Novel approaches to the pathophysiology of late-life depression

By

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Abstract

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University of Adelaide, 2015

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

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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>2-(1-{6-[2-[^{18}F]fluoroethyl}(methyl)-amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP)</td>
<td>Alzheimer’s disease (AD)</td>
</tr>
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<td>Amyloid β (Aβ)</td>
<td>Anterior cingulate cortex (ACC)</td>
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<td>Apathy Evaluation Scale (AES)</td>
<td>Beck Depression Inventory (BDI)</td>
</tr>
<tr>
<td>Blood brain barrier (BBB)</td>
<td>Body mass index (BMI)</td>
</tr>
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<td>cAMP responsive element binding protein (CREB)</td>
<td>Central nervous system (CNS)</td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF)</td>
<td>Chronic traumatic encephalopathy (CTE)</td>
</tr>
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<td>Citalopram (CIT)</td>
<td>Clinical Global Impression (CGI)</td>
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<tr>
<td>Cognitive control network (CCN)</td>
<td>Connor-Davidson Resilience Scale (CD-RISC)</td>
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<tr>
<td>C-reactive protein (CRP)</td>
<td>Cumulative Illness Rating Scale-Geriatric (CIRS-G)</td>
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<tr>
<td>Cytometric bead array (CBA)</td>
<td>Database for Annotation, Visualization and Integrated Discovery (DAVID)</td>
</tr>
<tr>
<td>Default Mode Network (DMN)</td>
<td>Diagnostic and Statistical Manual (DSM)</td>
</tr>
<tr>
<td>Diffusion tensor imaging (DTI)</td>
<td>Dopamine (DA)</td>
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<tr>
<td>Dorsal anterior cingulate cortex (dACC)</td>
<td>Dorsolateral prefrontal cortex (DLPFC)</td>
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<tr>
<td>Echo-planar imaging (EPI)</td>
<td>Effect size (ES)</td>
</tr>
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<td>Electrocardiogram (ECG)</td>
<td>Enzyme-linked immunosorbent assay (ELISA)</td>
</tr>
<tr>
<td>FMRIB Software Library (FSL)</td>
<td>Fractional anisotropy (FA)</td>
</tr>
<tr>
<td>Geriatric Depression Scale (GDS)</td>
<td>Global burden of disease (GBD)</td>
</tr>
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<td>Glucocorticoid receptor (GR)</td>
<td>Hamilton Anxiety Scale (HAS or HAM-A)</td>
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<td>Hamilton Depression Rating Scale (HDRS or HAM-D)</td>
<td>Hypothalamus-pituitary-adrenal (HPA)</td>
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<td>Hypoxia-inducible factors (HIF)</td>
<td>Independent components analysis (ICA)</td>
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<td>Indoleamine 2,3 dioxygenase (IDO)</td>
<td>Induced pluripotent stem cells (iPS)</td>
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<td>Institutional Review Board (IRB)</td>
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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)
Pittsburgh Compound B (PiB)
Positron emission tomography (PET)
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)
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<th>Term</th>
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<tr>
<td>SMA- and MAD-related protein 7 (SMAD 7)</td>
<td>TGFβ activated kinase-1 (TAK-1)</td>
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<tr>
<td>Standard deviation (SD)</td>
<td>T-helper (T&lt;sub&gt;h&lt;/sub&gt;)</td>
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<tr>
<td>Statistical parametric mapping (SPM)</td>
<td>Tumour necrosis factor (TNF)</td>
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<tr>
<td>Stress-activated protein kinase (SAPK)</td>
<td>Tumour, node, metastasis (TNM)</td>
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<td><em>Udvalg for Kliniske Undersogelser</em> (UKU)</td>
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<td></td>
<td>Uncinated fasciculus (UF)</td>
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<td></td>
<td>White matter lesions or hyperintensities (WMH)</td>
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<td></td>
<td>World Health Organization (WHO)</td>
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<td>Years lived with disability (YLD)</td>
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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.

Following, I would like to thank Prof Helen Lavretsky for her generosity in supporting my Fulbright Scholar period at the UCLA Division of Geriatric Psychiatry with her research group. My goal was to spend 12 months living the USA working with world class experts in a variety of fields. I certainly found this in spades within Prof Lavretsky’s group. This period at UCLA and in California has spurred me on in my career to continue exploring novel pathways of ‘adding
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.

Also, I would like to thank A/Prof David Merrill for his support through the articulation of the convergence psychiatry concept, which has developed through much iteration. A/Prof David Merrill has been supportive in helping me understand convergence psychiatry as it applies to research, as well as clinical medicine. A/Prof Merrill and I have many years of interesting work ahead of us.

To all collaborators, I am most grateful. From collaborators within the Discipline of Psychiatry at the University of Adelaide to those from Prof Lavretsky’s research group and the Brain Mapping Centre at UCLA.

Particular thanks also goes to the Australia-America Fulbright Commission who supported my travel and living in Los Angeles for 12 months. This period of time was life changing and enriching, with tremendous exposure to new scientific fields, the Californian bioentrepreneurial scene, many new friends and collaborators.