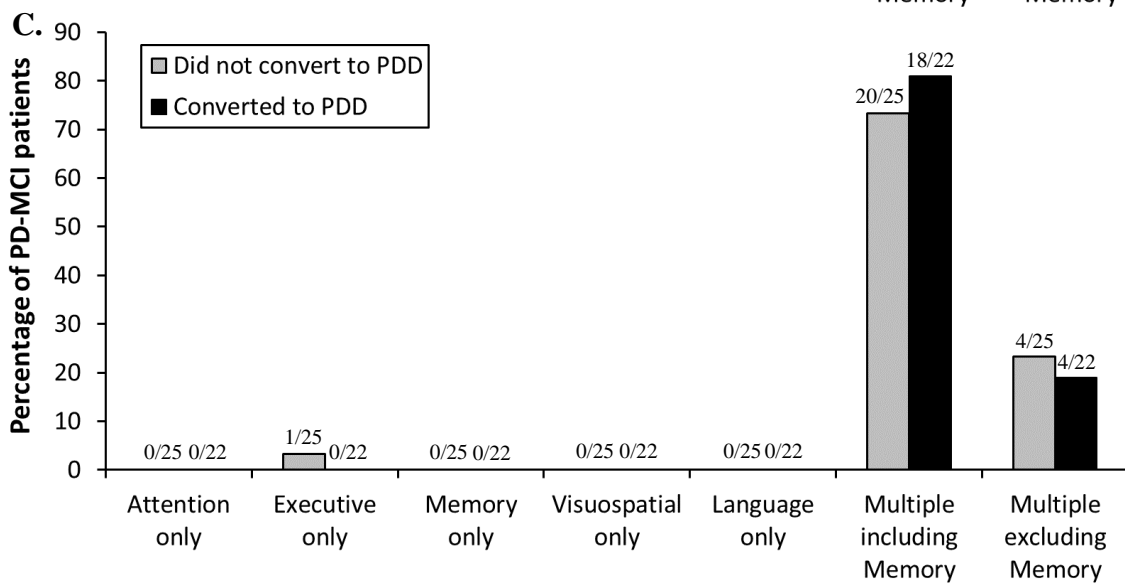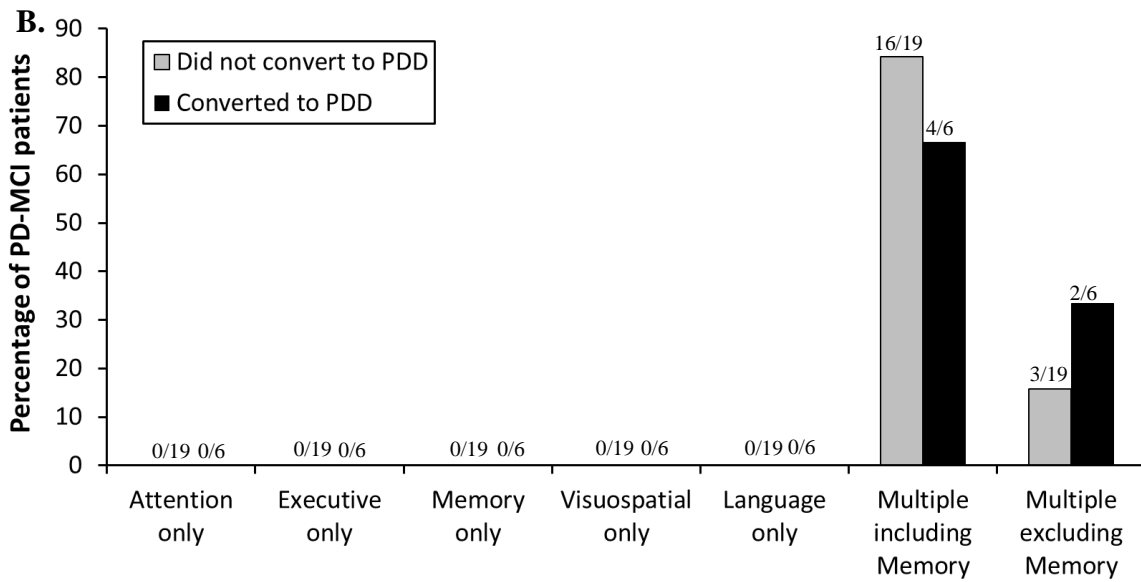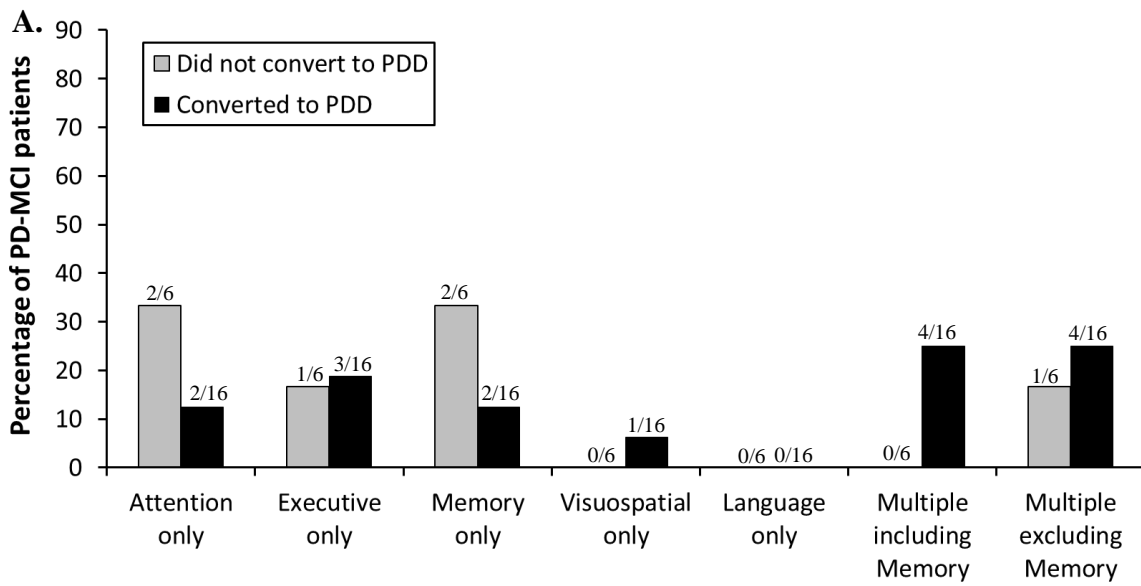
Figure 5-2. *Pattern of Domain Impairments using a reduced 10 neuropsychological test battery. (A) PD-MCI 'two impairments at -1.5SD in a single cognitive domain'. (B) PD-MCI 'one impairment in each of two cognitive domains'. (C) PD-MCI 'two impairments at -1.5SD anywhere'. The grey bars represent the percentage of patients who had two or more impairments in a simple cognitive domain only or two or more impairment in each of two or more cognitive domains and did not develop PDD. The black bars represent the percentage of patients who had two or more impairments in a simple cognitive domain only or two or more impairment in each of two or more cognitive domains and did develop PDD four-years later. The numbers above the bars show the number of patients who have that impairment out of the sub-group.*
NB. Multiple cognitive domain impairments are not equivalent in A, B and C. In A, a multiple cognitive domain impairment is defined as two impairments in each of (or more) cognitive domains, while in B and C, a multiple cognitive domain impairment is defined as two or more tests impaired across two (or more) cognitive domains. This is due to the PD-MCI criteria being different.

5.4. Discussion

We successfully identified a reduced 10 neuropsychological test battery from a comprehensive 24 neuropsychological test battery that both meets standard Level II PD-MCI criteria, and identifies patients who have a high risk of PDD in four-years' time. Our reduced 10 neuropsychological test battery consists of the Map Search and Digit ordering for the Attention domain, Stoop interference and Trails B for the Executive functioning domain, Picture completion and Rey copy for the Visuospatial domain, CVLT-II SF Free recall and Rey short delay for the Episodic Memory domain and DRS-2 similarities and the language components of the ADAS-Cog for the Language domain. Both PD-MCI criteria used in this study captured at risk patients who developed PDD four-years later. That is, when a reduced battery is used that is sensitive to progression to PDD, a PD-MCI criterion that does not restrict the two impairments to only a single cognitive domain is now also able to identify patients who are at high risk of future PDD. While this finding needs to be replicated, it suggests that the most critical factor of PD-MCI when looking at the progression to PDD is not *where* the impairments are located, but rather that the tests used for the evaluation of PD-

MCI status are sensitive at identifying future PDD.

There was no obvious pattern of domain impairment in terms of which cognitive domains were important for progression to PDD. The domain impairment patterns did however indicate that having only one impaired test in each of two or more cognitive domains did not increase an individual's risk of developing PDD four-years later. In fact, the cognitive domain impairment comparison across the three PD-MCI groups, showed that a PD-MCI criterion where a multiple cognitive domain impairment requires 'two impairments in each of two domains' (i.e. at least four impaired scores) does provide a useful indicator of PDD four-years later. This variation in cognitive domain impairment is consistent with the heterogeneous cognitive profile of PD patients who experience cognitive decline (Broeders, de Bie, et al., 2013; Jacobs et al., 1995; Janvin et al., 2006; Mahieux et al., 1998; Woods & Troster, 2003). Patients who had 'two impairments in each of two or more domains' were more likely to develop PDD by the end of the four-year follow-up period. Whereas PD-MCI patients who had 'two impairments in a single domain' were not as likely to progress to PDD at follow-up. The non-PD specific MCI literature supports the notion that impaired performance on multiple tests within a cognitive domain increases the likelihood of future cognitive decline (Jak et al., 2009; Teng et al., 2009). Other studies, using both reduced 10 neuropsychological and comprehensive neuropsychological test batteries and different PD-MCI criterions, have also found that multiple-domain impairments were more common in their PD-MCI cohorts (Goldman et al., 2013; Goldman et al., 2015; Marras et al., 2013) and can be associated with the conversion to dementia (Broeders, de Bie, et al., 2013). Due to the variation between the findings of this study and the literature, it is essential to ensure that PD-MCI Level II criteria recommendations are met and thus PD patients are assessed across all five cognitive domains. As PD-MCI patients who progress to PDD can exhibit a broad range

of different impairments, particularly impairments across multiple cognitive domains.

The sensitive tests selected for the reduced 10 neuropsychological test battery in this study are limited by the initial tests that were included in the comprehensive 24 neuropsychological test battery at the NZBRI. If different tests had been used, the 10 neuropsychological tests selected might be different. This is important to note, that if the same test selection methodology were applied to a different comprehensive neuropsychological test battery from an independent PD researching site, a test that was deemed sensitive in this study may not be selected. This difference in test selection is due to the specific composition of tests grouped together in each cognitive domain, thus if the tests are not identical to the tests which were employed in our original 24 neuropsychological, then there is a chance that different tests will be selected. For instance, Goldman et al. (2015) and this study had seven tests in common when comparing both studies comprehensive test batteries. In both cases, Digits forwards and backwards was not selected in the respective reduced 10 neuropsychological batteries, while Trails B was. In the Goldman et al. (2015) study, they selected category fluency and Boston naming as the two language tests, JLO as a visuospatial test and Trails A as an attention domain test in their reduced 10 neuropsychological test battery. All of these measures were part of our 24 neuropsychological test battery but none were selected as being sensitive to progression to PDD. In addition, tests were grouped into cognitive domains differently in the Goldman et al. (2015) study compared to our study, with category fluency classified as an executive functioning task in our study, but a language measure in Goldman et al. (2015). Similar variations were present when the reduced 10 neuropsychological test battery from this study was compared to the tests identified by Federico et al. (2017). Like Goldman et al. (2015), Federico et al. (2017) selected category fluency in their 10 neuropsychological test battery as

an executive functioning measure (same cognitive domain as our study). Like our study, Trails A, JLO, Digits forwards and backwards and Boston naming were not selected in the 10 neuropsychological battery, and Trails B was in selected in both studies. An important distinction to make is that in both of these comparison studies, tests were selected based on their ability to identify PD-MCI, whereas in this study tests were selected to identify progression to PDD four-years later. This alone should explain the variation in test selection between these studies, despite having some test overlap. This does, however, raise the interesting question of whether tests which are most sensitive to identifying PD-MCI are the same as tests most sensitive to progression to PDD. Given the tests selected by Goldman et al. (2015) and Federico et al. (2017) it would suggest that there could be differences in a tests ability to distinguish between the two cognitive conditions.

Although the test selection approach used in this study is a marked improvement compared to the approach used in Chapter 4, there are still significant limitations. Firstly, excluding patients who have missing tests score in the LR could have biased our results is an obvious limitation of this analysis. Instead, missing test scores could have been imputed using a method such as Flexible Imputation of Missing Data (Van Buuren, 2012). Secondly, using the logistic regression model to determine which two tests per cognitive domain are sensitive to future PDD conversion, and then validating PD-MCI criteria on their RR of future PDD leads to a degree of double dipping. This means the performance of the reduced test battery is likely to be worse than indicated. This could have been overcome by selecting the tests using the logistic regression model in the existing cohort and then testing the reduced test battery on an independent cohort to establish each PD-MCI criteria's ability to identify patients at a high risk of future PDD. Thirdly, LR was used without any form of regularisation, which can result in a poor method for feature selection, especially when

variables are correlated. Here, this is a real issue as the features are neuropsychological tests which are all measuring cognitive performance within the same cognitive domain, thus they will be highly correlated. In addition, using significance as a threshold is also a poor method for deciding what features to select in a multi-variable LR. To overcome these limitations a LASSO, elastic net, LR model could be used where there is a penalty for large coefficients in a model and regularisation to aid with not fitting to noise. This would also improve out-of-sample performance for the reduced 10 neuropsychological test battery generated. This approach to reducing the test battery will be investigated outside of this thesis, given time constraints.

To overcome the small number of patients who converted to PDD during the follow-up period, bootstrapping was used to calculate the CI in the RR analysis. This would have improved the generality of RR scores to other populations, but their use will not overcome the bias resulting from the above limitations. At the NZBRI, we are currently following a new cohort of patients and with time the findings from this analysis can be properly tested by using this second group of patients. The approach used in this Chapter (5) is, however, still a large improvement from that of the previous chapter (4), which based test selection on each test's ability to identify PD-MCI level impairment (i.e. scores below -1.5SD), which was most likely biased due to neuropsychological test constraints. Further improvements could also be made by adopting a leave one out approach. This would enable us to select tests deemed sensitive to progression and then evaluate their utility on an independent patient to determine whether the PD-MCI criterion applied is able to capture patients who later develop PDD.

There were different tests identified in the reduced 10 neuropsychological test batteries selected in Chapter 4 and 5. This is a direct result of the methods used to select the

reduced 10 neuropsychological batteries, as the method used in Chapter 4 selected tests based on the identification of impairment, while in Chapter 5 the tests were selected on their sensitivity to future PDD four-years later. Another approach we could have taken would be to preform ROC tests on the entire tests battery to determine which combination of tests, regardless of which cognitive domain they are from, are the most sensitive to progression to PDD four-years later. This may have highlighted a slightly different combination of tests as being the most sensitive to progression to PDD. Using these different methods to select the neuropsychological tests included in the reduced test batteries could explain why tests identified as being able to differentiate between PD-MCI and PDD in cross-sectional studies have performed poorly when applied to longitudinal studies which look at cognitive decline over time (Biundo et al., 2014; Jacobs et al., 1995; Janvin et al., 2006; Levy et al., 2002; Mahieux et al., 1998; Williams-Gray et al., 2013; Woods & Troster, 2003). Of the two approaches discussed in Chapters 4 and 5, I would recommend the Chapter 5 reduced 10 neuropsychological test battery to be used when one wants to identify patients at risk of progression to PDD over the next four-years. Although the methodology used to reduce the test battery to 10 neuropsychological has clear limitations, the Chapter 5 10 neuropsychological battery does perform better than that of Chapter 4. If this 10 neuropsychological test battery was to be implemented at the New Zealand Brain Research Institute it would take about one-and-a-half hours to conduct the neuropsychological assessment compared to the four-hours that the full 24 neuropsychological test battery currently takes. This would save a significant amount of time and money.

