Canterbury Medical Research Foundation
Final (1 year) Progress Report
Contract Title: Serial MRI: Clinical tracking of cognition in Parkinson's disease

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1 August 2014

I began the project on 1 June 2013, and officially finished on 31 May 2014. This is the final progress report. Since 1 June 2013, I have had two manuscripts published (in the Journal of Neurology, Neurosurgery, and Psychiatry, impact factor = 4.9 and the Journal of Cerebral Blood Flow and Metabolism, IF=5.4), one letter published in print (Movement Disorders, IF=4.6), and a total of 14 abstracts either presented or submitted to various national and international conferences. I attended the 18th Annual Meeting of the Organization for Human Brain Mapping (OHBM) in Seattle, WA, USA, and an imaging course in Melbourne, Australia. Also, I have recently returned from a visit to Harvard and the University of Vermont, USA, for a series of meetings and analysis sessions with collaborators.

Introduction

Of all the major medical conditions, brain disorders and neurodegeneration account for some of the greatest loss of healthy years. Parkinson's disease (PD) is the most common cause of neurodegeneration after Alzheimer's disease. Demographic projections suggest that the 10,000 people currently affected by PD in New Zealand will increase two-fold by 2035 and four-fold by 2050. While tremor, slowness of movement and stiffness are predominant on initial clinical presentation, cognitive decline becomes the most debilitating issue for patients and carers. Dementia eventually affects 80% of PD patients, causing early institutionalization and premature death, and is now the focus of research on this devastating disorder. However, considerable variation (2-20 years) between onset of the initial motor symptoms and eventual dementia offers a window for potential therapeutic intervention to delay or prevent that dementia. My research has been among the forefront in this regard, by examining brain images to characterize cognitive status in PD. However, in order to be clinically useful, imaging markers must also track progression of the disease. In order to help identify such markers, in this project, I have begun to investigate structural, diffusion, and perfusion MRI measures in patients with PD over 12 months; specifically, I hypothesize that change in blood flow and the integrity of principal white matter tracts will accurately track progression of PD-related cognitive decline and provide a superior measure to change in grey matter integrity.

Overview of the project

Aim: To establish in 24 PD patients the precision of key MRI measures as reliable biomarkers of PD status and progression, relative to 23 healthy controls.

Design: 24 PD patients (17 with normal cognition (PD-N) and 7 with mild cognitive impairment [PD-MCI]) and 23 healthy controls matched for age, sex, and years of education, completed detailed MRI scanning, neuropsychological, and clinical examination, at baseline and after a 12 month follow up period, in order to document the progression of the disease. I investigated whether changes in structure, blood flow, and diffusion were associated with PD-related cognitive or motor decline.

Results: Data acquisition was completed in 2013. We gathered quantitative measures of grey matter atrophy (using structural MRI), tissue microstructure (diffusion tensor imaging [DTI]), and blood flow (arterial spin labelling [ASL]) in 24 PD patients and 23 healthy controls at

baseline and at 12 months, along with clinical and neuropsychological measures at both time points.

Neuropsychology: At y1, 3 PD individuals had converted to a more severe cognitive state; 2 from PD-N to PDD and one from PD-N to PD-MCI. However, across all individuals over 1 year, there were no significant changes in global cognition. Within PD, there was no significant change in UPDRS III or LED.

Imaging: We identified widespread reduction in GM (figure 1) and WM volume over 1 year. The PD group exhibited significantly increased GM atrophy rate relative to controls in posterior cingulate/precuneus, right inferior-middle temporal cortex, and left orbito-frontal cortex (figure 2). Fractional anisotropy (FA, a diffusion tensor imaging metric of white matter structural integrity) showed widespread reduction in numerous principal white matter tracts (figure 3). We identified no significant change in cerebral perfusion over 1 year. Contrary to our stated hypothesis, we identified no further significant difference in rate of change in any of the other MRI measures between controls and PD participants. A significant association emerged between change in global cognitive score and change in grey matter volume, white matter volume, and DTI metrics. We identified no such relationship with change in cerebral perfusion. Within the PD group there was no significant association between change in UPDRS III and change in MRI metrics.

