My NMRC Research Training Fellowship Experience

By Dr Ng Kok Pin, Consultant, Department of Neurology, National Neuroscience Institute

Dr Ng Kok Pin is a recipient of the 2017 National Medical Research Council (NMRC) Research Training Fellowship award, conferred to him earlier this year. In this article, he shares some of his research findings and international experiences on this training fellowship.

After a long 24-hour flight, we finally reached Montreal. The following day, I met up with my supervisor, Professor Serge Gauthier, at the McGill University Research Centre for Studies in Aging (MCSA) to introduce myself and to discuss my learning objectives for the year. I was also introduced to my second supervisor, Dr Pedro Rosa-Neto and my team mates in the Centre.

Figure 1: McGill University Research Centre for Studies in Aging (MCSA)

Figure 2: Translational Neuroimaging Laboratory (TNL)

The MCSA is situated in a beautiful historic house at the Douglas Institute. The clinics and the Clinical Trials Unit are located at the first level while the Translational Neuroimaging Laboratory (TNL), where I spent most of my time during my fellowship, is located at the third level.

Under the guidance of my supervisors and team mates at the TNL, I learnt the steps of image processing, image co-registration, image analysis, and the organization of huge datasets, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI).

I selected cognitively normal individuals from the ADNI database to study my NMRC research proposal, with the aim to identify regional brain metabolic dysfunctions associated with neuropsychiatric symptoms (NPS) in preclinical Alzheimer Disease (AD). Using amyloid and tau biomarkers, I stratified the study participants into preclinical AD, asymptomatic at-risk for AD and healthy controls. We found that the magnitude of NPS in preclinical AD, driven by sleep behavior and irritability domains, is linked to transitory metabolic dysfunctions within the limbic networks vulnerable to the AD process, and predicts subsequent posterior cingulate cortex hypometabolism (Figure 3). Our findings support an emerging conceptual framework in which NPS constitute an early clinical manifestation of AD pathophysiology.[1]

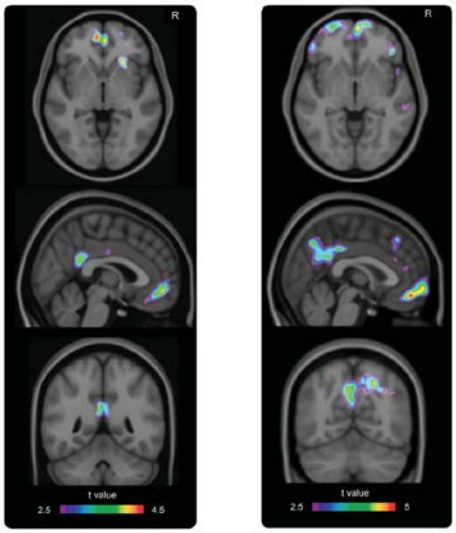


Figure 3: Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease.

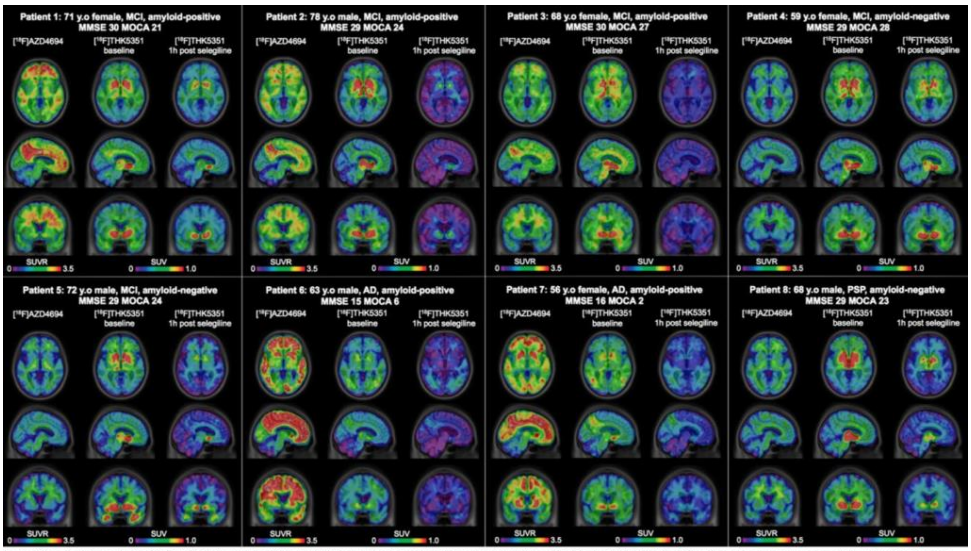
In August, Dr Pedro asked me if I would be keen to lead a positron emission tomography (PET) project and I said "yes!" without hesitation. Within the tight dateline of a week, I wrote the protocol and submitted it for ethics approval. With that, I started my journey in the world of PET imaging. I subsequently attended a course at the Montreal Neurological Institute on PET imaging, which covered tracer production, scanning protocol, in vitro and in vivo quantification of PET tracer binding and its application in research and clinical studies. With the help of my team mates who were fluent in French, we recruited 8 participants and the study commenced in late October.