5.5. Conclusions

We have shown that a restricted test battery, consisting of only 10 neuropsychological tests, is able to identify PD patients as PD-MCI who are at an imminent risk of PDD (~4yrs). We

also found that once sensitive tests are used, the two impairments needed for PD-MCI

classification do not have to fall only in a single cognitive domain to be able to identify

patients at the highest risk of future PDD, unlike Chapter 3. Thus, we reconcile the problem

of whether the two impairments needed for PD-MCI classification need to occur within a

single cognitive domain or across cognitive domains, as there was no evidence of a difference

between the RR of progression to PDD when the impairments were and were not restricted to

a single cognitive domain. External validation using an independent patient cohort to verify

whether the tests selected are able to identify PD-MCI patients at-risk of PDD is still needed.

This is essential to confirm the utility of this restricted test battery for future clinical research

and targeted intervention studies.

Chapter 6: Neuropsychiatric symptoms and progression to dementia

6.1. Background

Neuropsychiatric or behavioural symptoms, such as depression, anxiety and hallucinations, are common in Parkinson's disease (PD; Aarsland et al., 1999; Brown & MacCarthy, 1990; Kulisevsky et al., 2008; Lee & Weintraub, 2012; Riedel et al., 2010). There is an association between cognitive decline and an increase in neuropsychiatric symptoms in PD, particularly visual hallucinations (Aarsland et al., 2007; Aarsland et al., 2017; Fenelon, Mahieux, Huon, & Ziegler, 2000; Kulisevsky et al., 2008). Both cognitive decline and neuropsychiatric symptoms are precipitating factors for placement in full time residential care (Aarsland, Larsen, Tandberg, & Laake, 2000).

The highest burden of neuropsychiatric symptoms, particularly depression and hallucinations, occurs in those with dementia (PDD; Bronnick et al., 2005). For example, Aarsland et al. (2007) reported that 89% of patients with PDD experienced at least one neuropsychiatric symptom and 77% experienced two or more. In contrast, the reported presence of neuropsychiatric symptoms in non-demented PD patients has varied between 22% and 87% (Kulisevsky et al., 2008; Lee & Weintraub, 2012). When comparing the presence of neuropsychiatric symptoms, particularly depression, and cognitive status, most studies have found no differences between PD patients classified as having normal cognition (PD-N) and those classified as having mild cognitive impairment (PD-MCI; Dalrymple-Alford et al., 2010; Hobson & Meara, 2015; Pedersen et al., 2013). Broeders, de Bie, et al. (2013), however, reported that PD-MCI patients experienced more depression and anxiety symptoms than PD-N patients. There is a higher prevalence of depression, hallucinations and global neuropsychiatric symptoms in PDD than PD-N patients (Dalrymple-Alford et al.,

2010; Hobson & Meara, 2015) and of depression in PDD compared to PD-MCI patients (Hobson & Meara, 2015).

Despite the fact that neuropsychiatric symptoms often increase in PDD, few studies have directly examined the predictive validity of neuropsychiatric symptoms and progression to PDD. Some of the studies that have looked at the predictive value of neuropsychiatric symptoms, have found that anxiety and/or depression did not predict cognitive decline in PD patients five-years later (Broeders, Velseboer, et al., 2013; Pedersen et al., 2013). Whereas other studies have reported that visual hallucinations, visual illusions, thought disorders, depression and apathy were associated with the progression to dementia four-six years later (Anang et al., 2014; Fitts et al., 2015; Janvin et al., 2006; Pedersen et al., 2009). All of the studies which have found a relationship between neuropsychiatric symptoms and future PDD have not used Level II criteria to cognitively classify their patient samples.

Hallucinations are the most thoroughly studied behavioural symptom in regard to future PDD. In contrast to other behavioural symptoms, there is consistent evidence that hallucinations are linked to cognitive decline and are predictive of future dementia (Aarsland et al., 2003; Aarsland et al., 2004; Anang et al., 2014; Factor et al., 2003). All of these studies found that hallucinations were associated with progression to PDD two-eight years later. In contrast, Fenelon et al. (2000) found that cognitive impairment was an independent predictor of visual hallucinations, but they did not measure the relative influence of cognitive impairment in relation to hallucinations. Thus, it is unclear whether hallucinations are predictive of future PDD. In chapter 3 we observed that a greater proportion of patients who converted to PDD four-years later experienced hallucinations at study entry compared to those who did not develop PDD (Wood et al., 2016), but we did not determine whether the increased occurrence of hallucinations at study entry was predictive of future PDD.

A series of recent studies have confirmed a link between mild cognitive impairment in PD (PD-MCI) and the progression to dementia (Broeders, Velseboer, et al., 2013; Hobson & Meara, 2015; Janvin et al., 2006; Pedersen et al., 2013), but the relationship between neuropsychiatric symptoms in a Level II PD-MCI population and future progression to PDD has never been explored. In Part One of this study, we investigated the differences between three cognitive groups of PD patients (PD-N, PD-MCI and PDD) from a perspective of a range of neuropsychiatric measures (such as hallucinations, depression and apathy) reported by the patient and their significant other. In Part Two, we then examined prospectively the longitudinal cognitive outcome of the non-dementing patients (i.e. PD-N and PD-MCI patients) to determine whether there were differences in baseline neuropsychiatric measures between patients who developed PDD four-years later and those that did not. Finally, in Part Three, we examined whether the neuropsychiatric measures that were potentially predictive of future PDD could provide any additional value over and above global cognitive function, age and motor function, which are all known predictors of future PDD.

6.2. Methods

6.2.1. Participants

A convenience sample of 158 PD patients were used for Part One of the study, which evaluated the differences between neuropsychiatric symptoms and cognitive status (see Figure 6-1). This sample consisted of 77 PD-N, 46 PD-MCI and 35 PDD patients all of whom received comprehensive Level II neuropsychological and neuropsychiatric assessments (Table 6-1). Part Two of the study, which examined the association between the presence of neuropsychiatric symptoms at study onset and future progression to PDD (4 years later), comprised of the 123 non-demented PD patient sub-set of the Part One sample, that is,

those with PD-N and PD-MCI. The neuropsychological and neuropsychiatric assessments were repeated at the four-years follow-up assessment (range, 3.5-4.5 years; Figure 6-1). At study entry, two patients in the PDD group did not receive the Geriatric depression scale (GDS) and one of these patients also did not receive the Parkinson's disease questionnaire (PDQ). One PD-N patient, two PD-MCI patients and one PDD patient were not evaluated at baseline only with the Unified Parkinson's Disease Rating Scale (UPDRS). The comprehensive neuropsychological assessment, PD diagnostic procedure and exclusion criteria were the same as those detailed in Chapter 3. The average length of motor symptoms experienced by patients in this study was 5.8 years (SD = 4.3 years).

As in chapter 3, progression to PDD before the end of the 4.5-year follow-up period was treated as an a priori end-point, with no subsequent follow-up. All participants took their usual medications on the day of testing to allow optimal performance during the morning testing sessions. The study was approved by a local ethics committee of the New Zealand Ministry of Health, with informed consent provided by all participants.
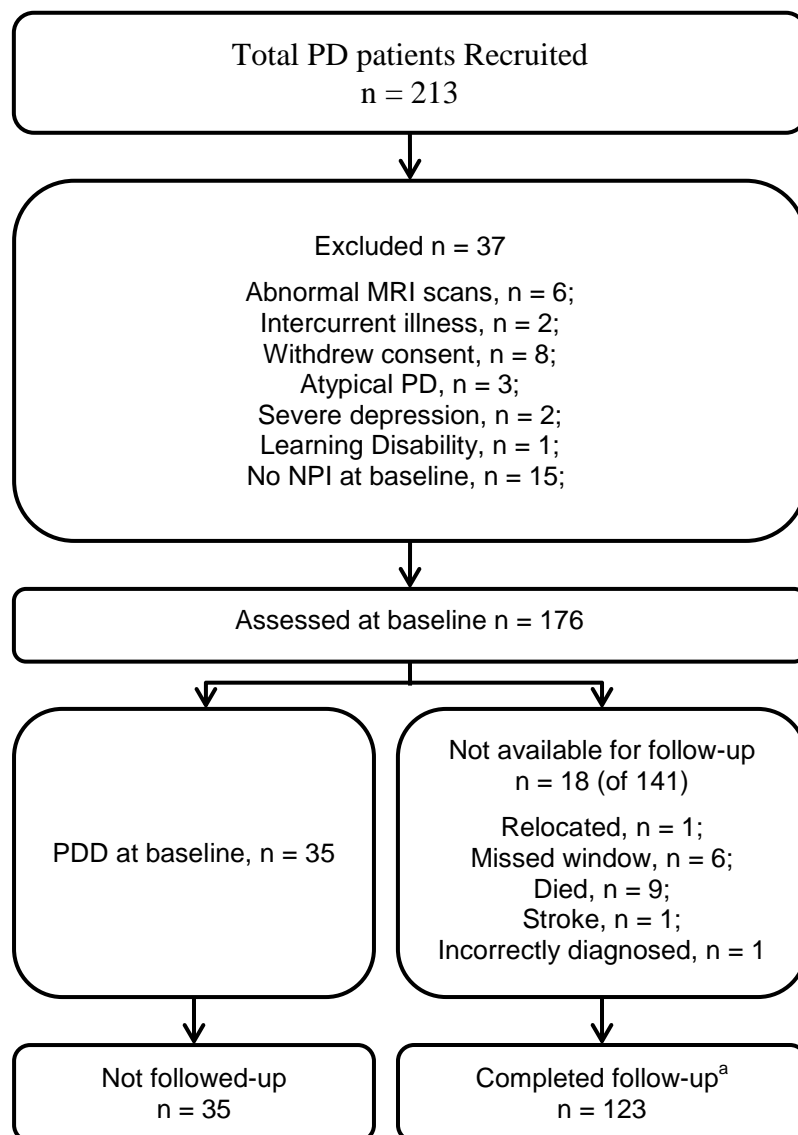
Figure 6-1. Participant recruitment, exclusions and total followed over 4 years. PD = Parkinson's disease; PDD = Parkinson's disease with dementia.
[a] Assessments were conducted at baseline and then again every one to two years later; patients with dementia were not followed further.

Table 6-1. Demographics and neuropsychological data at study entry [mean (SD)]

	PD-N	PD-MCI	PDD
Demographics			
Sample size (n)	77	46	35
Converted to PDD (n)	6	21	N/A
Sex, M:F	48:29	32:14	27:8
Age	66(8)	68(7)	73(7)[a,b]
Education (y)	13(3)	13(3)	13(3)
PD Specific Measures			
PD duration (y)	6.0(4.0)	6.7(4.1)	11.3(7.4)[a,b]
Hoehn and Yahr stage	2.0(0.5)	2.3(0.6)[a]	3.2(0.7)[a,b]
UPDRS (Motor)	26.0(11.4)	35.3(14.9)[a]	56.7(19.9)[a,b]
Activities of Daily Living			
CDR	0.1(0.2)	0.4(0.2)[a]	1.3(0.5)[a,b]
Reisberg IADL	0.5(0.5)	0.7(0.6)[a]	2.0(0.6)[a,b]
Cognitive Assessments			
Premorbid IQ (WTAR)	111.5(8.4)	108.8(8.40)	106.5(10.7)[a]
DRS-2 (AESS)	12.2(2.1)	10.1(2.6)[a]	5.0(2.6)[a,b]
ADAS-Cog	6.1(2.7)	9.8(3.4)[a]	22.4(8.8)[a,b]
MoCA	26.9(2.1)	23.4(3.2)[a]	17.1(3.9)[a,b]
Global Z score	+0.20(0.46)	-0.77(0.51)[a]	-1.84(0.48)[a,b]

Abbreviations: PDD = Patients who met Level II criteria for Parkinson's disease with dementia; PD-MCI = Patients who met Level II criteria for Parkinson's disease with mild cognitive impairment; PD-N = The remaining patients who did not met criteria for PDD or PD-MCI were classified as having normal cognition; PD duration = defined as the duration from the first symptom experienced by the patient; Global Z score = mean derived from attention, executive function, visuospatial and episodic memory domains; ADAS-Cog = Alzheimer's Dementia Assessment Scale-Cognitive; CDR = Clinical Dementia Rating; DRS-2 (AESS) = Dementia Rating Scale-2 (Age and Education Scaled Score); IADL = Instrumental Activities of Daily Living; MoCA = Montreal Cognitive Assessment; N/A = Not Applicable; UPDRS (Motor) = Unified Parkinson's Disease Rating Scale (Motor Component); WTAR = Wechsler Test of Adult Reading for premorbid IQ.
[a]Significantly different from PD-N, ANOVA followed by Tukey post hoc tests, $p<0.05$.
[b]Significantly different from PD-MCI, ANOVA followed by Tukey post hoc tests, $p<0.05$.

6.2.2. Determination of cognitive status

Patients were classified as PDD as described in Chapter 3 using established Movement

Disorder Society-Task Force (MDS-TF) PDD criteria (Emre et al., 2007). The remaining

patients were classified as either PD-MCI or PD-N. Patients were classified as PD-MCI using

the PD-MCI criterion of 'two impairments at -1.5SD in a single cognitive domain', which

was consistent with MDS-TF Level II PD-MCI criteria. As before, all remaining patients who

did not meet either the PD-MCI or PDD criteria were classified as having 'normal' cognition

(PD-N).

6.2.3. Materials

6.2.3.1. Neuropsychological assessment

The same comprehensive neuropsychological assessment was administered as described in

Chapter 3 (see Appendix A for neuropsychological test details).

6.2.3.2. Neuropsychiatric assessment

The Neuropsychiatric Inventory (NPI) was used to assess the frequency and severity of 12

common neuropsychiatric symptoms (delusions, hallucinations, agitation/aggression,

depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition,

irritability/lability, aberrant motor behaviour, sleep and night-time behaviour disorders and

appetite/eating changes) as reported by each patient's caregiver or significant other

(Cummings, 1997; Cummings et al., 1994). The caregiver rated the frequency of each

symptom experienced on a scale of one-four and the severity of each symptom on a scale of

one-three, based on scripted questions. These two scores were then multiplied together to

generate a sub-score for each neuropsychiatric symptom. The sub-scores for each

neuropsychiatric symptom were then added together to produce a total NPI 10-item score (scores from the sleep and night-time behaviour disorders and appetite/eating changes sub-scales were excluded in this total score). The original 10-item version of the NPI is a valid measure and is widely used. We decided to use the 10-item version in this study but also collected the additional information from the newer two-items (sleep and night-time behaviour disorders and appetite/eating changes).

The short form 15-point GDS (D'Ath, Katona, Mullan, Evans, & Katona, 1994) is comprised of 15 questions with yes or no answers, based on the patient's self-report of how they have been feeling over the past week. The GDS is recommended for use in PD populations by Weintraub, Saboe, and Stern (2007). The initial four questions act as screening questions and the questionnaire is terminated after these initial four questions if the individual's responses to all four indicate an absence of depression symptoms. Otherwise the questionnaire is continued until all 15 questions have been answered. Each question that is answered positively for a depression symptom is scored as one point, with 15 points being the highest (i.e. worst) possible total score.