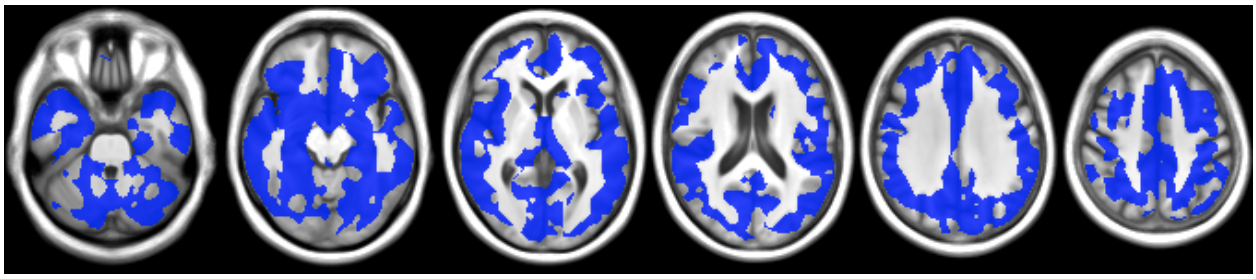

Figure 1. Blue indicates significant grey matter atrophy over 12 months across PD and controls.

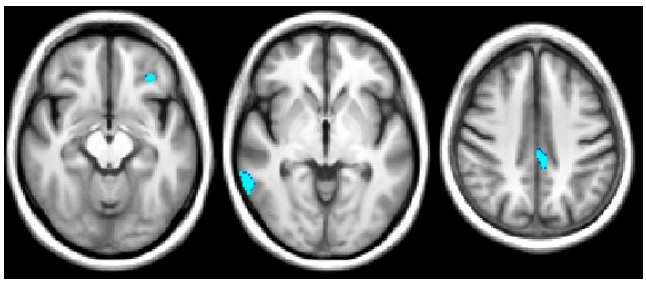

Figure 2. Blue indicates regions where the PD group exhibited significantly more grey matter atrophy than healthy controls over 12 months.

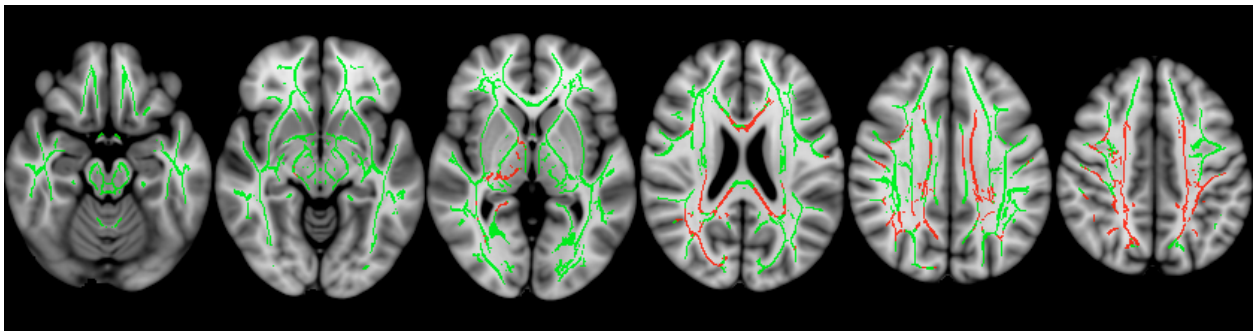

Figure 2. Red indicates significant reduction in fractional anisotropy (loss of microstructural integrity) over 12 months in PD and control groups. Green indicates the centres of principle white matter tracts. There was no significant difference in the rate of change between PD and control groups.

