Quantitative Neostriatal Neuroanatomy as a Basis of Frontostriatal Circuit Dysfunction in Neuropsychiatric Disease

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Statement of the Candidate's Contribution to the Research

The research undertaken for this thesis was based on studies led by the candidate, conducted across three centres: the Research Centre for the Neurosciences of Ageing, Academic Unit of Psychological Medicine, ANU Medical School, Canberra, Australia; the Stockholm Medical Imaging Laboratory (SMILE), Division of Clinical Geriatrics, Department of Neurobiology, Caring Sciences & Society, Karolinska Institute, Stockholm, Sweden; and the Neuropsychiatric Institute, University of New South Wales, Sydney, Australia. The candidate is a Senior Specialist and Associate Professor of Psychiatry, Academic Unit of Psychological Medicine, at the Australian National University Medical School, Canberra Hospital, Canberra, Australia; and a Visiting Guest Researcher at the Karolinska Institute, Huddinge, Stockholm, Sweden.

The candidate was lead investigator and guarantor on all research in the thesis, developed the research hypotheses, and: designed; obtained funding for; was first author; performed statistical analysis; performed manual tracing of the caudate nucleus or putamen (studies 1, 2, 3, & 4) and stroke volume (study 5); supervised manual tracing (study 5); performed recruitment, medical, neurological and psychiatric assessments (study 5). Segments of text have been reproduced verbatim from these publications. Published papers have been reproduced with permission. The candidate independently drafted all chapters of this thesis and revised them in the context of anonymous peer review and supervisor feedback.

None of the published works have been previously considered for a degree previously granted in any University.

Jeffrey Chee Leong Looi

Thesis Structure

This thesis comprises two parts.

Part I: Thesis introduction and published papers

The first part consists of the original body of research on the quantitative neuroanatomy of the neostriatum as a structural basis for frontostriatal dysfunction in neuropsychiatric disease. This first part comprises an introduction and extended context statement to the thesis, Chapter 1, followed by published thesis papers appended as Chapters 2-6 to preserve their original formatting, with each paper preceded by a title page and schematic of the role in the thesis. Within the body of the introduction, the thesis papers are referenced by study number and/or citation, as appropriate.

Part II: Additional papers and book chapters

The second part of the thesis consists of six additional papers and/or book chapters in the research field of cognitive neuropsychiatry constituting a background and context to the thesis studies.

Part I: List of Thesis Papers

1. **<u>Chapter 2, Study 1:</u> Looi, J.C.L.**, Lindberg, O., Liberg, B., Tatham, V., Kumar, R., Maller, J., Millard, E., Sachdev, P., Hogberg, G., Pagani, M., Botes, L., Engman, E-L., Zhang, Y., Svensson, L., Wahlund, L-O. (2008a) Volumetrics of the caudate nucleus: reliability and validity of a new manual tracing protocol. Psych Research Neuroimaging 163, 279-288.

2. **<u>Chapter 3, Study 2:</u> Looi, J.C.L.**, Maller J., Lindberg, O., Liberg, B., Hogberg, G., Pagani, M., Botes, L., Engman, E-L., Zhang, Y., Svensson, L., Wahlund, L-O. (2009a) Caudate volumes in public transportation workers exposed to trauma in the Stockholm train system. Psychiatry Research Neuroimaging 171, 138-143.

3. **<u>Chapter 4, Study 3:</u> Looi, J.C.L.**, Lindberg, O., Zandbelt, B.B., Ostberg, P., Andersen, C., Botes, L., Svensson, L., Wahlund, L-O. (2008b) Caudate nucleus volume in frontotemporal lobar degeneration – differential atrophy in subtypes of FTLD. AJNR American Journal of Neuroradiology 29, 1537-1543.

4. **<u>Chapter 5, Study 4:</u> Looi, J.C.L.**, Svensson, L., Lindberg, O., Zandbelt, B.B., Ostberg, P., Orndahl, E., Wahlund, L-O. (2009b) Putaminal volume in frontotemporal lobar degeneration and Alzheimer's Disease – differential volumes in subtypes of FTLD, AD, and controls. AJNR American Journal of Neuroradiology 30, 1552-1560.

5. **<u>Chapter 6, Study 5:</u> Looi, J.C.L.**, Tatham, V., Kumar, R., Maller, J.J., Millard, E., Wen, W., Brodaty, H., Sachdev, P.S. (2009c) Caudate nucleus volumes in stroke and in vascular dementia. Psychiatry Research Neuroimaging 174, 67-75.

Part II: List of additional papers and book chapters in cognitive neuropsychiatry

1. **Looi J.C.L.**, Matias M., Ruzich M.J. (2005) Conceptualisation of depression in Parkinson's Disease. Neuropsychiatric Disease and Treatment, 1: 135-143.

