Novel approaches to the pathophysiology of late-life depression

By

Dr Harris A Eyre

MBBS with Honours, James Cook University, 2011

Fulbright Scholar, UCLA, 2014/2015

PhD Candidate in the Discipline of Psychiatry

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This dissertation is written by

Dr Harris A Eyre

This dissertation was supported by:

Primary supervisor: Professor Bernhard Baune, MD, PhD, Chair and Professor of Psychiatry, Discipline of Psychiatry, University of Adelaide

External co-supervisor: Assistant Professor David Merrill, MD, PhD, Department of Geriatric Psychiatry, UCLA

External co-supervisor: Professor Helen Lavretsky, MD, MS, Professor-in-Residence, Department of Geriatric Psychiatry, UCLA

Abstract

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The growing impact of under-recognised and under-treated late-life depression (LLD) stands to negatively affect our societies within the context of an ageing world. LLD is a complex disorder where past studies have explored a narrow set of characteristics in isolation (e.g. clinical, neuropsychological, brain imaging, genomics and proteomics). These isolated analyses have yielded useful findings, and continue to do so, however they are limited given the neurobiological mechanisms of LLD are complex and involve interplay between many brain systems, and can manifest in various investigative modalities. Fortunately, there are novel methods for advancing mental health research. In this dissertation, a variety of novel approaches are used to develop a more comprehensive understanding of the pathophysiology of LLD. This is achieved by exploring discreet studies of peripheral biomarkers (i.e. immunology and genomics), as well as neuroimaging biomarkers (i.e. functional and molecular imaging), and contextualising them against each other. Novel applications of these principles and research tools including machine learning may yield more effective diagnostic, treatment and preventive options for LLD.

Thesis declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and, where applicable, any partner institution responsible for the joint award of this degree.

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List of Abbreviations

2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)-amino]-2-naphthyl}ethylidene) malononitrile ([^{18}F]FDDNP)

Alzheimer's disease (AD)

Amyloid β (Aβ)

Anterior cingulate cortex (ACC)

Apathy Evaluation Scale (AES)

Beck Depression Inventory (BDI)

Blood brain barrier (BBB)

Body mass index (BMI)

cAMP responsive element binding protein (CREB)

Central nervous system (CNS)

Cerebrospinal fluid (CSF)

Chronic traumatic encephalopathy (CTE)

Citalopram (CIT)

Clinical Global Impression (CGI)

Cognitive control network (CCN)

Connor-Davidson Resilience Scale (CD-RISC)

C-reactive protein (CRP)

Cumulative Illness Rating Scale-Geriatric (CIRS-G)

Cytometric bead array (CBA)

Database for Annotation, Visualization and Integrated Discovery (DAVID)

Default Mode Network (DMN)

Diagnostic and Statistical Manual (DSM)

Diffusion tensor imaging (DTI)

Dopamine (DA)

Dorsal anterior cingulate cortex (dACC)

Dorsolateral prefrontal cortex (DLPFC)

Echo-planar imaging (EPI)

Effect size (ES)

Electrocardiogram (ECG)

Enzyme-linked immunosorbent assay (ELISA)

FMRIB Software Library (FSL)

Fractional anisotropy (FA)

Geriatric Depression Scale (GDS)

Global burden of disease (GBD)

Glucocorticoid receptor (GR)

Hamilton Anxiety Scale (HAS or HAM-A)

Hamilton Depression Rating Scale (HDRS or HAM-D)

Hypothalamus-pituitary-adrenal (HPA)

Hypoxia-inducible factors (HIF)

Independent components analysis (ICA)

Indoleamine 2,3 dioxygenase (IDO)

Induced pluripotent stem cells (iPS)

Institutional Review Board (IRB)

Interferon (IFN)

Interferon γ-induced protein (IP)

Interleukin (IL)

International Classification of Diseases (ICD)

Janus kinase (JNK)

Late-life depression (LLD)

Macrophage inflammatory protein (MIP)

Macrophages migration inhibitory factor (MIF)

Major depressive disorder (MDD)

Major histocompatibility complex, class II, DR β 5 (HLA-DRB5)

Medial prefrontal cortex (mPFC)

Medial temporal lobe (MTL)

Medical Outcomes Study Short Form 36-Item Health Survey (SF-36)

Methylphenidate (MPH)

Mild cognitive impairment (MCI)

Mini-Mental State Examination (MMSE)

Mitogen-activated protein kinase (MAPK)

Monocyte chemotactic protein (MCP)

Montgomery-Asberg Depression Rating Scale (MADRS)

Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC)

Neural stem cells (NSCs)

Neurofibrillary tangles (NFTs)

Noradrenaline (NA)

Nuclear factor-κB (NF-κB)

Nucleus accumbens (NAcc)

Peripheral blood mononuclear cells (PBMC)

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Posterior cingulate cortex (PCC)

Posterior superior temporal sulcus (pSTS)

Preferred reporting items for systematic reviews and meta-analyses (PRISMA)

Reactive oxygen species (ROS)

Regions of interest (ROIs)

Relative distribution volume (DVR)

Relative risk (RR)

Resting-state functional magnetic resonance imaging (rs-fMRI)

Selective serotonin reuptake inhibitors (SSRIs)

Selenium binding protein 1 (SELENBP1)

Serotonin (5-HT)

Serotonin noradrenaline reuptake inhibitors (SNRIs)

Sialic acid binding immunoglobulin-like lectin, pseudogene 3 (SIGLECP3)

Signal transducer and activator of transcription (STAT)

SMA- and MAD-related protein 7 (SMAD 7)

Standard deviation (SD)

Statistical parametric mapping (SPM)

Stress-activated protein kinase (SAPK)

TGFβ activated kinase-1 (TAK-1)

T-helper (T_h)

Tumour necrosis factor (TNF)

Tumour, node, metastasis (TNM)

Udvalg for Kliniske Undersogelser (UKU)

Uncinated fasciculus (UF)

White matter lesions or hyperintensities (WMH)

World Health Organization (WHO)

Years lived with disability (YLD)

PREFACE

There are many, many people to thank in the completion of this PhD dissertation, which has taken me from tropical Townsville, to Adelaide, Los Angeles and finally Melbourne.

Firstly, I would like to thank Professor Bernhard T Baune for his support and mentorship not only during this PhD period, but also since the initiation of my engagement in research some 7 years ago. Prof Baune has supported me tirelessly through my development as a medical student, researcher, intern and now psychiatry registrar. During this time, I have developed not only as a researcher and clinician but also on a personal level. If it was not for his ongoing support, I may not have made it this far. It is through Prof Baune's work in psychiatric neuroscience that I have found tremendous meaning – the complexities of the brain, the importance of high quality science, and the benefits of a rich convergence or transdisciplinary approach to enquiry. Prof Baune has been supportive in enabling me to pursue my interests in travelling to the United States of America on a Fulbright Scholarship, as well as my settling back in Melbourne, Australia. This kind of unwavering support is very rare as I have asked a lot through this unique research career, and I will be forever grateful.

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value' to patient care. Through Prof Lavretsky's group, I have particularly taken stock of innovations in positive psychiatry, as well as evidence generation in novel fields (e.g. integrative psychiatry). This has been fascinating and enriching to observe, and in small part, contribute to.

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