Serial imaging from related fields has previously shown significantly less atrophy in controls than in a number of diseases over a year, including Huntington's disease, Alzheimer's disease, and multiple sclerosis. It is interesting that we only identified a significant difference in rate of change between PD and controls in terms of grey matter atrophy—DTI and blood flow change were not significantly different between the two groups. This may be a real finding in that the accelerated structural changes that we see in PD are the driving force behind progression, or it may be that the more advanced MRI techniques (DTI and ASL) are either not as stable over time or do not reflect progression. Of note, our PD group was relatively intact and at an early disease stage. Indeed, while 1 year is sufficient to show difference in rate of brain change in other neurodegenerative diseases, perhaps PD progresses more slowly than these other diseases. In light of this possibility, we have now collected a large cohort of PD patients and healthy controls over 6 years of follow up. In this larger cohort, we investigated the progression of small vessel cerebrovascular disease as visualized by the presence of 'white matter lesions' (WMLs). We examined WMLs in 130 participants with PD and 50 matched healthy individuals. Of these participants, 69 PD and 41 controls had multiple assessments over 1-6 years. WML volume increased significantly with age and higher WML volume was associated with greater levels of cognitive impairment (figure 4). PD patients who developed dementia over the follow-up period had significantly higher WML volume relative to PD participants who did not develop dementia. These findings suggest that WMLs are associated with the development of dementia in PD and may provide an easily accessible, non-invasive MRI-based marker of future cognitive decline in PD.

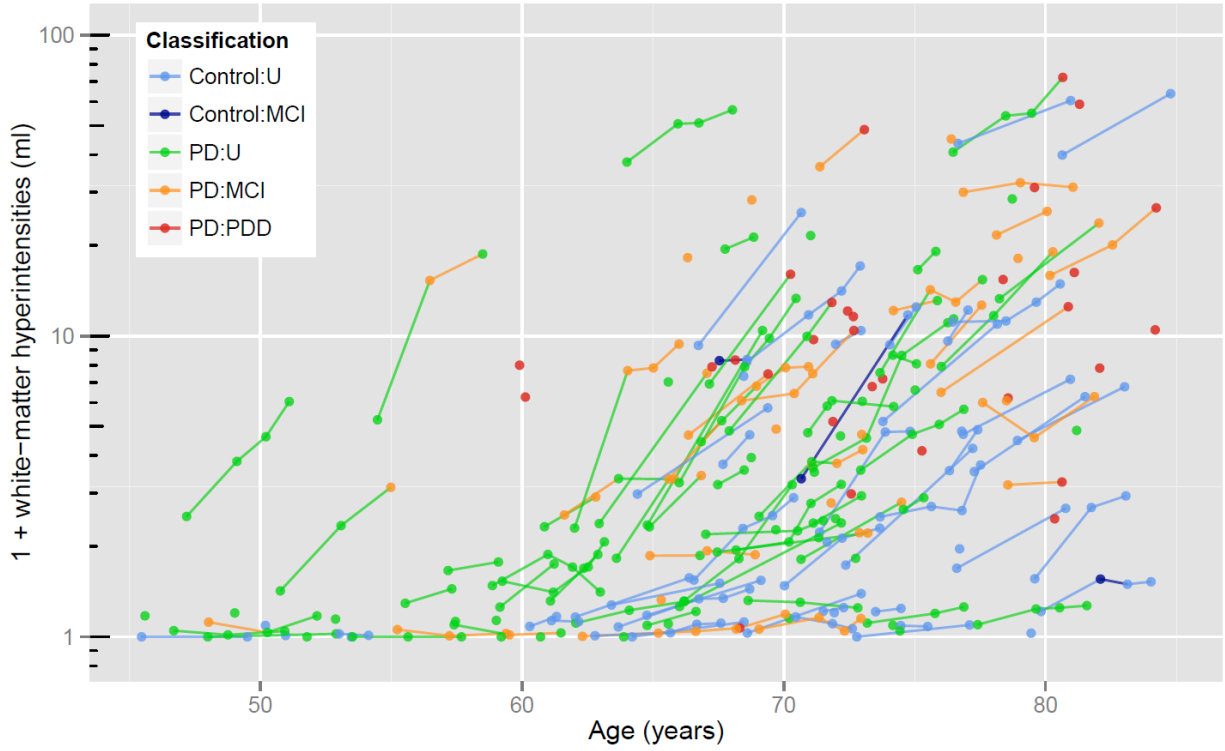

Figure 4. The progression of white matter lesions over time. White matter lesion (WML) volume is displayed on a log scale on the y axis, measured in ml. Age is depicted on the x axis. Points indicate WML volume at each scan. Lines connect multiple scans within the same individual. Colour represents group status: U-cognitively unimpaired, MCI-mild cognitive impairment, PD-Parkinson's disease, PDD-Parkinson's disease with dementia. As age increases, so too does the amount of damaged white matter. Statistically, WML volume increased with age and was

associated with great levels of cognitive impairment. PD patients who developed dementia had higher WML volume.