The PDQ (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995) comprises 39 PD-specific self-rated questions. Patients are required to rate how their PD has affected them over the past month on a scale of zero-four (never, occasionally, sometimes, often or always/cannot do at all). In this study, only the hallucinations, distressing dreams and the four-items from the emotional well-being sub-section (totalling six items) of the PDQ were used.

Two items, indicative of hallucinations and depression, were extracted from Part I of the original UPDRS (Fahn, Elton, & Committee, 1987) and again from the revised Movement Disorders Society-UPDRS (MDS-UPDRS; (Goetz et al., 2008). Each patient rated their

experience of each symptom over the past week on a severity scale of zero-four (normal, slight, mild, moderate and severe). Two different versions of the UPDRS were employed in the study as the newer MDS-UPDRS scale was released in 2008 after the initial data collection had begun and it was therefore introduced after baseline testing had commenced. Seventy-seven patients received the original UPDRS and 77 received the revised MDS-UPDRS, with four patients receiving neither scale. These two versions of the UPDRS are comparable (Goetz et al., 2008). The only difference in the hallucination scales of the two versions is that the MDS-UPDRS does not include vivid dreams. The depression items are conceptually similar in each version but the emphasis is slightly different (Goetz et al., 2008). With both versions of the UPDRS being comparable we took each patient's score for the hallucinations and then depression items and combined each scale to form a single UPDRS score for hallucinations and then depression for each patient, termed the 'Unified Hallucination' and 'Unified Depression' scores respectively.

6.2.4. Analysis

In Part One, we compared several baseline neuropsychiatric symptoms across the three cognitive groups (n = 158; PD-N vs. PDD; PD-MCI vs. PDD; PD-MCI vs. PD-N) using paired Receiver Operator Curve (ROC) tests to determine whether the prevalence of behavioural symptoms differed across groups. In Part Two, the association between progression to PDD four-years later and baseline neuropsychiatric symptoms was examined using paired ROC tests in all non-demented patients (n = 123). If two tests which measured the same neuropsychiatric symptom were associated with future progression to PDD, the difference between these two ROCs was tested to determine whether one measure was a better discriminator than the other. In Part Three, a logistic regression model, comprising of cognition, age, motor function and those neuropsychiatric symptoms that were associated

with progression to PDD, was used to determine whether neuropsychiatric symptoms added any additional predictive value over and above cognition, age and motor function in terms of future progression to PDD. The ROC and logistic regression analyses were conducted in R (v.3.3.2) using the pROC open-source package developed by Robin et al. (2011) with confidence intervals produced by a bootstrapping procedure.

6.3. Results

6.3.1. Part One: Neuropsychiatric symptoms and cognitive status at study entry

Table 6-1 describes the demographic and neuropsychological profiles of the three groups of patients included in this study at study entry. There was approximately double the number of males than females in each of the three cognitive groups but no significant differences in levels of education. The PDD group was significantly older, had experienced PD symptoms for longer, had more advanced Hoehn and Yahr staging, UPDRS III, ADL, ADAS-Cog, total NPI, GDS, lower MoCA and global cognitive scores than both the PD-N and PD-MCI groups. The PDD group had significantly lower premorbid IQ, higher CDR and lower DRS-2 scores than the PD-N group, but there were no differences on these measures between the PDD and PD-MCI groups. The PD-MCI group did however have significantly worse Hoehn and Yahr staging, UPDRS III, ADL, ADAS-Cog scores, MoCA and global cognitive scores than the PD-N group.

Table 6-2 shows the baseline neuropsychiatric scores for each of the cognitive groups (PD-N, PD-MCI and PDD). There were no differences in any of the neuropsychiatric measure scores between the PD-N and PD-MCI groups. In contrast, the PDD group had higher aggression, apathy, delusion and NPI total scores on the NPI, were more isolated and lonely and had more distressing dreams on the PDQ, had higher hallucination and depression

scores on the UPDRS and higher GDS scores then both the PD-N and PD-MCI groups,

respectively. The PDD group also had higher hallucination scores on the NPI, hallucination,

depression, anxiety and aggression scores on the PDQ compared to the PD-N group.

Table 6-2. Neuropsychiatric measures at study entry [mean (SD)]

	PD-N	PD-MCI	PDD
NPI			
Total score	4.0(7.2)	4.2(7.5)	9.8(8.1)[a,b]
Hallucinations	0.2(1.2)	0.5(1.7)	1.4(3.0)[a]
Depression	0.7(1.8)	1.0(2.3)	1.5(2.6)
Anxiety	0.8(1.9)	1.4(2.1)	1.5(2.2)
Aggression	0.2(1.5)	0.2(1.3)	1.3(2.2)[a,b]
Apathy	0.9(2.3)	0.6(1.8)	2.1(2.9)[a,b]
Delusions	0.1(0.9)	0.0(0.1)	0.8(2.6)[a,b]
Euphoria	0.1(0.3)	0.0(0.0)	0.0(0.0)
Irritability and Liability	0.6(2.0)	0.2(1.0)	0.7(1.7)
Aberrant Motor Behaviour	0.2(1.4)	0.2(0.5)	0.3(0.9)
Sleep and Night time Behaviour Disorders	1.3(2.5)	1.4(2.6)	1.3(2.5)
Appetite and Eating Disorders	0.4(1.7)	0.3(1.2)	0.5(1.8)
PDQ			
Hallucinations	0.4(1.0)	0.6(0.9)	1.1(1.4)[a]
Depression	0.6(1.0)	0.8(1.0)	1.2(1.1)[a]
Anxiety	1.0(0.9)	1.2(1.0)	1.5(1.2)[a]
Aggression	0.4(0.7)	0.4(0.7)	0.8(1.0)[a]
Isolated and Lonely	0.4(0.8)	0.3(0.5)	0.9(1.0)[a,b]
Weepy and Tearful	0.6(1.0)	0.8(1.1)	0.6(0.7)
Worried about future	1.1(1.1)	1.0(1.2)	1.1(1.0)
Distressing dreams	0.5(0.9)	0.5(0.8)	1.3(1.4)[a,b]
UPDRS			
Unified Hallucinations	0.3(0.6)	0.7(0.9)	1.2(1.2)[a,b]
Unified Depression	0.4(0.8)	0.4(0.6)	1.1(1.0)[a,b]
GDS	0.9(2.4)	1.2(2.3)	2.8(3.2)[a,b]

Abbreviations: PDD = Patients who met Level II criteria for Parkinson's disease with dementia; PD-MCI = Patients who met Level II criteria for Parkinson's disease with mild cognitive impairment; PD-N = The remaining patients who did not met criteria for PDD or PD-MCI where classified as having normal cognition; GDS = Geriatric Depression Score; NPI = Neuropsychiatric Inventory; PDQ =Parkinson's disease Questionnaire; UPDRS = Unified Parkinson's disease Rating Scale.
[a]*Significantly different from PD-N, ANOVA followed by Tukey post hoc tests, p<0.05.*
[b]*Significantly different from PD-MCI, ANOVA followed by Tukey post hoc tests, p<0.05.*

Figure 6-2 depicts the ROC AUC values for each neuropsychiatric symptom to describe their ability to distinguish between the cognitive groups (PD-N vs. PDD; PD-N vs. PD-MCI; PD-MCI vs. PDD). Several symptoms were assessed across each of the NPI, PDQ and UPDRS scales and these measures provided consistent evidence of greater levels of hallucinations, depression, anxiety, and aggression in PDD versus PD-N groups. There were also sub-components of the NPI and PDQ which indicated greater levels of apathy, loneliness, and distressing dreams in PDD versus PD-N groups. When the PDD group was compared to the PD-MCI group, a similar overall pattern persisted. However, the ROC AUC values were generally smaller, and there was reduced evidence for differences in several of the sub-components measured, especially in anxiety, hallucinations and depression. There were few differences between the PD-N and PD-MCI groups, with only UPDRS hallucinations significantly differing between the two groups.
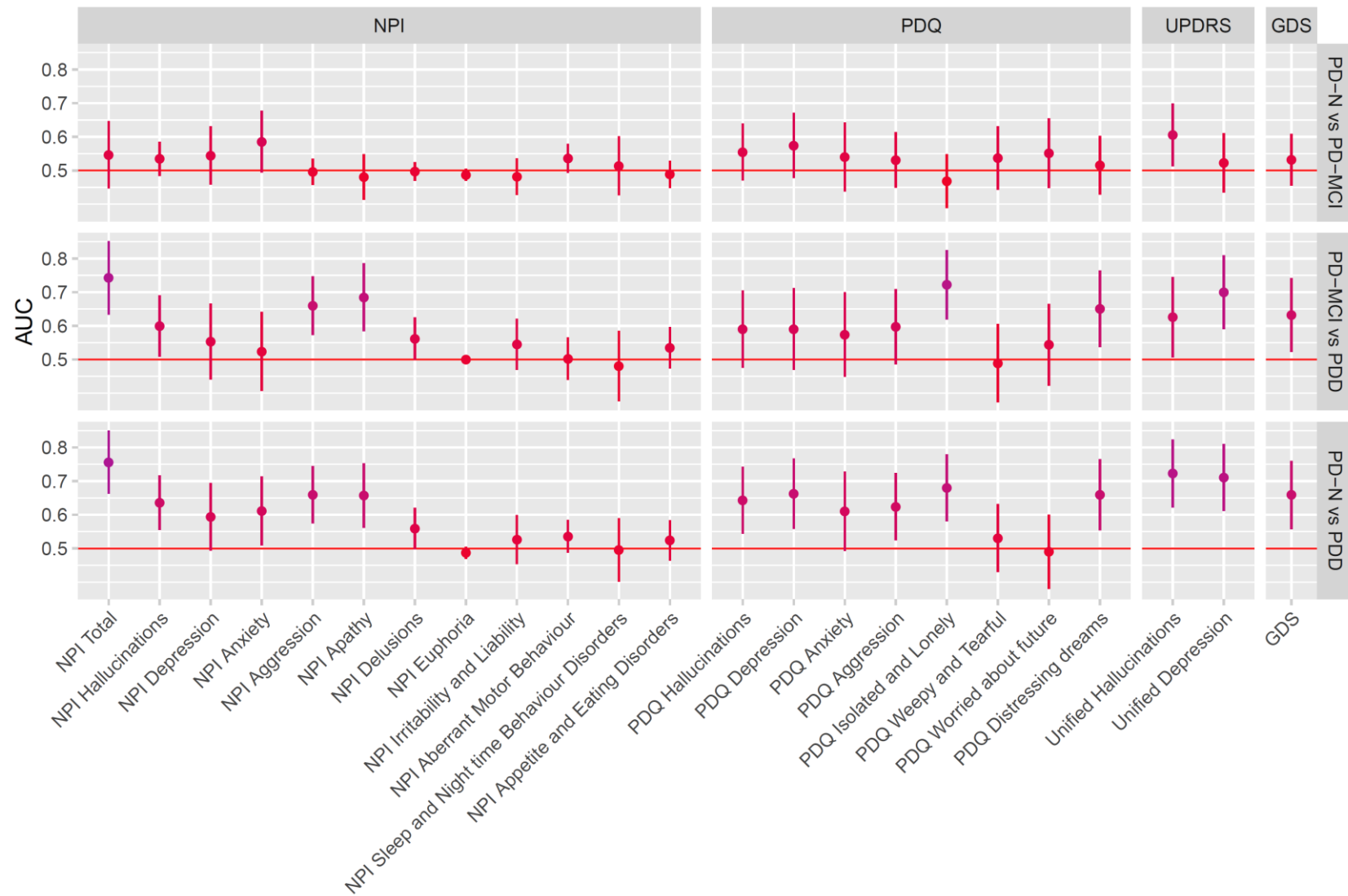
Figure 6-2. *ROC AUC values for each behavioural symptom and the difference in prevalence between cognitive groups*

6.3.2. Part Two: Progression to PDD and neuropsychiatric symptoms

Part one confirmed that PDD patients have a greater prevalence of behavioural symptoms than non-dementing PD patients, while there were few differences between the PD-N and the PD-MCI groups. Next, the relationship between conversion to PDD during the 4-year follow-up period and neuropsychiatric symptoms was examined. In the non-demented patients at study entry, baseline neuropsychiatric symptoms were examined for differences in those who converted to PDD over the follow-up period (n = 27; 21 PD-MCI, 6 PD-N) in comparison to those that did not develop dementia (n = 96).

There were very few neuropsychiatric symptoms which indicated an ability to distinguish patients who converted to PDD from those that did not convert over the four-year follow-up period (Figure 6-3). NPI total score (AUC = 0.62, 95% CI = 0.50-0.75) exhibited a small association with future progression to PDD. Most of the NPI sub-scale scores and GDS (AUC all < 0.62) were not significantly associated with PDD conversion, except for the anxiety sub-scale of the NPI which showed a marginal relationship to future PDD (AUC = 0.62, 95% CI = 0.50-0.73). Patient-reported hallucinations, using items from the PDQ and UPDRS, had the strongest relationship of all the neuropsychiatric symptoms to future conversion to PDD (PDQ: AUC = 0.70, 95% CI = 0.60-0.80; UPDRS: AUC = 0.69, 95% CI = 0.57-0.80). In contradistinction, the hallucination sub-scale score on the NPI (reported by the significant other) was not significantly associated with progression to PDD (AUC = 0.55, 95% CI = 0.48-0.62). Furthermore, when the AUCs of the three hallucination scales were directly compared, those from the PDQ and UPDRS each had a stronger relationship to future dementia than the NPI sub-scale (p < 0.05). In contrast to the majority of the neuropsychiatric symptoms examined in this study, cognition (AUC = 0.87, 95% CI = 0.79-0.94), age (AUC =