2. Ruzich M.J., **Looi J.C.L.**, Robertson M.D. (2005) Delayed onset of post-traumatic stress disorder among male combat veterans: a case series. American Journal of Geriatric Psychiatry 13: 424-427.

3. Lindberg, O., Ostberg, P., Zandbelt, B.B., Oberg, J., Zhang, Y., Botes, L., Andersen, C., **Looi, J.C.L.**, Bogdanovic, N., Wahlund, L-O. (2009) Cortical morphometric subclassification of frontotemporal lobar degeneration. AJNR American Journal of Neuroradiology, 30: 1233-1239.

4. **Looi J.C.L.**, Sachdev P.S. (2003) Structural neuroimaging of the ageing brain. In Sachdev P.S. The Ageing Brain: The Neurobiology and Neuropsychiatry of Ageing. Swets & Zietlinger: Lisse, The Netherlands. pp49-62

5. **Looi J.C.L.**, Trollor J.N., Sachdev P.S. (2007) Neurological aspects of normal aging. In Feigin V, Bennet DA, (eds) Handbook of Clinical Neuroepidemiology. Nova Science Publishers: New York, pp 465-502.

6. **Looi J.C.L.**, Pagani M., Nardo D., Wahlund L-O, Raphael, B. (In Press) Update on structural and functional imaging in PTSD. In Sher L, Vilens A. Neurobiology of Post-traumatic Stress Disorder. Nova Science Publishers: New York

Thesis Abstract

Background and Purpose:

Neuropsychiatric diseases are protean, affecting cognition, emotion and behaviour, including such diseases as reactions to traumatic stress (post-traumatic stress disorder), cerebrovascular disease and the neurodegenerative dementias.

There has been much interest in understanding the neural basis of neuropsychiatric disease. A model that has been employed to investigate such disease has been the endophenotype, a restricted set of phenotypic or clinical features that may have a more specific structural and hence, genetic basis. An example of an endophenotype is frontal-executive neuropsychological function, localised to the neural substrate of dorsolateral prefrontal cortex frontostriatal circuit. Consequently, it is possible to explore the structural basis of an endophenotype by studying the components of neural circuits carrying such functions.

Thus, frontostriatal circuits may be useful as a structural basis for endophenotypes related to frontal cognitive function. These circuits extensively mediate cognition, emotion and behaviour within humans. The caudate nucleus and putamen, comprising the human neostriatum, serve crucial roles within frontostriatal circuits. The caudate and putamen may thus serve as a potential, quantifiable component of the structural basis for endophenotypes.

It was hypothesized that functional change may be reflected in structural changes in the neostriatum due to neuroplasticity. Thus functional activation or disconnection

might impact upon the structure of the caudate or putamen. Other corticostriatal circuits in addition to frontostriatal circuits may thus be affected. These studies were designed to measure the volume of the neostriatum as a quantified neuroanatomical basis of the endophenotype of frontostriatal dysfunction within specific neuropsychiatric diseases.

Methods:

Thesis Study 1 (Looi et al., 2008a) A method was developed to quantify the volume of the caudate nucleus and putamen in vivo on magnetic resonance images (MRIs) of persons suffering from neuropsychiatric disease. This involved manual tracing or segmentation, by a single tracer, blinded to diagnosis, via visual inspection and outlining of caudate or putamen on the MRI data displayed using image analysis software on a personal computer. This protocol was standardized by the production of reference images and assessed for reliability and validity at intra- and inter-rater levels (Thesis Study 1 and Thesis Study 4).

Results:

The manual tracing protocol was used quantify the volume of the head and body of the caudate, and putamen, in specific neuropsychiatric disease in which frontostriatal dysfunction has been implicated. All analyses were adjusted for brain volume and other relevant covariates or confounders, such as age or gender.

Thesis Study 2 (Looi et al., 2009) investigated caudate nucleus volumes in persons exposed to trauma in the Stockholm train system, with regard to whether they suffered from post-traumatic stress disorder (PTSD). It was found that right caudate

nucleus volume was significantly greater in those with PTSD compared to those without PTSD, supporting either increased connectivity or altered neurodevelopment in the caudate.

Thesis Study 3 (Looi et al., 2008b) investigated caudate nucleus volumes in frontotemporal lobar degeneration (FTLD) and its subtypes, in comparison with healthy controls and those with Alzheimer's disease. It was found that left caudate nucleus volume varied significantly across these groups, in accordance with the expected degree of frontostriatal dysfunction and was correlated with a basic measure of cognition, the MMSE.

Thesis Study 4 (Looi et al., 2009b) investigated putaminal volumes in FTLD and its subtypes, finding the right putamen was significantly smaller than in AD and controls on the right potentially supporting the role of the putamen in frontostriatal dysfunction.