Milestones achieved in the past 12 months

1. Data collection and analyses completed. Twenty four PD and 23 healthy control participants have completed both baseline and 12 month follow up neuropsychological, clinical, and MRI assessment. I have completed analysis on all 3 MR imaging types (structural, diffusion, and perfusion).
2. I have prepared these results for publication. The manuscript will be submitted very shortly. Additional publications and abstracts are discussed later in the report.
3. Both baseline and 1 year follow up results derived during this fellowship formed an integral part of 3 successful grant submissions. I was awarded the Neurological Foundation of New Zealand's Philip Wrightson Postdoctoral Fellowship as well as an HRC emerging researcher grant. I was also a named investigator on Prof Tim Anderson and Prof John Dalrymple-Alford's successful HRC project grant and the Brain Research NZ CoRE.

Personal development

Overseeing all MR research scanning at the New Zealand Brain Research Institute has provided me with a spectacular opportunity to collaborate with a number of different research groups that work on varied, interesting projects. In this role, I have helped collaborators develop and implement MRI research protocols, identified and ameliorated their scanning problems, and advised on analysis methods and interpretation of results. The responsibility of this position has motivated me—and in some instances forced me—to learn much more about MRI sequence design, implementation, and troubleshooting. It has also allowed me to begin collaborating as an independent researcher.

Collaborations

I have become an integral part of the Canterbury Child Development group, headed by Prof Lianne Woodward's (previously of Washington University, St. Louis, MO, now Harvard, USA). This study uses MRI to investigate development in 12-year-old children. The fostering of a close collaboration with the Paediatric Neurology Department at Washington University, St. Louis, MO, USA, and Brigham and Women's Hospital, Boston, USA, has been a great career development; it has been my first experience with overseas collaboration as the NZ point of contact. I have had to learn how to identify problems, communicate via teleconference/skype, and devise and implement solutions. For example, investigators from St. Louis requested help and advice with processing a specific type of image we acquired here at the NZBRI. I had never worked with this type of scan (used to improve fMRI data quality); once again this collaboration enabled me to acquire new skills. The outcome has been very beneficial, as I now have applied this technique to my Parkinson's disease research. The St. Louis/Harvard relationship has certainly added to my development, not only directly working with the leaders of the field, but also learning first-hand how to manage overseas collaboration. With completion of data collection, we presented 2 abstracts to the Paediatric Academic Societies Annual Meeting and have submitted the first of many imaging publications.

I have also become intimately involved with a wide range of other projects involving MRI in Christchurch. These include: (1) a study investigating multiple sclerosis, in collaboration with neurologist and world MS expert Prof David Miller, University College London, (2) Prof Brian Darlow's (Paediatrics, University of Otago) follow up study of all NZ babies born with very low birth weights in 1986, (3) Prof John Dalrymple-Alford's

(University of Canterbury) study investigating cognitive enrichment in early Alzheimer's disease as a method to combat dementia, and (4) Prof Richard Porter's (Psychological Medicine, University of Otago) study of earthquake-related post-traumatic stress disorder. In addition, we will shortly begin a University of Pennsylvania and NASA-funded study that will investigate the effects of spending the winter in Antarctica.

I was invited and attended a 'sandpit' meeting organized by Dr Shieak Tzeng at the University of Otago, Wellington, on 26 July 2013. This meeting brought together 17 clinicians and researchers from 5 different institutions to address 'Cardiovascular health in NZ'. This was an exciting meeting that introduced me to a diverse range of individuals from different backgrounds and laid the groundwork for subsequent collaboration.

I have now also been invited to give a presentation to the imaging workshop hosted by the Centre for Bioengineering and Nanomedicine at the University of Otago, Dunedin, on 29 August.

Committees

I continue (from 2011) as Secretary of the Health Research Society of Canterbury, a local society that provides a forum for the presentation of health research and to promote research in general. Researchers from the Universities of Otago and Canterbury, Lincoln University, and the Canterbury District Health Board sit on the executive. This has exposed me to a variety of health research topics, involved me with planning and executing meetings, and reviewing abstracts.

Students

I continue to co-supervise a number of students and research assistants.