0.73, 95% CI = 0.63-0.84) and motor function (AUC = 0.78, 95% CI = 0.64-0.91) were all

more useful when predicting future conversion to PDD.
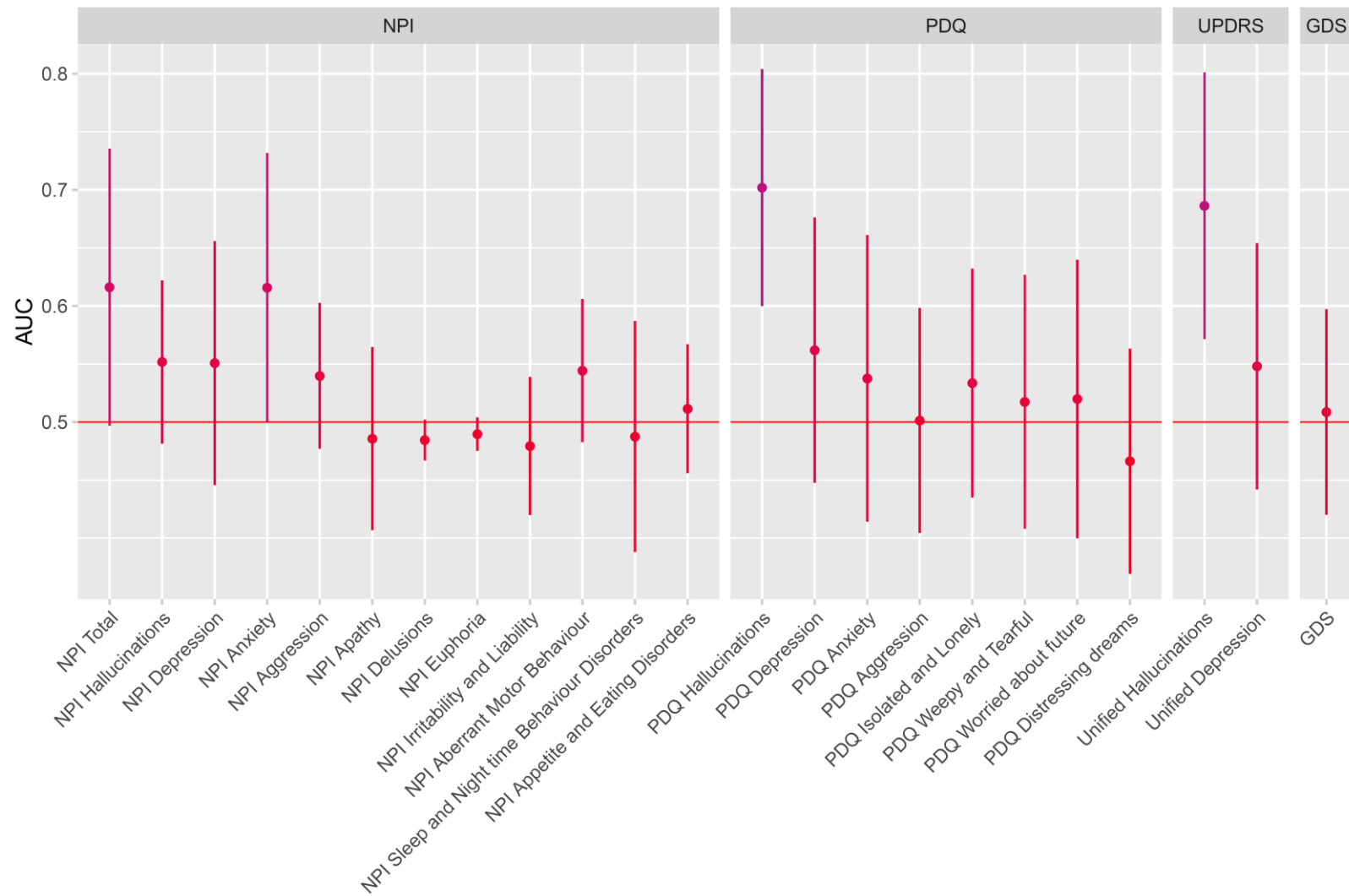
Figure 6-3. *The ability of ROC AUC values of behavioural measures to predict future PDD (within 4-years)*

Of the 27 patients who converted to PDD during the four-year follow-up period, 21 were classified as PD-MCI and six as PD-N at baseline. Due to the small number of patients who converted to PDD from the PD-N baseline group we were only able to examine the relationship between behavioural symptoms and future progression to PDD in the PD-MCI sub-group of 21 patients. Once again there were few behavioural measures that were associated with progression to PDD four-years later. Patient-reported hallucinations on the PDQ and UPDRS were associated with progression to PDD (PDQ: AUC = 0.67, CI = 0.54-0.81; UPDRS: AUC = 0.66, CI = 0.51-0.81), but this association was weaker than when the entire group of non-demented PD patients was considered. The baseline characteristics with the strongest associations to future progression in the PD-MCI sub-group were cognition (AUC = 0.80, CI = 0.67-0.93) and age (AUC = 0.76, CI = 0.62-0.90).

Of the 21 PD-MCI patients who converted to PDD four-years later, 11 reported hallucinations on the PDQ hallucinations question (scores ranging from one-three), 12 reported hallucinations on the UPDRS hallucinations question (scores ranging from one-three) but only four were reported to experience hallucinations by their significant other on the NPI hallucinations sub-scale. Of the six patients in the PD-N group at study entry who converted to PDD, five experienced hallucinations according to the PDQ hallucinations question (scores ranging from one-two), three according to the UPDRS hallucinations questions (scores ranging from one-two) and none were reported to experience hallucinations by their significant other with the NPI hallucinations sub-scale.

6.3.3. Part Three: Are patient-reported hallucinations indicative of future progression to PDD?

Previously (Chapter 3) we reported that patients classified as PD-MCI using the specific criterion of 'two impairments at -1.5SD in a single cognitive domain' were at a much greater risk of developing dementia than those not captured by this criterion (Relative Risk = 7.2, 95% CI 3.4-16.6, p <0.001). Patient-reported hallucinations were the only neuropsychiatric symptom found to be associated with future PDD from the ROC analysis. A logistic regression model was developed to assess whether patient-reported hallucinations added any extra predictive value on top of age, cognitive ability and motor function to progression to PDD. The model was first applied to all the non-demented baseline PD patients (n = 123) and then again to the PD-MCI sub-group (n = 46) only. The model comprised of each patient's global cognitive Z scores, age, motor function and unified hallucinations score. The unified hallucination score was used as the patient-reported hallucination measure because clinically it is more widely utilised than the PDQ hallucination measure. When we interrogated the model with all 123 non-dementing PD patients we found that neither hallucinations (OR = 1.70, 95% CI = 0.73-4.03) nor motor function (OR = 1.02, 95% CI = 0.97-1.09) added any significant information when distinguishing patients who progressed to PDD 4 years later from those that did not beyond that provided by their global cognitive ability (OR = 26.34, 95% CI = 6.24-184.71) or age (OR = 1.28, 95% CI = 1.11-1.54). In the model looking only at PD-MCI patients, we once again found that global cognitive ability (OR = 40.63, 95% CI = 3.42-1605.52) and age (OR = 1.21, 95% CI = 1.05-1.48) were useful and that neither patient-reported hallucinations (OR = 1.52, 95% CI = 0.58-4.32) or motor function (OR = 1.01, 95% CI = 0.95-1.09) were useful when distinguishing between the patients who progressed to

PDD 4 years later and those that who did not. This suggests that patient-reported hallucinations at baseline are not very useful when age and cognitive ability is known.

6.4. Discussion

The main finding from this study was that most neuropsychiatric and behavioural measures, especially those reported by a significant other, were not useful in predicting future conversion to dementia (PDD) over four years in non-demented Parkinson's patients. However, NPI total score and the NPI anxiety sub-scale showed a small association with increased risk of developing PDD four-years later. Patient-reported hallucinations (as ascertained from the PDQ and UPDRS) had the strongest relationship to future PDD but hallucinations were not found to be as useful as already established predictors, such as age and cognitive ability, when distinguishing between those who developed PDD and those who did not.

The patients classified as having dementia at baseline experienced more neuropsychiatric symptoms compared to those classified as PD-MCI and PD-N. PDD patients as a group were also older, had significantly worse motor function (UPDRS III) and poorer cognition than the PD-N group. There was consistent evidence across all measures for a greater prevalence of hallucinations (both patient and significant other reported), depression, anxiety, and aggression in PDD compared to PD-N group. In addition, there was an indication that there were higher rates of apathy, loneliness, and distressing dreams in the PDD group compared to the PD-N group, however, only one measure was used to assess the presence of each of these symptoms. When the PDD group were compared to the PD-MCI group, a similar overall pattern persisted, where the PDD group showed higher rates of hallucinations and depression on most scales tested. There were also higher rates of anxiety

and apathy reported on the NPI only, as well as greater reports of loneliness and distressing dreams reported on the PDQ in the PDD group. The ROC AUC values, however, were generally smaller than those seen when comparing the PDD and PD-N groups, especially in the hallucinations and depression sub-components. There was also no difference in anxiety levels reported between the PDD and PD-MCI patient groups. The only difference between the PD-N and PD-MCI groups in terms of neuropsychiatric symptoms was on the UPDRS hallucinations measure, were the PD-MCI group reported experiencing more hallucinations than the PD-N group. These cross-sectional findings at study entry are in line with other studies which have looked the prevalence of neuropsychiatric symptoms across cognitive groups in PD, with PDD patients have more marked differences when compared to the PD-N and PD-MCI groups respectively (Bronnick et al., 2005; Dalrymple-Alford et al., 2010; Hobson & Meara, 2015). Thus, it is clear that PDD patients have a higher neuropsychiatric burden than non-dementing PD patients.

The PD-MCI group had significantly worse cognition, as expected, and slightly worse motor function than the PD-N group. In contradistinction, there were no differences in the prevalence of behavioural symptoms experienced, except UPDRS hallucinations, when the PD-MCI and PD-N groups were directly compared. These observations accord with the previous findings of Dalrymple-Alford et al. (2010), who reported no differences in terms of depression and NPI total scores, and Hobson and Meara (2015), who found no difference in levels of depression and hallucinations, in these two non-demented PD groups. We did find that PD-MCI patients experience greater amounts of hallucinations than PD-N patients, unlike Hobson and Meara (2015), but we only saw this on the UPDRS measure and not on the hallucination measures in the NPI and PDQ. In contrast to our findings, Broeders, de Bie, et al. (2013) found that their PD-MCI patient group had higher depression and anxiety rates

than those classified as PD-N. This difference could be due to the fact that different tests were used to measure depression and anxiety. We used a selection of tests to measure depression (NPI depression score, PDQ depression score, UPDRS depression and the GDS) and anxiety (NPI anxiety and PDQ anxiety), while Broeders, de Bie, et al. (2013) used the Hospital Anxiety and Depression Scale (HADS) to measure these two neuropsychiatric symptoms. Like our study, the GDS was used as the depression measure in both Dalrymple-Alford et al. (2010) and Hobson and Meara (2015), thus variations in the test employed to measure each neuropsychiatric symptom could be the cause of these differences between studies.

There were few differences when behavioural symptoms in non-demented patients who progressed to PDD four-years later were compared to those patients who did not progress. This was the dominant and more novel finding in this study. In fact, cognition, rather than the increased presence of neuropsychiatric symptoms, was a better predictor of progression to PDD. The observation that most neuropsychiatric symptoms, such as anxiety or depression, with the notable exception of patient-reported hallucinations, showed no evidence of an association with progression to PDD supports some of the literature (Broeders, Velseboer, et al., 2013; Pedersen et al., 2013). Unlike other studies we did not find an association between apathy (Fitts et al., 2015; Pedersen et al., 2009) or depression (Anang et al., 2014; Janvin et al., 2006) and future progression to PDD. These differences are probably due to difference in cognitive classification, as we used Level II criteria for PD-MCI classification whereas the other studies did not. This suggest that while neuropsychiatric symptoms are commonly experienced in non-demented PD populations (Kulisevsky et al., 2008; Lees et al., 2009) and have a negative impact on quality of life (Aarsland et al., 2000;

Marsh, 2000), they are not useful on their own (i.e. independently) in the prediction of future progression to PDD.

We did, however, find an association between hallucinations and the progression to PDD. This association between the presence of hallucinations and the future development of PDD has also been reported by others (Aarsland et al., 2003; Aarsland et al., 2004; Anang et al., 2014; Factor et al., 2003), our study however is the first to find this relationship when Level II PD-MCI criteria has been used to classify patients cognitively. All of these studies used the hallucination measure from the UPDRS, except Factor et al. (2003) who used clinical data, to determine the presence of hallucinations, which was one of the patient-reported hallucination measures we found to be associated with future PDD in our study.

The association between hallucinations and the progression to PDD however, was only present when patient-reported hallucination scales were used (PDQ and UPDRS), not significant-other reported hallucination scales (NPI). This inconsistency between patient-reported and significant-other-reported symptoms is not a new observation and can be influenced by many different factors. These factors include the amount of insight a patient has about their own symptoms, how much the patient is willing to sharing with the significant-other, whether the symptom is observable or not, the relationship between the patient and their significant-other, as well as the scales used to report the symptoms. (Fenelon et al., 2000; Martinez-Martin et al., 2016; McKinlay et al., 2008). The finding that patient-reported hallucinations are associated with progression to PDD four years later but not the hallucination scale reported by their significant other could suggest that patients are under-reporting the existence and/or extend of the hallucinations they experience to those around them or that the significant-other is under-reporting to either protect the patient or as a means of coping (McKinlay et al., 2008). All of the patients who were used in the longitudinal part

of the study were not showing signs of dementia when they reported that they experienced hallucinations. This would suggest that they had sufficient insight. One can therefore assume that the inconsistencies between patient-reported and significant-other reported hallucinations was due to a relationship or scale factor, rather than the patient unreliably reporting the extent of their hallucinations during the study period.

On some neuropsychiatric sub-scales, such as the Delusions, Euphoria, and Aberrant Motor Behaviour measures from the NPI, there were very few patients who experienced certain symptoms despite including 123 patients in the study. This could be due in part to the lack of sensitivity for detecting neuropsychiatric/behavioural symptoms of some of the sub-scales and items employed in this analysis. Aside from the GDS, all the other measures used were quite restricted in extent and not specifically designed to be used as single measures in isolation, separate from the more encompassing scales within which they sit. Thus, those scores may not be as sensitive in detecting the true extent and prevalence of neuropsychiatric symptoms in this population of PD patients. I recognise that the use of a single item from larger scales, especially when trying to determine the predictive nature of specific neuropsychiatric symptoms, is a limitation if this study. In saying this, in most other studies which have look at hallucinations and their relationship future PDD, single hallucination measures from the UPDRS (Aarsland et al., 2003; Aarsland et al., 2004; Anang et al., 2014) have also been used. It would therefore be useful to repeat this study using specific targeted neuropsychiatric symptom scales (such as the Psychosis and Hallucinations Questionnaire (Shine et al., 2015) or the Hospital Anxiety and Depression Scale) in order to confirm (or not) the findings of the present study in determining the true predictive value of each behavioural symptom.

There were only six patients in the PD-N group who developed PDD over the four-year follow-up period and thus it was difficult to determine whether there were neuropsychiatric symptoms measured in this study that were predictive of future PDD. For instance, five of the six PD-N patients who converted to PDD reported to experience hallucinations on one or more of the hallucination scales. This could perhaps suggest that hallucinations have the potential to be helpful when identify patients with intact cognition who are at risk of developing dementia over the next four-years, but could also be coincidental in this dataset. Thus, further research into this relationship between hallucinations and the imminent progression to PDD should be conducted using a larger sample and targeted neuropsychiatric symptom scales, such as the Psychosis and Hallucinations Questionnaire (Shine et al., 2015) or the Hospital Anxiety and Depression Scale to more thoroughly test this finding.

6.5. Conclusions

This study found that patients classified with PDD experience a greater number of neuropsychiatric symptoms than those who were classified as PD-MCI or PD-N. Only patient-reported hallucinations were associated with an increased probability of conversion to PDD within four-years, but with hallucinations reported by a patient's significant-other were not helpful in this regard. However, hallucinations do not appear to add any independent information beyond that provided by cognitive testing and age.