Thesis Study 5 (Looi et al., 2009c) investigated caudate nucleus volume in a stroke cohort with and without vascular dementia, in comparison with healthy controls. Those with vascular dementia had the smallest caudate volumes, the stroke group was intermediate and the control group had the largest volume. These differences were bilateral, and showed an inverse relationship with white matter hyperintensity and stroke volume.

Conclusions:

These studies have contributed to understanding of the alterations in neuroanatomy of the neostriatum in specific neuropsychiatric disease. The studies have involved development of reliable and valid methods for quantitative manual segmentation of the caudate nucleus and putamen on magnetic resonance images. Using these robust methods, significant findings were made.

The volume of the head and body of the caudate nucleus was found to vary as predicted by theoretical involvement of frontostriatal dysfunction: with significant atrophy noted in FTLD, stroke and cerebrovascular disease in a gradient consistent with expected dysfunction; the putamen was found to be affected in the FTD subtype of FTLD; and potential functional activation of both frontostriatal or corticostriatal circuits was associated with enlargement in active PTSD. Therefore, structural change in the neostriatum in neuropsychiatric disease with putative frontostriatal dysfunction, and functional activation or disconnection of frontostriatal or corticostriatal circuits, has been substantiated across FTLD, stroke, vascular dementia.

Furthermore, a variation in caudate volume has been found, consistent with that which might be predicted due to relative frontostriatal dysfunction within FTLD and functional disconnection in cerebrovascular disease and stroke. Thus, the caudate nucleus may serve as a structural component basis for the endophenotype of frontostriatal dysfunction in specific neuropsychiatric disease, whilst the putamen may play a lesser role, at least in FTLD.

Thus these findings establish that there is not only significant change in the volume of the neostriatum in specific neuropsychiatric disease; potential evidence of directionality of volumetric change was established, with potential overactivity of the frontostriatal circuits associated with larger volumes of the caudate in PTSD – a potential neuroplastic enlargement; whilst neuropsychiatric disease which might result in disconnection, decreased cortical input (in FTLD), or loss of blood supply to the caudate and disconnection (in stroke), is associated with reduced volumes of the caudate; all in comparison to matched healthy controls.

Future studies to explore and confirm the importance of such structural change include: larger studies to better assess significance; use of semi-automated segmentation methods to improve speed of analysis; morphometric (shape analysis) of the neostriatum; correlation studies with clinical features (neuropsychological and neuropsychiatric); and correlation with functional imaging.

List of Abbreviations/Glossary

AD: Alzheimer's disease

ACC: anterior cingulate circuit, a frontostriatal circuit

DLPFC: dorsolateral prefrontal circuit, a frontostriatal circuit

FLAIR: fluid attenuation inversion recovery sequence used in magnetic resonance imaging to enhance the visualisation of deep white matter structures/disease

Frontostriatal circuits: neural circuits comprising fronto-striato-pallido-thalamic-frontal pathways

F: degrees of freedom in MANCOVA statistical analysis

FTLD: Frontotemporal lobar degeneration, superordinate category of neurodegenerative disease resulting in atrophy of frontal and temporal lobes

FTD: frontotemporal dementia, subtype of frontotemporal lobar degeneration

ICA: intracranial area, a manual measurement of the widest cross-sectional area of the inner rim of the cranium in a specified plane

ICC: intra-class correlation, descriptive statistic of consistency or reliability of measurements within and between observers

MANCOVA: multivariate analysis of covariance, general linear statistical method for more than one continuous dependent outcome variable, which cannot be simply combined and one or more factor (categorical – group) variables

MMSE: mini-mental state examination, a cognitive assessment scale

Neuroplastic: neural structure hypertrophy due to increased connectivity

MRI: magnetic resonance imaging

n: number in study

OCD: obsessive-compulsive disorder

OFC: orbitofrontal circuit, a frontostriatal circuit

p: significance value of statistical test

Partial eta-squared: effect-size statistic

Pathoplastic: neural structure atrophy due to disconnection or diaschisis

PET: positron emission tomography, type of radionuclide imaging

PTSD: post-traumatic stress disorder

PNFA: progressive non-fluent aphasia, subtype of frontotemporal lobar degeneration

r: partial correlation value

rCBF: regional cerebral blood flow, a measure derived from PET

ROI: region of interest, boundary used in MRI segmentation to define an anatomical region in two dimensions

SD: Semantic dementia, subtype of frontotemporal lobar degeneration

SPECT: Single-photon emission computed tomography, type of radionuclide imaging

VaD: vascular dementia

VOI: volume of interest, boundary used in MRI segmentation to define an anatomical volume in three dimensions, which may be composed of serial summation of ROIs

WM: white matter

WMH: white matter hyperintensities, image inhomogeneities visualised on FLAIR MRI, corresponding to regions of demyelination, dysmyelination, inflammation and/or microinfarction

- 14 -

If the map differs from the terrain, believe the terrain – Norse proverb