	PhD	Masters	Honours	Research Fellows/Assistants	Summer Students
Completed	Dr Nadia Borlase[2]	Sophie Grenfell[2] Jeremy Goh[2] Bob Young[2]	Caitlin McCurrie[2]	Dr Campbell Le Heron[3]	Hannah Janssens[1] Caitlin McCurrie[2]
Current	Simon Feng[1] Mustafa Al-Muqbel[1] (as primary supervisor) Amy Wang[2] Kyla Wood[2]	-	-	Geoff Scott[3] Rachel Lean[2] Sophie Grenfell[2]	-

[1]University of Otago, [2]University of Canterbury, [3]New Zealand Brain Research Institute

Conference attendance

I attended the 18th Annual Meeting of the Organization for Human Brain Mapping (OHBM) in Seattle, WA, USA, June 16-20, 2013. OHBM is the world's most significant neuroimaging conference, which provided a venue for approximately 2500 scientists to present and discuss the functional organization of the human brain. The meeting focuses on neuroscience and applications of brain mapping techniques to investigate sensory and motor systems, attention, memory, and cognition in normal and pathological states.

This is the fifth time that I have attended OHBM, and each year has been very beneficial. This year, I solidified relationships with a number of scientists, and was impressed with the new developments in diffusion MRI.

I presented three posters: One from my longitudinal PD work and two from my collaboration with the MS group. All three were very well received. I was happy with the number of truly interested people. A number of well-respected scientists commented on my work and gave

great suggestions. I feel that the enthusiasm attendees showed toward my poster indicates that my work is both interesting and important to the wider Parkinson's disease community. Attending the conference was a very positive experience. I was exposed to exciting, new research and established new connections with fellow researchers while solidifying current relationships. The abstract was published in the meeting proceedings. In addition to attending, I also reviewed 40 abstracts for OHBM 2013.

November 11-12, I was one of 18 individuals from Australia and New Zealand to attend the 'Clinical interpretation of Amyloid PET Images'. The course was spectacular. I was able to have all my questions on amyloid PET acquisition, processing, and analysis answered by the leaders in the field. Additionally, I was instructed on how to provide a clinical read for amyloid PET images. We plan to add this exciting imaging technique to the MRI scanning we currently perform in all PD and control participants.

In addition, I visited St. Louis in June 2013 and Boston in July 2014, for a series of very productive meetings and manuscript planning sessions.

Publications and abstracts appearing or prepared in the first 6 months of this fellowship

I have had two manuscripts published (in the Journal of Neurology, Neurosurgery, and Psychiatry, impact factor = 4.9 and the Journal of Cerebral Blood Flow and Metabolism, IF=5.4), one letter published in print (Movement Disorders, IF=4.6), and a total of 14 abstracts either presented or submitted to various national and international conferences. My published letter was in response to a review of MRI to investigate cognition in PD. This review reprinted an image from my earlier work. I responded by drawing attention to the marked improvement in imaging quality over the span of imaging investigations into PD.

Published manuscripts:

Le Heron CJ, Wright SL, **Melzer TR**, Myall DJ, MacAskill MR, Livingston L, Keenan RJ, Watts R, Dalrymple-Alford JC, Anderson TJ (2014). Comparing cerebral perfusion in Alzheimer's disease and Parkinson's disease dementia—An ASL-MRI study. *J Cereb Blood Flow Metab*. 34: 964-970.

Melzer TR (2013). The evolution of diffusion tensor imaging in Parkinson's disease research. *Movement Disorders*. **28**(9): 1316.

Debernard L, **Melzer TR**, Van Stockum S, Graham C, Wheeler-Kingshott CAM, Dalrymple-Alford JC, Miller DH, Mason DF (2013). Reduced grey matter perfusion without volume loss in early relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry.* doi:10.1136/jnnp-2013-305612

ABSTRACTS: Presented

Almuqbel M, **Melzer TR**, Myall DJ, MacAskill MR, Livingston L, Pitcher TL, Dalrymple-Alford JC, Anderson TJ (2014). Magnetic Resonance Spectroscopy: a potential marker for cognitive impairment in Parkinson's disease. Journal of the New Zealand Medical Association, 127 (1396).