Chapter 7: Summary, limitations and concluding remarks

7.1. Summary

This thesis examined the relationship between cognitive and neuropsychiatric symptoms and the progression to dementia in Parkinson's disease over a four-year period. The first two studies addressed uncertainty in the MDS-TF PD-MCI Level II criteria, which allow a wide margin of variation within the specified guidelines. By applying key variations to those criteria, we contributed to a validation of specific PD-MCI criteria as a signal for future progression to dementia over a four-year period. First, using the complete cognitive test battery in use at the NZBRI, we found that the PD-MCI criterion defined as 'two impairments at -1.5SD in a single cognitive domain' identified patients who were at a 7-fold increased risk and thus high risk of progressing to PDD within the next four-years. Second, we found that an abbreviated 10 neuropsychological Level II neuropsychological test battery was also effective for identifying patients at high risk of progressing to dementia. We used two different approaches to reduce the test battery from 24 items to 10, such that two tests remained within each cognitive domain. However, the second approach was optimal, in which tests were selected based on their sensitivity to future PDD. Furthermore, we found that when applied to this reduced 10 neuropsychological test battery, the PD-MCI criterion could then be relaxed to 'two impairments at -1.5SD <u>anywhere</u>', irrespective of whether the impairments fell within a single cognitive domain or across multiple cognitive domains. That is, we no longer needed to restrict the two impairments to occur only within a single cognitive domain, as had been suggested by the first study when all 24 measures were employed. When sensitive tests are used (i.e., tests included within the reduced, 10 neuropsychological battery), two impairments occurring anywhere is sufficient to capture the patients with a high risk of progression to PDD. Lastly, we found that although cognitive

performance and age have the strongest association with risk of progression to PDD, patient-reported hallucinations at study entry were also found to have a moderate relationship with future PDD. Our study was the first to examine the predictive nature of neuropsychiatric symptoms in a PD population who had received Level II cognitive testing. Interestingly, patient-reported hallucinations were the only neuropsychiatric symptom that was associated with future conversion to PDD four-years later. All the other neuropsychiatric symptoms measured, including reports of hallucinations by the patient's significant other, had no predictive utility for identifying patients at risk of developing PDD over the next four years.

7.2. Implications for Parkinson's disease

In this thesis,

1. We validated the MDS-TF Level II PD-MCI criteria for use as an early identification of patients at high risk of progression to PDD within the next four years. By using the PD-MCI criterion of 'two impairments at -1.5SD in a single cognitive domain', an enriched patient sample can be selected for future intervention or treatment studies. Based on the findings of this thesis we would expect at least 50% of patients who meet this PD-MCI criterion should develop PDD over the next four years. Thus, the PD-MCI criterion of 'two impairments at -1.5SD in a single cognitive domain' could be used to evaluate the efficacy of potential therapeutic treatments that are developed in the future and potential biomarkers for such treatments.

2. We showed that even an abbreviated 10 neuropsychological battery, when it included tests sensitive for progression, can be used to identify MDS-TF PD-MCI Level II patients at risk of progressing to PDD. Moreover, a PD-MCI criterion of 'two impairments at -1.5SD <u>anywhere</u>' was now sufficient to identify the patients at high risk. Reducing the

test battery to only 10 neuropsychological tests consistent with MDS-TF Level II PD-MCI criteria would mean that cognitive testing times for each patient could be reduced from four hours to only one-and-a-half hours at the New Zealand Brain Research Institute. Implementing such a battery would have a direct benefit on patients and assessors by reducing fatigue and freeing up resources.

3. We demonstrated that neuropsychiatric symptoms do not have a strong predictive value of progression to PDD over a four-year follow-up period. Furthermore, only patient-reported hallucinations demonstrated an association with future progression. Global cognitive ability and age were much stronger predictors of progression to PDD than patient-reported-hallucinations when compared in a Logistic regression model.

The overall findings of this thesis are supported by a recent review by Aarsland et al. (2017), which highlighted both cognitive impairment and hallucinations as the most robust clinical features of dementia risk in PD patients. However, we have illustrated that cognition is a far better predictor of future cognitive decline whereas hallucinations add no additional predictive value even in PD-MCI patients.

7.3. Limitations

The major strength of this study was the prospective use of longitudinal data and detailed assessments at frequent follow-up intervals. Like any long-term research project, however, there are a number of limitations. One such limitation, as mentioned in Chapter 3, was that this thesis had a modest sample size (sample size of 121-138 patients across analyses) and there was potential for bias due to an attrition rate of 13-18% across analyses. Nonetheless, the sample size was among the largest included in a separate validation of the predictive value of a PD-MCI status (Hoogland et al, 2017). However, when the patients were

categorised into separate MCI subgroups, the number of converters within each group was small. This was particularly true for the PD-N groups (n ≤ 6 for PD-N converters across the three samples used). Although this suggests that the PD-MCI criteria utilised in this study are sensitive to progression to PDD, it did limit the conclusions that we could draw from the comparison PD-N group. This was primarily a statistical issue when doing the RR analysis, but we were able to overcome this issue with bootstrapping. This was particularly an issue when looking for differences between the PD-MCI and PD-N converters. The current data has, however, contributed to an international consortium which looked to validate the MDS-TF PD-MCI criteria with a much larger sample (Geurtsen et al., 2014; Hoogland et al., 2017). That larger sample meant that there was better statistical precision for determining the risk of PDD, and especially the ability to assess the influence of potential modifiers such as age and education. Hoogland et al. (2017) found that cognitive impairment, as defined by Level II PD-MCI criteria increased the risk of dementia, but age and the severity of motor symptoms had a weaker influence. The finding that Level II PD-MCI is related to progression to PDD in their study mirrors what we found in our smaller cohort of PD patients.

Another limitation of this thesis concerns the methodology employed to reduce the neuropsychological test battery to an optimised 10 neuropsychological battery (Chapters 4 and 5). The logistic regression approach was a marked improvement on my first attempt to select the 'best' 10 tests. It was, however, limited due to confounding factors such as a small group of patients who converted to PDD over the four-year period. This meant we were unable to properly validate our findings in an independent population of patients. Upon consultation with my co-supervisor Dr Daniel Myall, we devised a new approach to optimising the test battery to include only the tests useful in classifying patients at high risk of future PDD. Ideally, we would use an advanced mathematical model based on LASSO

regression combined with a leave-one-out procedure. Unfortunately, this approach could not be completed within the time frame of my thesis, but our research group will publish the findings from this alternative approach in the near future.

A third limitation of this study was the neuropsychiatric scales used to investigate the relationship between neuropsychiatric symptoms and progression to PDD, as discussed in Chapter 6. The data available for this aspect of my thesis was limited, aside from measures of depression (GDS). Some scales, such as the Hospital Anxiety and Depression scale, were only included in the longitudinal assessment after the majority of patients included in this thesis had completed their baseline assessment. Of greatest relevance, the findings have highlighted that we should explore additional scales that may provide more informative information about the nature of particular hallucinations. Our hallucination measures were limited to sub-sections of larger tests, such as the NPI or MDS-UPDRS.

7.4. Future Directions

An alternative perspective on cognition and progression to PDD, the focus of this thesis, is the 'dual-syndrome hypothesis' of Kehagia et al. (2012). These authors suggest that different underlying neural correlates of PD lead to heterogeneous cognitive impairment profiles in PD patients. In this thesis, there was clear evidence of heterogeneity in cognitive impairments in PD-MCI patients (Chapter 3-5). There was no specific pattern of impairment that could distinguish between patients who progressed to PDD and those that did not. Kehagia et al. (2012) proposed that two independent processes contribute to cognitive impairments in PD. The first process is based on the traditional view of PD pathology, where dopaminergic dysfunction disrupts fronto-striatal pathways, causing cognitive impairment. However, they suggest that this first process is unrelated to the pathology resulting in dementia and that the

first process is instead a progressive fronto-striatal disorder that affects all PD patients. This disruption is exacerbated by decline in the mesofrontal dopaminergic network and is the pathology which underpins dysexecutive symptoms commonly identified in patients with PD. The second process interferes with posterior cortical networks and this different disruption is the catalyst for progression to PDD, which is exacerbated by a failing cholinergic forebrain system. If true, PD-MCI may incorporate two separate sub-groups of patients, which would explain why some patients progress to PDD while others remain relatively stable cognitively for a longer period of time. Addressing this dual-syndrome hypothesis to further characterise PD patients who are a part of the New Zealand Brain Research Institute's longitudinal study would be useful. This future direction would involve looking at the 'dual-syndrome hypothesis' in the context of a well-characterised longitudinal cohort from an imaging, neuropsychological and neuropsychiatric perspectives to determine whether dual-syndromes do exist in PD populations and, if so, evaluate their usefulness as markers of future cognitive decline in PD populations.

In Chapter 6, we demonstrated that patient-reported hallucinations have some relevance to progression to PDD, but are a relatively weak predictor compared to cognition and age. Moreover, this association did not hold for hallucinations reported by the patients' significant others. This is a clinically relevant finding, as clinicians frequently rely on reports from a patient's spouse or carer rather than that of the individual diagnosed with Parkinson's. This is particularly the case when the patient suffers from cognitive impairment. A future direction of this study would be to further explore the relationship between patient- and caregiver-reported hallucinations, as this is a relatively unexplored area of Parkinson's research. A collaboration with Prof. Lewis at the University of Sydney is planned, as he and his colleagues have developed two in-depth hallucination scales. One of their scales is

designed as a patient-reported hallucination scale (Shine et al., 2015) and the second is an equivalent scale for caregiver-reported hallucinations (currently under-review). Both scales report the type, frequency and severity of hallucinations. We hope that the use of these hallucination measures will provide (1) more informative hallucination data and (2) additional information about their role in progression to PDD.

Another application of these findings is to use MR imaging techniques to help us further understand the differences between patients who develop PDD relatively quickly at any given point in time and those who will remain dementia-free for prolonged periods. The BrainAGE framework, developed by Franke, Ziegler, Klöppel, and Gaser (2010), is one such method. BrainAGE uses structural MRI scans to define a pattern of normal brain ageing, based on healthy control data. The model can then be used to predict an individual's structural "brain age" from their MRI scan. The difference between the individual's chronological age and the model's predicted age is termed their BrainAGE score, with positive BrainAGE scores indicative of accelerated brain ageing (that is, predicted age > chronological age). The relative effects of PD, including mild cognitive impairment, could then be quantified. Baseline, cross-sectional data could be used from the longitudinal PD study at the New Zealand Brain Research Institute to categorise brain ageing across PD-N, PD-MCI and PDD groups. In addition to this, the BrainAGE metrics could be used to track cognitive decline within this existing longitudinal cohort, with a particular focus on the PD-MCI patient group. The BrainAGE model has already been applied to several other conditions which affect brain health, such as Alzheimer's disease, traumatic brain injury and type II diabetes, but it has yet to be tested in a PD population (Cole, Leech, & Sharp, 2015; Franke & Gaser, 2012; Franke, Gaser, Manor, & Novak, 2013; Gaser, Franke, Kloppel, Koutsouleris, & Sauer, 2013; Lowe, Gaser, & Franke, 2016).

7.5. Concluding remarks

Specific PD-MCI criteria may be a valuable tool when enriching samples for disease modifying interventions, due to high progression rates to dementia. In this thesis, we were the first to look at the predictive nature of neuropsychiatric symptoms in a PD sample who met Level II PD-MCI criteria. We found that patient-reported hallucinations were moderately associated with progression to PDD; however cognitive ability and age were stronger predictors. In addition to this, most neuropsychiatric symptoms, especially those reported by a patient's significant other, were not useful for predicting future PDD. We have also shown that the MDS-TF PD-MCI Level II criteria do have utility in the early identification of patients at a high risk of developing PDD, even when applied to a reduced 10 neuropsychological test battery. We have shown that over a four-year follow-up period, the PD-MCI criterion of 'two impairments of -1.5SD in <u>a single domain</u>' is optimal for capturing those who develop PDD during this period, when applied to a comprehensive 24 neuropsychological test battery. When a reduced 10 neuropsychological test battery of tests sensitive to future dementia is used, the PD-MCI criterion of '2 impairments at -1.5SD <u>anywhere</u>' was sufficient to capture patients at risk of progression to PDD.

References

Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A., & Kragh-Sorensen, P. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol, 60*(3), 387-392.

Aarsland, D., Andersen, K., Larsen, J. P., Perry, R., Wentzel-Larsen, T., Lolk, A., & Kragh-Sorensen, P. (2004). The rate of cognitive decline in Parkinson disease. *Arch Neurol, 61*(12), 1906-1911. doi: 10.1001/archneur.61.12.1906

Aarsland, D., Bronnick, K., Ehrt, U., De Deyn, P. P., Tekin, S., Emre, M., & Cummings, J. L. (2007). Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *J Neurol Neurosurg Psychiatry, 78*(1), 36-42. doi: 10.1136/jnnp.2005.083113

Aarsland, D., Bronnick, K., & Fladby, T. (2011). Mild cognitive impairment in Parkinson's disease. *Curr Neurol Neurosci Rep, 11*(4), 371-378. doi: 10.1007/s11910-011-0203-1

Aarsland, D., Bronnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., . . . Emre, M. (2010). Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology, 75*(12), 1062-1069. doi: 10.1212/WNL.0b013e3181f39d0e

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nat Rev Neurol, advance online publication*. doi: 10.1038/nrneurol.2017.27

Aarsland, D., & Kurz, M. W. (2010). The epidemiology of dementia associated with Parkinson's disease. *Brain Pathol, 20*(3), 633-639. doi: 10.1111/j.1750-3639.2009.00369.x

Aarsland, D., Larsen, J. P., Lim, N. G., Janvin, C., Karlsen, K., Tandberg, E., & Cummings, J. L. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry, 67*(4), 492-496.

Aarsland, D., Larsen, J. P., Tandberg, E., & Laake, K. (2000). Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc, 48*(8), 938-942. doi: 10.1111/j.1532-5415.2000.tb06891.x

Abbott, R. D., Petrovitch, H., White, L. R., Masaki, K. H., Tanner, C. M., Curb, J. D., . . . Ross, G. W. (2001). Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology, 57*(3), 456-462.

Abbott, R. D., Ross, G. W., Petrovitch, H., Tanner, C. M., Davis, D. G., Masaki, K. H., . . . White, L. R. (2007). Bowel movement frequency in late-life and incidental Lewy bodies. *Movement Disorders, 22*(11), 1581-1586. doi: 10.1002/mds.21560

Agid, Y. (1991). Parkinson's disease: Pathophysiology. *Lancet, 337*(8753), 1321.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi: 10.1016/j.jalz.2011.03.008

Alegret, M., Junque, C., Pueyo, R., Valldeoriola, F., Vendrell, P., Tolosa, E., & Mercader, J. M. (2001). MRI atrophy parameters related to cognitive and motor impairment in Parkinson's disease. *Neurologia, 16*(2), 63-69.

Anang, J. B., Gagnon, J. F., Bertrand, J. A., Romenets, S. R., Latreille, V., Panisset, M., . . . Postuma, R. B. (2014). Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology, 83*(14), 1253-1260. doi: 10.1212/WNL.0000000000000842

Antonini, A., Tolosa, E., Mizuno, Y., Yamamoto, M., & Poewe, W. H. (2009). A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *The Lancet Neurology, 8*(10), 929-937.

Barker, R. A., & Williams-Gray, C. H. (2014). Mild cognitive impairment and Parkinson's disease--something to remember. *J Parkinsons Dis, 4*(4), 651-656. doi: 10.3233/JPD-140427

Beach, T. G., Adler, C. H., Lue, L., Sue, L. I., Bachalakuri, J., Henry-Watson, J., . . . Arizona Parkinson's Disease, Consortium. (2009). Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol, 117*(6), 613-634. doi: 10.1007/s00401-009-0538-8

Berg, D., Postuma, R. B., Bloem, B., Chan, P., Dubois, B., Gasser, T., . . . Deuschl, G. (2014). Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. *Mov Disord, 29*(4), 454-462. doi: 10.1002/mds.25844

Bezard, E., & Gross, C. E. (1998). Conpensatory mechanisms in experimental and human parkinsonism: Towards a dynamic approach. *Progress in Neurobiology, 55*, 93-116.