In this study, we tested the effects of monoamine oxidase B (MAO-B) inhibition on [18F]THK5351 brain uptake, using a single dose of selegiline. [18F]THK5351 is a quinoline-derived tau imaging agent with high affinity to paired helical filaments (PHF). However, high levels of [18F]THK5351 retention in brain regions with negligible concentrations of PHF raise questions about the interpretation of the PET signals, particularly given previously described interactions between quinolone derivatives and monoamine oxidase B (MAO-B). Five mild cognitive impairment, two AD and one progressive supranuclear palsy patients had baseline [18F]AZD4694 and [18F]THK5351 scans to quantify brain amyloid and PHF tau load, respectively.

A second [18F]THK5351 scan was conducted one week later, one hour after a 10-mg oral dose of selegiline. We found that at baseline, the mean [18F]THK5351 standardized uptake values (SUV) were highest in the basal ganglia and thalamus, brain regions rich in MAO-B.

In the post-selegiline scans, the regional SUVs were reduced on average by 36.7% to 51.8% (Figure 4), with the greatest reduction noted in the thalamus (51.8%) and basal ganglia (51.4%).

Our results indicate that the interpretation of [18F]THK5351 PET images, with respect to tau, is confounded by the high MAO-B availability across the entire brain.[2]



Selegiline reduces brain ^{18}F-THK5351 standardized uptake value. Standardized uptake value (SUV) and SUV ratio (SUVR) map overlaid on a structural MRI scan showing the SUVR from 40 to 70 min after ^{18}F-AZD4694 injection, and baseline and 1 h post-selegiline SUV from 50 to 70 min after 18F-THK5351 injection in the eight patients.

Figure 4: Monoamine oxidase B inhibitor, selegiline, reduces [18F]THK5351 uptake in the human brain

I was also given opportunities to present my research work at international conferences.

For my tau imaging project, I had a poster presentation at the 11th Human Amyloid Imaging held in Miami, Florida, as well as an oral presentation at the biannual Berlin BRAIN & BRIAN PET 2017 conference. I was further awarded the Early Career Investigator Travel Bursary at BRAIN & BRAIN PET 2017. Subsequently, I had a poster presentation on my NPS project at the American Academy of Neurology (AAN) 2017 Annual Meeting held in Boston. It was a great learning experience attending these conferences.

Despite a busy working schedule, my family and I had many opportunities to explore the regions around Montreal. Canada is a very beautiful country with many experiences to be had during the amazing four seasons (although the winter in Montreal is long and harsh!). We visited places such as the Niagara Falls and New Hampshire, and in autumn, my kids and I had lots of fun picking apples! I also met up with my friend and colleague, Carol, from NNI Neurology, in Banff.

Figure 5: Dr Ng and his family

Figure 6: Dr Ng with supervisors and team mates

I would like to thank my supervisors, Professor Serge Gauthier and Dr Pedro Rosa-Neto, and my team mates for their support, guidance, trust and friendship. It was indeed an amazing year and I will never forget the memories we shared at the MCSA/TNL.

I would also like to thank my mentor Dr Nagaendran Kandiah, for giving me the opportunity to undergo my fellowship at the MCSA and taking time off to visit with the dementia team in February'17.

Lastly, I would like to thank the NMRC for supporting my research training fellowship at the MCSA.

References

[1] Ng, Kok Pin, et al. "Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease." *Neurology* 88.19 (2017): 1814-1821.

[2] Ng, Kok Pin, et al. "Monoamine oxidase B inhibitor, selegiline, reduces 18 F-THK5351 uptake in the human brain." *Alzheimer's research & therapy* 9.1 (2017): 25.

About the Author

Dr Ng Kok Pin is a Consultant at the Department of Neurology, National Neuroscience Institute, Tan Tock Seng Hospital Campus. After graduating from the Yong Loo Lin School of Medicine, National University of Singapore in 2006, he obtained his MRCP(UK) in 2011 and was accredited as a Neurologist by the Ministry of Health Singapore in 2015. In 2016, he obtained his Master of Clinical Investigation (NUS). Dr Ng subspecializes in dementia and his research interest is PET imaging in neurocognitive diseases.