Innes CRH, Kelly PT, Hlavac M, **Melzer TR**, JC Jones RD (2014). Moderate-severe obstructive sleep apnoea is associated with decreased regional cerebral perfusion while awake. *Sleep in Aotearoa - Australasian Sleep Association / Australasian Sleep Technologists Association New Zealand Conference* (9–10 May, 2014), Christchurch, New Zealand.

Mangin KS, **Melzer TR**, Inder TE, Austin NC, Spencer C, Woodward LJ (2014). Corpus callosum development in children born very preterm. *Pediatric Academic Societies Annual Meeting.*

Smyser CD, Inder TE, **Melzer TR**, Watts R, Smyser TA, Schlaggar BL, Woodward LJ (2014). Functional brain network differences in preterm infants persist into childhood. *Pediatric Academic Societies Annual Meeting.*

Melzer T R, Watts R, MacAskill M R, Pitcher T L, Livingston L, Keenan R, Dalrymple-Alford J C, Anderson T J (2013). Longitudinal microstructural change is related to cognitive decline in Parkinson's disease. *Proceedings of the 19th Annual Meeting of the Organization for Human Brain Mapping.*

Debernard L, **Melzer T R**, Van Stockum S, Eagle J, Graham C, Dalrymple-Alford J C, Miller D H, Mason D F (2013). Extensive grey matter perfusion abnormalities but preserved grey matter volume in early relapsing-remitting multiple sclerosis. *Proceedings of the 19th Annual Meeting of the Organization for Human Brain Mapping.*

Grenfell S, **Melzer T R**, Young B, Wang A, Livingston L, Keenan R, MacAskill M R, Anderson T J, Dalrymple-Alford J C (2013). Reduced default mode network connectivity and autobiographical memory in mild cognitive impairment. *The 31st International Australasian Winter Conference on Brain Research*.

Wood K, Livingston L, **Melzer TR**, Pitcher TL, MacAskill MR, Anderson TJ, Dalrymple-Alford JC (2013). Criteria for Parkinson's disease with mild cognitive impairment associated with increased progression to dementia. *The 31st International Australasian Winter Conference on Brain Research*.

Debernard L, **Melzer T R**, Van Stockum S, Graham C, Dalrymple-Alford J C, Miller D H, Mason D F (2013). Volumetric, diffusion and perfusion imaging of grey matter in early relapsing-remitting multiple sclerosis. *29th Congress of the European Committee for Research and Treatment in Multiple Sclerosis.*

Debernard L, Alla S, **Melzer T R**, Van Stockum S, Graham C, Dalrymple-Alford J C, Miller D H, Mason D F (2013). Cortical hypoperfusion is associated with cognitive function in relapsing-remitting multiple sclerosis patients. *29th Congress of the European Committee for Research and Treatment in Multiple Sclerosis.*

ABSTRACTS: Submitted

Melzer TR, Myall DJ, Livingston L, Wood K, Pitcher TL, Keenan RJ, MacAskill MR, Dalrymple-Alford JC, Anderson TJ (2014). White matter lesions – a factor in developing dementia in patients with Parkinson's disease. *The 32st International Australasian Winter Conference on Brain Research*, Queenstown, New Zealand.

Myall DJ, Wood K, Livingston L, Pitcher TL, **Melzer TR** MacAskill MR, Anderson TJ, Dalrymple-Alford JC (2014). Individualised medicine: Predicting dementia in Parkinson's disease. *The 32st International Australasian Winter Conference on Brain Research*, Queenstown, New Zealand.

Almuqbel M, **Melzer TR**, Myall DJ, MacAskill MR, Livingston L, Wood KL, Pitcher TL, Dalrymple-Alford JC, Anderson TJ (2014). Cognitive status in Parkinson's disease characterised by Magnetic Resonance Spectroscopy. *The 32st International Australasian Winter Conference on Brain Research*, Queenstown, New Zealand.

Wood K, Myall DJ, Livingston L, **Melzer TR**, Pitcher TL, MacAskill MR, Anderson TJ, Dalrymple-Alford JC (2014). Comparing mild cognitive impairment criteria in Parkinson's disease: influence on dementia onset. *The 32st International Australasian Winter Conference on Brain Research*, Queenstown, New Zealand.