Biundo, R., Weis, L., Facchini, S., Formento-Dojot, P., Vallelunga, A., Pilleri, M., & Antonini, A. (2014). Cognitive profiling of Parkinson disease patients with mild cognitive impairment and dementia. *Parkinsonism Relat Disord, 20*(4), 394-399. doi: 10.1016/j.parkreldis.2014.01.009

Bossuyt, P. M., Reitsma, J. B., Bruns, D. E., Gatsonis, C. A., Glasziou, P. P., Irwig, L. M., . . . Vet, H. C. W. de. (2003). Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ, 326*, 41-44.

Braak, H., Bohl, J. R., Muller, C. M., Rub, U., de Vos, R. A., & Del Tredici, K. (2006). Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord, 21*(12), 2042-2051. doi: 10.1002/mds.21065

Braak, H., & Del Tredici, K. (2008). Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. *Exp Neurol, 212*(1), 226-229. doi: 10.1016/j.expneurol.2008.04.001

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res, 318*(1), 121-134. doi: 10.1007/s00441-004-0956-9

Broeders, M., de Bie, R. M., Velseboer, D. C., Speelman, J. D., Muslimovic, D., & Schmand, B. (2013). Evolution of mild cognitive impairment in Parkinson disease. *Neurology, 81*(4), 346-352. doi: 10.1212/WNL.0b013e31829c5c86

Broeders, M., Velseboer, D. C., de Bie, R., Speelman, J. D., Muslimovic, D., Post, B., . . . Schmand, B. (2013). Cognitive change in newly-diagnosed patients with Parkinson's

disease: a 5-year follow-up study. *J Int Neuropsychol Soc, 19*(6), 695-708. doi: 10.1017/S1355617713000295

Bronnick, K., Aarsland, D., & Larsen, J. P. (2005). Neuropsychiatric disturbances in Parkinson's disease clusters in five groups with different prevalence of dementia. *Acta Psychiatr Scand, 112*(3), 201-207. doi: 10.1111/j.1600-0447.2005.00562.x

Brown, R. G., & MacCarthy, B. (1990). Psychiatric morbidity in patients with Parkinson's disease. *Psychol Med, 20*(1), 77-87. doi: 10.1017/s0033291700013246

Buter, T. C., van den Hout, A., Matthews, F. E., Larsen, J. P., Brayne, C., & Aarsland, D. (2008). Dementia and survival in Parkinson disease: a 12-year population study. *Neurology, 70*(13), 1017-1022. doi: 10.1212/01.wnl.0000306632.43729.24

Calabresi, P., Picconi, B., Parnetti, L., & Di Filippo, M. (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *The Lancet Neurology, 5*(11), 974-983. doi: 10.1016/s1474-4422(06)70600-7

Chaudhuri, K. R., & Schapira, A. H. V. (2009). Non-motor symtoms of Parkinson's disease: Dopaminergic pathophysiology and treatment. *Lancet Neurol, 8*, 464-474.

Cole, J. H., Leech, R., & Sharp, D. J. (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Ann Neurol, 77*(4), 571-581. doi: 10.1002/ana.24367

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual's Test Score Against Norms Derived from Small Samples. *The Clinical Neuropsychologist, 12*(4), 482-486.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology, 48*, S10-S16.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology, 44*(12), 2308-2314.

D'Ath, P., Katona, P., Mullan, E., Evans, S., & Katona, C. (1994). Screening, Detection and Management of Depression in Elderly Primary Care Attenders. I: The Acceptability and Performance of the 15 Item Geriatric Depression Scale (GDS15) and the Development of Short Versions. *Family Practice, 11*(3), 260-266. doi: 10.1093/fampra/11.3.260

Dalrymple-Alford, J. C., Livingston, L., MacAskill, M. R., Graham, C., Melzer, T. R., Porter, R. J., . . . Anderson, T. J. (2011). Characterizing mild cognitive impairment in Parkinson's disease. *Mov Disord, 26*(4), 629-636. doi: 10.1002/mds.23592

Dalrymple-Alford, J. C., MacAskill, M. R., Nakas, C. T., Livingston, L., Graham, C., Crucian, G. P., . . . Anderson, T. J. (2010). The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology, 75*(19), 1717-1725. doi: 10.1212/WNL.0b013e3181fc29c9

Delis, D. C. (2000). *CVLT-II SF: California verbal learning test: adult version*: Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. (2001a). *Delis-Kaplan Executive Function System*. San Antonio: Psychological Corporation.

Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R. G., Broe, G. A., . . . Emre, M.
(2007). Diagnostic procedures for Parkinson's disease dementia: recommendations
from the movement disorder society task force. *Mov Disord, 22*(16), 2314-2324. doi:
10.1002/mds.21844

Eberling, J., Vincent, L., Goldman, J. G., Weintraub, D., Kulisevsky, J., Marras, C., . . .
Kieburtz, K. (2014). Therapeutic development paths for cognitive impairment in
Parkinson's disease: report of a regulatory roundtable. *J Parkinsons Dis, 4*(4), 585-
589. doi: 10.3233/JPD-140385

Eckert, T., Tang, C., & Eidelberg, D. (2007). Assessment of the progression of Parkinson's
disease: a metabolic network approach. *The Lancet Neurology, 6*(10), 926-932. doi:
10.1016/s1474-4422(07)70245-4

Efron, B. (1979). Bootstrap Methods: another look at the jackknife. *The Annals of Statistics,
7*, 1-26.

Emre , M., Aarsland , D., Albanese , A., Byrne , J. E., Deuschl , G., De Deyn , P. P., . . .
Lane, R. (2004). Rivastigmine for Dementia Associated with Parkinson's Disease.
New England Journal of Medicine, 351(24), 2509-2518. doi:
10.1056/NEJMoa041470

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., . . . Dubois, B.
(2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease.
Mov Disord, 22(12), 1689-1707; quiz 1837. doi: 10.1002/mds.21507

Emre, M., Ford, P. J., Bilgic, B., & Uc, E. Y. (2014). Cognitive impairment and dementia in Parkinson's disease: practical issues and management. *Mov Disord, 29*(5), 663-672. doi: 10.1002/mds.25870

Emre, M., Tsolaki, M., Bonuccelli, U., Destée, A., Tolosa, E., Kutzelnigg, A., . . . Jones, R. (2010). Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *The Lancet Neurology, 9*(10), 969-977.

Factor, S. A., Feustel, P. J., Friedman, J. H., Comella, C. L., Goetz, C. G., Kurlan, R., . . . Parkinson Study, Group. (2003). Longitudinal outcome of Parkinson's disease patients with psychosis. *Neurology, 60*(11), 1756-1761.

Fahn, S., Elton, R., & UPDRS Development Committee. (1987). In. Fahn S., Marsden CD, Calne DB, Goldstein M. *Recent Developments in Parkinson's disease, 2*, 153-164.

Federico, A., Trentin, M., Zanette, G., Mapelli, D., Picelli, A., Smania, N., & Tamburin, S. (2017). Diagnosing mild cognitive impairment in Parkinson's disease: Which tests preform best in the Italian population. *Neurol Sci*.

Fenelon, G., Mahieux, F., Huon, R., & Ziegler, M. (2000). Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain, 123 (Pt 4)*, 733-745.

Fitts, W., Weintraub, D., Massimo, L., Chahine, L., Chen-Plotkin, A., Duda, J. E., . . . Dahodwala, N. (2015). Caregiver report of apathy predicts dementia in Parkinson's disease. *Parkinsonism Relat Disord, 21*(8), 992-995. doi: 10.1016/j.parkreldis.2015.06.009

Foltynie, T., Brayne, C. E. G., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain, 127*(3), 550-560. doi: 10.1093/brain/awh067

Fox, S. H., Katzenschlager, R., Lim, S. Y., Ravina, B., Seppi, K., Coelho, M., . . . Sampaio, C. (2011). The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Mov Disord, 26 Suppl 3*, S2-41. doi: 10.1002/mds.23829

Franke, K., & Gaser, C. (2012). Longitudinal Changes in IndividualBrainAGEin Healthy Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *GeroPsych, 25*(4), 235-245. doi: 10.1024/1662-9647/a000074

Franke, K., Gaser, C., Manor, B., & Novak, V. (2013). Advanced BrainAGE in older adults with type 2 diabetes mellitus. *Front Aging Neurosci, 5*, 90. doi: 10.3389/fnagi.2013.00090

Franke, K., Ziegler, G., Klöppel, S., & Gaser, C. (2010). Estimating the age of healthy subjects from T 1-weighted MRI scans using kernel methods: Exploring the influence of various parameters. *Neuroimage, 50*(3), 883-892. doi: 10.1016/j.neuroimage.2010.01.005

Gaser, C., Franke, K., Kloppel, S., Koutsouleris, N., & Sauer, H. (2013). BrainAGE in Mild Cognitive Impaired Patients: Predicting the Conversion to Alzheimer's Disease. *PLoS One, 8*(6), e67346. doi: 10.1371/journal.pone.0067346

Gelb, D. J., Oliver, E., & Gilman, S. (1999). Diagnostic criteria for Parkinson disease. *Arch Neurol, 56*(1), 33-39.

Geurtsen, G. J., Hoogland, J., Goldman, J. G., Schmand, B. A., Troster, A. I., Burn, D. J., . . . Criteria, M. D. S. Study Group on the Validation of PD-MCI. (2014). Parkinson's disease mild cognitive impairment: application and validation of the criteria. *J Parkinsons Dis, 4*(2), 131-137. doi: 10.3233/JPD-130304

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T, Counsell, C., . . . Wenning, G. K. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations the Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Movement disorders, 19*(9), 1020-1028.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders, 23*(15), 2129-2170. doi: 10.1002/mds.22340

Goldman, J. G., Holden, S., Bernard, B., Ouyang, B., Goetz, C. G., & Stebbins, G. T. (2013). Defining optimal cutoff scores for cognitive impairment using Movement Disorder Society Task Force criteria for mild cognitive impairment in Parkinson's disease. *Mov Disord, 28*(14), 1972-1979. doi: 10.1002/mds.25655

Goldman, J. G., Holden, S., Ouyang, B., Bernard, B., Goetz, C. G., & Stebbins, G. T. (2015). Diagnosing PD-MCI by MDS Task Force criteria: how many and which neuropsychological tests? *Mov Disord, 30*(3), 402-406. doi: 10.1002/mds.26084

Goris, A., Williams-Gray, C. H., Clark, G. R., Foltynie, T., Lewis, S. J. G., Brown, J., . . . Burn, D. J. (2007). Tau and α-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Annals of neurology, 62*(2), 145-153.

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson's disease dementia: a neural networks perspective. *Brain, 138*(6), 1454-1476. doi: 10.1093/brain/awv104

Guttman, M., Kish, S. J., & Furukawa, Y. (2003). Current concepts in the diagagnosis and management of Parkinson's disease. *Canadian Medical Association Journal, 168*(3), 293-301.

Hattori, T., Orimo, S., Aoki, S., Ito, K., Abe, O., Amano, A., . . . Mizusawa, H. (2012). Cognitive status correlates with white matter alteration in Parkinson's disease. *Hum Brain Mapp, 33*(3), 727-739. doi: 10.1002/hbm.21245

Hawkes, C. H., Del Tredici, K., & Braak, H. (2010). A timeline for Parkinson's disease. *Parkinsonism Relat Disord, 16*(2), 79-84. doi: 10.1016/j.parkreldis.2009.08.007

Hely, M. A., Reid, W. G., Adena, M. A., Halliday, G. M., & Morris, J. G. (2008). The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord, 23*(6), 837-844. doi: 10.1002/mds.21956

Hindle, S., Afsari, F., Stark, M., Middleton, C. A., Evans, G. J., Sweeney, S. T., & Elliott, C. J. (2013). Dopaminergic expression of the Parkinsonian gene LRRK2-G2019S leads to non-autonomous visual neurodegeneration, accelerated by increased neural demands for energy. *Hum Mol Genet, 22*(11), 2129-2140. doi: 10.1093/hmg/ddt061

Hobson, P., & Meara, J. (2015). Mild cognitive impairment in Parkinson's disease and its progression onto dementia: a 16-year outcome evaluation of the Denbighshire cohort. *Int J Geriatr Psychiatry, 30*(10), 1048-1055. doi: 10.1002/gps.4261

Holdnack, H. A. (2001). *Wechsler Test of Adult Reading: WTAR.* San Antonio.: The Psychological Corporation.

Hoogland, J., Boel, J. A., de Bie, R. M. A., Geskus, R. B., Schmand, B. A., Dalrymple-Alford, J. C., . . . Geurtsen, G. J. (2017). Mild cognitive impairment as a risk factor for Parkinson's disease dementia. *Mov Disord, 32*(7), 1056-1065. doi: 10.1002/mds.27002

Hoover, J. E., & Strick, P. L. (1993). Multiple Output Channels in the Basal Ganglia. *Science, 259*(5096), 819-821. doi: 10.1126/science.7679223

Huang, C., Mattis, P., Tang, C., Perrine, K., Carbon, M., & Eidelberg, D. (2007). Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage, 34*(2), 714-723. doi: 10.1016/j.neuroimage.2006.09.003

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry, 55*(3), 181-184.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *Br J Psychiatry, 140*, 566-572.

Irwin, D. J., Lee, V. M., & Trojanowski, J. Q. (2013). Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. *Nat Rev Neurosci, 14*(9), 626-636. doi: 10.1038/nrn3549

Jacobs, D. M., Marder, K., Cote, L. J., Sano, M., Stern, Y., & Mayeux, R. (1995). Neuropsychological characteristics of preclinical dementia in Parkinson's disease. *Neurology, 45*(9), 1691-1696.

Jak, A. J., Bondi, M. W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D. P., & Delis, D. C. (2009). Quantification of five neuropsychological approaches to defining

mild cognitive impairment. *Am J Geriatr Psychiatry, 17*(5), 368-375. doi: 10.1097/JGP.0b013e31819431d5

James, M., & Warrington, E. (1991). Visual Object and Space Perception Battery (VOSP): Oxford: Pearson.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry, 79*(4), 368-376. doi: 10.1136/jnnp.2007.131045

Janvin, C. C., Larsen, J. P., Aarsland, D., & Hugdahl, K. (2006). Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord, 21*(9), 1343-1349. doi: 10.1002/mds.20974

Jellinger, K. A. (2008). A critical reappraisal of current staging of Lewy-related pathology in human brain. *Acta Neuropathol, 116*(1), 1-16. doi: 10.1007/s00401-008-0406-y

Jellinger, K. A. (2009). A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochim Biophys Acta, 1792*(7), 730-740. doi: 10.1016/j.bbadis.2008.07.006

Jellinger, K. A. (2012). Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Mov Disord, 27*(1), 8-30. doi: 10.1002/mds.23795

Jurica, P. J., Leitten, C. L., & Mattis, S. (2001). *DRS-2 Dementia Rating Scale-2: Professional Manual*. Florida, USA: Psychological Assessment Reseaorces, Inc.

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2012). Cognitive Impairment in Parkinson's Disease: The Dual Syndrome Hypothesis. *Neurodegenerative Diseases, 11*(2), 79-92. doi: 10.1159/000341998

Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., García-Sánchez, C., & Gironell, A. (2008). Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Movement Disorders, 23*(13), 1889-1896. doi: 10.1002/mds.22246

Lansing, A. E., Ivnik, R. J., Cullum, C. M., & Randolph, C. (1999). An Empirically Derived Short Form of the Boston Naming Test. *Archives of Clinical Neuropsychology, 14*(6), 481-487. doi: http://dx.doi.org/10.1016/S0887-6177(98)00022-5

Lawson, R. A., Yarnall, A. J., Duncan, G. W., Khoo, T. K., Breen, D. P., Barker, R. A., . . . Burn, D. J. (2014). Severity of mild cognitive impairment in early Parkinson's disease contributes to poorer quality of life. *Parkinsonism Relat Disord, 20*(10), 1071-1075. doi: 10.1016/j.parkreldis.2014.07.004

Lee, A. H., & Weintraub, D. (2012). Psychosis in Parkinson's disease without dementia: common and comorbid with other non-motor symptoms. *Mov Disord, 27*(7), 858-863. doi: 10.1002/mds.25003

Lees, A. J., Hardy, J., & Revesz, T. (2009). Parkinson's disease. *The Lancet, 373*(9680), 2055-2066. doi: 10.1016/S0140-6736(09)60492-X

Leroi, I., Brandt, J., Reich, S. G., Lyketsos, C. G., Grill, S., Thompson, R., & Marsh, L. (2004). Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. *International journal of geriatric psychiatry, 19*(1), 1-8.

Leroi, I., McDonald, K., Pantula, H., & Harbishettar, V. (2012). Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden. *Journal of Geriatric Psychiatry and Neurology, 25*(4), 208-214.

Levy, G., Jacobs, D. M., Tang, M. X., Cote, L. J., Louis, E. D., Alfaro, B., . . . Marder, K. (2002). Memory and executive function impairment predict dementia in Parkinson's disease. *Mov Disord, 17*(6), 1221-1226. doi: 10.1002/mds.10280

Lewis, S. J. G., Cools, R., Robbins, T. W., Dove, A., Barker, R. A., & Owen, A. M. (2003). Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. *Neuropsychologia, 41*, 645–654.

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5 ed.). New York: Oxford Univercity Press.

Lezak, M. D. (2004). *Neuropsychological assessment*: Oxford University Press, USA.

Liepelt-Scarfone, I., Graeber, S., Feseker, A., Baysal, G., Godau, J., Gaenslen, A., . . . Berg, D. (2011). Influence of different cut-off values on the diagnosis of mild cognitive impairment in Parkinson's disease. *Parkinsons Dis, 2011*, 540843. doi: 10.4061/2011/540843

Litvan, I., Goldman, J. G., Troster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., . . . Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord, 27*(3), 349-356. doi: 10.1002/mds.24893

Lowe, L. C., Gaser, C., & Franke, K. (2016). The Effect of the APOE Genotype on Individual BrainAGE in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *PLoS One, 11*(7), e0157514. doi: 10.1371/journal.pone.0157514

Mahieux, F., Fenelon, G., Flahault, A., Manifacier, M. J., Michelet, D., & Boller, F. (1998). Neuropsychological prediction of dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry, 64*(2), 178-183.

Marras, C., Armstrong, M. J., Meaney, C. A., Fox, S., Rothberg, B., Reginold, W., . . . Duff-Canning, S. (2013). Measuring mild cognitive impairment in patients with Parkinson's disease. *Mov Disord, 28*(5), 626-633. doi: 10.1002/mds.25426

Marsh, L. (2000). Neuropsychiatric aspects of Parkinson's disease. *Psychosomatics, 41*(1), 15-23. doi: 10.1016/S0033-3182(00)71169-8

Martinez-Martin, P., Falup-Pecurariu, C., Rodriguez-Blazquez, C., Serrano-Duenas, M., Carod Artal, F. J., Rojo Abuin, J. M., & Aarsland, D. (2011). Dementia associated with Parkinson's disease: applying the Movement Disorder Society Task Force criteria. *Parkinsonism Relat Disord, 17*(8), 621-624. doi: 10.1016/j.parkreldis.2011.05.017

Martinez-Martin, P., Leentjens, A. F., de Pedro-Cuesta, J., Chaudhuri, K. R., Schrag, A. E., & Weintraub, D. (2016). Accuracy of screening instruments for detection of neuropsychiatric syndromes in Parkinson's disease. *Mov Disord, 31*(3), 270-279. doi: 10.1002/mds.26522

Massano, J., & Bhatia, K. P. (2012). Clinical approach to Parkinson's disease: features, diagnosis, and principles of management. *Cold Spring Harb Perspect Med, 2*(6), a008870. doi: 10.1101/cshperspect.a008870

McKinlay, A., Grace, R. C., Dalrymple-Alford, J. C., Anderson, T. J., Fink, J., & Roger, D. (2008). Neuropsychiatric problems in Parkinson's disease: comparisons between self

and caregiver report. *Aging Ment Health, 12*(5), 647-653. doi: 10.1080/13607860802343225

Melzer, T. R., Watts, R., MacAskill, M. R., Pearson, J. F., Rueger, S., Pitcher, T. L., . . . Anderson, T. J. (2011). Arterial spin labelling reveals an abnormal cerebral perfusion pattern in Parkinson's disease. *Brain, 134*(Pt 3), 845-855. doi: 10.1093/brain/awq377

Melzer, T. R., Watts, R., MacAskill, M. R., Pitcher, T. L., Livingston, L., Keenan, R. J., . . . Anderson, T. J. (2012). Grey matter atrophy in cognitively impaired Parkinson's disease. *J Neurol Neurosurg Psychiatry, 83*(2), 188-194. doi: 10.1136/jnnp-2011-300828

Melzer, T. R., Watts, R., MacAskill, M. R., Pitcher, T. L., Livingston, L., Keenan, R. J., . . . Anderson, T. J. (2013). White matter microstructure deteriorates across cognitive stages in Parkinson disease. *Neurology, 80*(20), 1841-1849. doi: 10.1212/WNL.0b013e3182929f62

Meyers, J. E, & Meyers, K. R. (1995). *Rey Complex Figure Test and recognition trial professional manual*: Psychological Assessment Resources.

Mohs, R. C., Knopman, D., Petersen, R. C., Ferris, S. H., Ernesto, C., Grundman, M., . . . Thal, L. J. . (1997). Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Disease & Associative Disorders., 11(Suppl2)*, S13-21.

Morley, J. F., & Hurtig, H. I. (2010). Current understanding and management of Parkinson disease: five new things. *Neurology, 75*(18 Suppl 1), S9-15. doi: 10.1212/WNL.0b013e3181fb3628

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology, 43*(11), 2412.

Myall, D. J., Pitcher, T. L., Pearson, J. F., Dalrymple-Alford, J. C., Anderson, T. J., & MacAskill, M. R. (2017). Parkinson's in the oldest old: Impact on estimates of future disease burden. *Parkinsonism Relat Disord*. doi: 10.1016/j.parkreldis.2017.06.018

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699. doi: 10.1111/j.1532-5415.2005.53221.x

O'Connell, M. E., Tuokko, H., Graves, R. E., & Kadlec, H. (2004). Correcting the 3MS for Bias Does Not Improve Accuracy When Screening for Cognitive Impairment or Dementia. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 970-980. doi: 10.1080/113803390490510998

O'Connell, M. E., & Tuokko, H.. (2010). Age Corrections and Dementia Classification Accuracy. *Archives of Clinical Neuropsychology, 25*(2), 126-138. doi: 10.1093/arclin/acp111

Obeso, J. A., Rodriguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., & Rodriguez, M. (2008). Functional organization of the basal ganglia: therapeutic

implications for Parkinson's disease. *Mov Disord, 23 Suppl 3*, S548-559. doi: 10.1002/mds.22062

Obeso, J. A., Rodriguez-Oroz, M. C., Rodriguez, M., Lanciego, J. L., Artieda, J., Gonzalo, N., & Olanow, C. W. (2000). Pathophysiology of the basal ganglia in Parkinson's disease. *Trends Neurosci, 23*(10 Suppl), S8-19.

Obeso, J. A., & Schapira, A. H. (2009). Compensatory mechanisms in Parkinson's disease. *Movement Disorders, 24*(1), 153-154. doi: 10.1002/mds.22177

Oosterveld, L. P., Allen, J. C., Jr., Reinoso, G., Seah, S. H., Tay, K. Y., Au, W. L., & Tan, L. C. (2015). Prognostic factors for early mortality in Parkinson's disease. *Parkinsonism Relat Disord, 21*(3), 226-230. doi: 10.1016/j.parkreldis.2014.12.011

Palavra, N. C., Naismith, S. L., & Lewis, S. J. (2013). Mild cognitive impairment in Parkinson's disease: a review of current concepts. *Neurol Res Int, 2013*, 576091. doi: 10.1155/2013/576091

Pedersen, K. F., Alves, G., Aarsland, D., & Larsen, J. P. (2009). Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *J Neurol Neurosurg Psychiatry, 80*(11), 1279-1282. doi: 10.1136/jnnp.2008.170043

Pedersen, K. F., Larsen, J. P., Tysnes, O. B., & Alves, G. (2013). Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. *JAMA Neurol, 70*(5), 580-586. doi: 10.1001/jamaneurol.2013.2110

Petersen, R. C., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., Smith, G. E., . . . Jack, C. R. (2009). Mild Cognitive Impairment: Ten Years Later. *Archives of neurology, 66*(12), 1447-1455. doi: 10.1001/archneurol.2009.266

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res, 4*(3), 241-248.

Pfeffer, R. I., Kurosaki, T. T., Harrah Jr, C. H., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of gerontology, 37*(3), 323-329.

Piatt, A. L., Fields, J. A., Paolo, A. M., & Troster, A. I. . (1999). Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity. *Neuropsychologia, 37*(13), 1499-1503.

Poewe, W., Gauthier, S., Aarsland, D., Leverenz, J. B., Barone, P., Weintraub, D., . . . Dubois, B. (2008). Diagnosis and management of Parkinson's disease dementia. *Int J Clin Pract, 62*(10), 1581-1587. doi: 10.1111/j.1742-1241.2008.01869.x

Postuma, R. B., Aarsland, D., Barone, P., Burn, D. J., Hawkes, C. H., Oertel, W., & Ziemssen, T. (2012). Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord, 27*(5), 617-626. doi: 10.1002/mds.24996

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., . . . Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord, 30*(12), 1591-1601. doi: 10.1002/mds.26424

Reeve, A., Simcox, E., & Turnbull, D. (2014). Ageing and Parkinson's disease: why is advancing age the biggest risk factor? *Ageing Res Rev, 14*, 19-30. doi: 10.1016/j.arr.2014.01.004

Reisberg, B. (1988). Functional assessment staging (FAST). *Psychopharmacol Bull, 24*(4), 653-659.

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). Global Deterioration Scale. *American Journal of Psychiatry Res, 139*, 1136-1139.

Reisberg, B., Finkel, S., Overall, J., Schmidt-Gollas, N., Kanowski, S., Lehfeld, H., . . . Heininger, K. (2001). The Alzheimer's disease activities of daily living international scale (ADL-IS). *International Psychogeriatrics, 13*(2), 163-181.

Reisberg, B., Ferris, S. H., Kluger, A., Franssen, E., Wegiel, J., & de Leon, M. J. (2008). Mild cognitive impairment (MCI): a historical perspective. *International Psychogeriatrics, 20*(01), 18-31. doi: 10.1017/S1041610207006394

Reitan, R. M., & Wolfson, D. (1985). *The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation.* . Tucson, AZ: Neuropsychological Press.

Reitan, R. M., & Wolfson, D. (1995). Influence of age and education on neuropsychological test results. *The Clinical Neuropsychologist, 9*(2), 151-158. doi: 10.1080/13854049508401597

Riedel, O., Klotsche, J., Spottke, A., Deuschl, G., Forstl, H., Henn, F., . . . Wittchen, H. U. (2010). Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. *J Neurol, 257*(7), 1073-1082. doi: 10.1007/s00415-010-5465-z

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J. C., & Muller, M. (2011). pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics, 12*, 77. doi: 10.1186/1471-2105-12-77

Rodriguez-Oroz, M. C., Rodriguez, M., Guridi, J., Mewes, K., Chockkman, V., Vitek, J., . . . Obeso, J. A. (2001). The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. *Brain, 124*(9), 1777-1790.

Schapira, A. H. V., Emre, M., Jenner, P., & Poewe, W. (2009). Levodopa in the treatment of Parkinson's disease. *European Journal of Neurology, 16*(9), 982-989.

Sebastiani, P., Bae, H., Sun, F. X., Andersen, S. L., Daw, E. W., Malovini, A., . . . Perls, T. T. (2013). Meta-analysis of genetic variants associated with human exceptional longevity. *Aging (Albany NY), 5*(9), 653-661.

Sharma, S., Moon, C. S., Khogali, A., Haidous, A., Chabenne, A., Ojo, C., . . . Ebadi, M. (2013). Biomarkers in Parkinson's disease (recent update). *Neurochemistry International, 63*(3), 201-229. doi: 10.1016/j.neuint.2013.06.005

Shine, J. M., Mills, J. M. Z., Qiu, J., O'Callaghan, C., Terpening, Z., Halliday, G. M., . . . Lewis, S. J. G. (2015). Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease. *Movement Disorders Clinical Practice, 2*(2), 175-181. doi: 10.1002/mdc3.12139

Sliwinski, M., Lipton, R., Buschke, H., & Wasylyshyn, C. (2003). Optimizing cognitive test norms for detection. *Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York: Oxford University Press, Inc*, 89-104.

Sliwinski, M., Buschke, H., Stewart, W. F., Masur, D., & Lipton, R. B. (1997). The effect of dementia risk factors on comparative and diagnostic selective reminding norms. *Journal of the International Neuropsychological Society, 3*(4), 317-326. doi: undefined

Strauss, E, Sherman, E. M. S., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests* (3 ed.). New York: Oxford University Press.

Svenningsson, P., Westman, E., Ballard, C., & Aarsland, D. (2012). Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. *The Lancet Neurology, 11*(8), 697-707. doi: 10.1016/s1474-4422(12)70152-7

Teng, E., Tingus, K. D., Lu, P. H., & Cummings, J. L. (2009). Persistence of neuropsychological testing deficits in mild cognitive impairment. *Dement Geriatr Cogn Disord, 28*(2), 168-178. doi: 10.1159/000235732

Theodosopoulos, P. V., Marks, W. J., Christine, C., & Starr, P. A. (2003). Locations of movement-related cells in the human subthalamic nucleus in Parkinson's disease. *Movement Disorders, 18*(7), 791-798. doi: 10.1002/mds.10446

Troster, A. I. (2011). A Precis of Recent Advances in the Neuropsychology of Mild Cognitive Impairment(s) in Parkinson's Disease and a Proposal of Preliminary Research Criteria. *J Int Neuropsychol Soc*, 1-14. doi: 10.1017/S1355617711000257

Truong, D. D., Bhidayasiri, R., & Wolters, E. (2008). Management of non-motor symptoms in advanced Parkinson disease. *J Neurol Sci, 266*(1-2), 216-228. doi: 10.1016/j.jns.2007.08.015

Van Buuren, S. (2012). Flexible imputation of missing data: CRC press.

Vanderploeg, R. D., Axelrod, B. N., Sherer, M., Scott, J., & Adams, R. L. (1997). The importance of demographic adjustments on neuropsychological test performance: A response to reitan and wolfson (1995). *The Clinical Neuropsychologist, 11*(2), 210-217. doi: 10.1080/13854049708407054

Wechsler, D. (2008a). *Wechsler Adult Intelligence Scale - Fourth Edition*. San Antonio: TX: The Psychological Corporation.

Wechsler, D. (2008b). *Wechsler Adult Intelligence Scale - Fourth Edition: Technical and interpretive manual*. San Antonio, : TX: The Psychological Corporation.

Wechsler, D. (2011). *WASI-II: Wechsler abbreviated scale of intelligence*: Psychological Corporation.

Weintraub, D., Saboe, K., & Stern, M. B. (2007). Effect of age on geriatric depression scale performance in Parkinson's disease. *Mov Disord, 22*(9), 1331-1335. doi: 10.1002/mds.21369

Weintraub, D., Mamikonyan, E., Papay, K., Shea, J. A., Xie, S. X., & Siderowf, A. (2012). Questionnaire for impulsive-compulsive disorders in Parkinson's Disease–Rating Scale. *Movement Disorders, 27*(2), 242-247.

Williams-Gray, C. H., Evans, J. R., Goris, A., Foltynie, T., Ban, M., Robbins, T. W., . . . Barker, R. A. (2009). The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain, 132*(Pt 11), 2958-2969. doi: 10.1093/brain/awp245

Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry, 84*(11), 1258-1264. doi: 10.1136/jnnp-2013-305277

Wood, K-L., Myall, D. J., Livingston, L., Melzer, T. R., Pitcher, T. L., MacAskill, M. R., . . . Dalrymple-Alford, J. C. (2016). Different PD-MCI criteria and risk of dementia in Parkinson's disease: 4-year longitudinal study. *npj Parkinson's Disease, 2*(1), 15027. doi: 10.1038/npjparkd.2015.27

Woods, S. P., & Troster, A. I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *J Int Neuropsychol Soc, 9*(1), 17-24.

Xu, Y., Yang, J., & Shang, H.. (2016). Meta-analysis of risk factors for Parkinson's disease dementia. *Translational neurodegeneration, 5*(1), 11. doi: 10.1186/s40035-016-0058-0

Yarnall, A. J., Rochester, L., & Burn, D. J. (2013). Mild cognitive impairment in Parkinson's disease. *Age Ageing, 42*(5), 567-576. doi: 10.1093/ageing/aft085

Zigmond, M. J., & Stricker, E. M. (1989). Animal models of parkinson's using selective neurotoxins: Clinical and basic implications. *International Review of Neurobiology, 31*, 1-79.

Appendix A: Description of the standardised neuropsychological and neuropsychiatric tests

A.1. Premorbid intelligence tests

A.1.1. Wechsler Test of Adult Reading (WTAR)

The WTAR is a premorbid IQ test that provides assessors with a measure that reflects an individual's intellect before they developed cognitive difficulties. The WTAR uses 50 spelt words that are commonly used. Patients are asked to pronounce each word out loud and are scored accordingly (Holdnack, 2001).

A.2. Global cognitive functioning

A.2.1. Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is used as a measure of global cognitive function. It is more sensitive to PD-MCI than the Mini Mental State Examination (MMSE), as the tasks are more difficult and test a wider range of cognitive domains, including visuospatial, executive function, memory and attention. Naming ability, language, abstraction and orientation to time/place are also tested (Nasreddine et al., 2005). This measure is scored out of 30, with higher scores indicating better performance. If a patient has 12 or less years of education, then one point is added to their total score to account for a lower level of education. Scores below 26 are considered to indicate PD-MCI and those below 21 indicate PDD (Dalrymple-Alford et al., 2010).

A.2.2. Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog)

The ADAS-Cog consists of 11 tasks, measuring a range of cognitive abilities which are thought to be affected in AD (Mohs et al., 1997). These tasks assess word recall, naming objects and fingers, ability to follow commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test directions, spoken language, comprehension and word-finding difficulties. Scores are out of 70, with higher scores representing a greater level of cognitive impairment.

A.2.3. Dementia Rating Scale-2 (DRS-2)

The DRS-2was originally developed as a brief, standardised tool which could be used to track cognitive change over time in impaired individuals. It is comprised of 37-items which cover five global cognitive domains (Attention, Initiation/Perseveration, Construction, Conceptualisation and Memory; Jurica, Leitten, & Mattis, 2001).

A.3. Executive functioning domain

A.3.1. Action Fluency

Action fluency requires patients to name as many verbs (action words) as they can in one minute (Piatt, Fields, Paolo, & Troster, 1999; Strauss et al., 2006).

A.3.2. Trials B

The Trails B test requires patients to draw a line connecting a number, then a letter, then the next number, then the next letter, and so on. The numbers span from 1-13 and letters from A-L. The test is timed and patients are required to complete the task as quickly as possible.

They are corrected by bringing them back to their last correct answer when mistakes are made (Reitan & Wolfson, 1985).

A.3.3. Stroop Interference

The Stroop test measures attention and response inhibition, thought to be involved in executive function. Stroop interference is the last condition of three from the Delis-Kaplan Executive Function System (D-KEFS) version. In the interference condition participants are timed and asked to name the ink colour each word is printed in, not the colour of the word itself. This creates a conflict between the written word and the ink colour (Delis et al., 2001a).

A.3.4. Category Switching

Category switching requires patients to name as many fruit – furniture word pairings they can in one minute (Delis et al., 2001a).

A.3.5. Letter Fluency

Letter fluency is measured for three different letters (F, A and S). To assess a participant's ability, they are asked to name as many words as they can, starting with a specific letter of the alphabet (e.g. 'F'), in one-minute (Strauss et al., 2006).

A.3.6. Category Fluency

Category Fluency is measured by asking participants to name as many words as they can, relating to a specific category in one minute. The two separate categories we use are animals and boy's names. PD patients tend to have a greater impairment in category fluency than letter fluency, however in AD this is more extreme (Strauss et al., 2006).

A.4. Attention domain

A.4.1. Map Search Test of Everyday Attention (TEA)

The Test of Everyday Attention-Map Search tests selective attention, working-memory and attention. Participants search a realistic map of Philadelphia and circle targets (e.g. restaurant symbols) among distractors for two sets of one-minute. Their total score is the number of targets found per minute, with their first minute score used in the analysis of this thesis. This test is based on an established theory of attention (Strauss et al., 2006).

A.4.2. Digit Ordering

Digit ordering requires patients to listen while an assessor reads out loud a series of numbers. They then must repeat it back to the assessor in ascending orders, including saying numbers twice if necessary. The trials are staged and after two successful recalls the numbers series increases by one (Wechsler, 2008a, 2008b).

A.4.3. Trials A

Similar to Trails B, Trails A requires patients to draw a line connecting numbers. The numbers span from 1-25. The test is timed and patients are required to complete the task as quickly as possible. They are corrected by bringing them back to their last correct answer when mistakes are made (Reitan & Wolfson, 1985).

A.4.4. Stroop Colour

Stroop Colour is one of three conditions from the D-KEFS version. In the colour condition participants name the colour of the patches as quickly as they possible (Delis et al., 2001a).

A.4.5. Stroop Word

Stroop word is one of three conditions from the D-KEFS version. In the word condition participants read colour words printed in black ink row by row as quickly as they possible (Delis et al., 2001a).

A.4.6. Digits Forward and Backward

The Digit span (forwards and backwards) is used to measure working memory and attention. Participants must repeat back to the assessor a series of random numbers; firstly, in the forwards direction (i.e. exactly how the assessor reads the number series to them), and then in the backwards order (i.e. the reverse order from how the assessor reads the number series to them). Their score is the maximum number of digit spans that they correctly recalled (Wechsler, 2008a, 2008b).

A.5. Episodic memory domain

A.5.1. CVLT-II SF Free Recall

This test requires patients to listen carefully while the assessor reads out a list of nine words. These words are each related to one of three categories (fruit, clothing or tools). Once the assessor has finished reading the patient must recall as many words as they can. This is then repeated three more times (Delis, 2000).

A.5.2. CVLT-II SF Short Delay

This test comes about one minute after the CVLT-II SF-II Free Recall section has finished. In between the free recall and short delay components patients are asked to count backwards

from one-hundred until they are asked to stop (approximately 30 seconds later). At this point they are asked to recall all the words they can from the free recall list (Delis, 2000).

A.5.3. CVLT-II SF Long Delay

Like the CVLT-II SF short delay component, the long delay task requires patients to recall as many words as they can, but this time after a period of about 10 minutes (Delis, 2000).

A.5.4. The Rey Complex Figure Test (RCFT) Immediate Delay

The Rey Immediate Delay requires patients to draw the Rey figure from memory after a delay of approximately three minutes (Meyers & Meyers, 1995). Time to completion and organisation of the reproduced drawing are recorded.

A.5 5. .RCFT Long Delay

The Rey Long Delay requires patients to draw the Rey figure from memory after a delay of approximately thirty minutes (Meyers & Meyers, 1995). Time to completion and organisation of the reproduced drawing are recorded.

A.6. Visuospatial domain

A.6.1. RCFT Copy

The Rey copy test requires patients to copy the complex Rey figure onto a piece of blank paper as accurately as they can. This is done with the original figure in front of them (Meyers & Meyers, 1995). The time it takes for them to finish copying the figure and the thinking methods they use to complete the drawing are recorded.

A.6.2. Judgement of Line Orientation (JLO)

The Judgement of Line Orientation (JLO) measures visuospatial/visuoperceptual ability. Participants are required to identify the orientation of two lines from eleven possible options. Their score is the number of line pairs that are correctly orientated. It has a good internal consistency (Strauss et al., 2006) and PD patients have shown a consistent pattern of visuospatial impairments (Alegret et al., 2001).

A.6.3. Picture Completion

The participant is presented with a picture of an object or a scene, where one element in the drawing is missing. Within the specified time of 25 seconds, the patient must tell the assessor what important part of the drawing is missing. There are 25 pictures in total (David Wechsler, 2011).

A.6.4. Visual Object and Space Perception Assessment (VOSP)

The incomplete letters task in VOSP is a measure of visuospatial/visuoperceptual performance. Participants must identify letters that have been visually degraded. The degradation continues until most of the cognitive features are removed, resulting in a better visuoperceptual test (James & Warrington, 1991).

A.7. Language domain

A.7.1. Boston Naming

The revised 15-item Boston Naming test is used to assess language ability in our patients. This test was revised by Lansing, Ivnik, Cullum, and Randolph (1999) and requires patient to name 15 items that are presented to them as black and white drawings.

A.7.2. ADAS-Cog Language Components

The ADAS-Cog Language Components uses five sub-scale tasks from the wider ADAS-Cog scale; naming objects and fingers, commands, comprehension, word-finding difficulty and spoken language (Mohs et al., 1997). For the naming objects and fingers task, patients have presented with 12 different objects which they have to name. The assessor then points to each of the patient's fingers on one hand and asks what each finger is called. During the commands task, the patient is asked to do five commands, which increase in difficulty. Comprehension, word-finding and spoken language are all assessed by the assessor and then rated to quantify impairment in each of these areas.

A.7.3. DRS-2 Similarities

Tasks W-Z from the DRS-2 are used as a composite language measure. These tasks involve identifying similarities between items (Jurica et al., 2001).

A.8. Significant Other (S.O.) measures

A.8.1. Activities of Daily Living (ADL-IS)

The ADL scale comprises of everyday activity items that are related to global and cognitive decline. These 40 items relate to 13 wider categories of activities. This assessment is not done with the patient themselves but with their chosen significant other. The S.O. is asked to rate the patient's performance on a scale of 0-4 for each of the various day to day activities (Reisberg et al., 2001).

A.8.2. Clinical Dementia Rating Scale (CDR)

The CDR is global, clinical staging measure of dementia in older populations The CDR has good reliability at being able to distinguish between older adults who have a range of cognitive abilities. The CDR is a semi-structured interview which comprises of six domains of functioning: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care of the participant. (Hughes, Berg, Danziger, Coben, & Martin, 1982).

A.8.3. The Functional Activities Questionnaire (FAQ)

The patient is rated by the significant on 10 complex higher order abilities using the FAQ. These range from keeping track of current events through to coping with balancing finances. Each of the 10-items are rated on a zero-four scale, where zero means no difficulty with the task and four means that they are dependent on others to do the task for them (Pfeffer, Kurosaki, Harrah Jr, Chance, & Filos, 1982).

A.8.4. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease- Rating Scale (QUIP-RS)

The QUIP-RS measures the severity of symptoms related to impulse control disorders in PD. This measure is administered both with patients and their S.O. to ensure that they are not suffering from this condition, as it can be exacerbated by PD medications (Weintraub et al., 2012).

A.8.5. Functional Assessment Staging (FAST)

FAST is a reliable measure for tracking functional change over time which was originally developed for use in AD populations. It has a good range of accuracy for identifying

functional issues that occur throughout the progression of a disease, even in the more severe stages (Reisberg, 1988).

A.8.6. Global Deterioration Scale

The global deterioration scale is used to categories individuals with cognitive decline into stages. These stages range from (1) no impairment living independently, (2) very mild cognitive impairment but still living independently, (3) mild cognitive decline, still remaining independent and (4) moderate cognitive decline and needs supervision (Reisberg, Ferris, de Leon, & Crook, 1982).

A.9. Neuropsychiatric measures

A.9.1. The Neuropsychiatric Inventory (NPI)

As described in Chapter 6, the NPI is used to assess the frequency and severity of 12 common neuropsychiatric symptoms (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and night-time behaviour disorders, and appetite/eating changes) as reported by each patient's caregiver or significant other (Cummings, 1997; Cummings et al., 1994). The caregiver rated the frequency of each symptom experienced on a scale of one-four and the severity of each symptom on a scale of one-three, based on scripted questions. These two scores were then multiplied together to generate a sub-score for each neuropsychiatric symptom. The sub-scores for each neuropsychiatric symptom were then added together to produce a total NPI 10-item score (scores from the sleep and night-time behaviour disorders and appetite/eating changes sub-scales were excluded from this total score).

A.9.2. Geriatric Depression Scale (GDS)

As described in Chapter 6, the short form 15-point GDS (D'Ath et al., 1994) is comprised of 15 questions with yes or no answers, based on the patient's self-report of how they have been feeling over the past week. The initial four questions act as screening questions and the questionnaire is terminated after these initial four questions if the individual's responses to all four indicate an absence of depression symptoms. Otherwise, the questionnaire is continued until all 15 questions have been answered. Each question that is answered positively for a depression symptom is scored as one point, with 15 points being the highest (i.e. worst) possible total score.

A.10. PD scales

A.10.1. Parkinson's Disease Questionnaire – 39 (PDQ)

As described in Chapter 6, the PDQ (Peto et al., 1995) comprises of 39 PD-specific self-rated questions. Patients are required to rate how their PD has affected them over the past month on a scale of zero-four (never, occasionally, sometimes, often or always/cannot do at all).

A.10.2. Unified Parkinson's Disease Rating Scale (UPDRS)

The original UPDRS (Fahn et al., 1987) and the revised Movement Disorders Society-UPDRS (MDS-UPDRS; (Goetz et al., 2008) are both used in this study. Both versions, which have been used on the PD patient cohort in this thesis, comprise of three parts. All questions are based on the participant's average experiences in the past week. Part One concerns Non-motor aspects of PD that affect daily living, such as mod, sleep and cognition. Part Two concerns Motor aspects of PD that affect daily living, including speech, handwriting and dressing. Part Three represents the patient's motor impairments that are directly related to

their PD. High scores equal higher levels of impairment. Each patient rated their experience

of each symptom over the past week on a severity scale of zero-four (normal, slight, mild,

moderate, or severe). Two different versions of the UPDRS were employed in the study as

the newer MDS-UPDRS scale was released in 2008 after the initial data collection had begun

and it was therefore introduced after baseline testing had commenced. These two versions of

the UPDRS are comparable (Goetz et al., 2008).

A.10.3. Modified Hoehn and Yahr Scale

The Hoehn and Yahr scale is a commonly used clinical rating scale of motor impairments in

PD. The scale ranges from one-five, where one is 'unilateral involvement only' and five is

'wheelchair bound or bedridden unless aided' (Goetz et al., 2004).