

# Novel approaches to the pathophysiology of late-life depression

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## **Abstract**

# **Novel approaches to the pathophysiology of late-life depression**

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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.

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### List of Abbreviations

2-(1-{6-[(2-[ <sup>18</sup> F]fluoroethyl)(methyl)-amino]-2-naphthyl}ethylidene) malononitrile ([ <sup>18</sup> F]FDDNP)	Connor-Davidson Resilience Scale (CD-RISC)	Enzyme-linked immunosorbent assay (ELISA)
Alzheimer's disease (AD)	C-reactive protein (CRP)	FMRIB Software Library (FSL)
Amyloid $\beta$ (A $\beta$ )	Cumulative Illness Rating Scale-Geriatric (CIRS-G)	Fractional anisotropy (FA)
Anterior cingulate cortex (ACC)	Cytometric bead array (CBA)	Geriatric Depression Scale (GDS)
Apathy Evaluation Scale (AES)	Database for Annotation, Visualization and Integrated Discovery (DAVID)	Global burden of disease (GBD)
Beck Depression Inventory (BDI)	Default Mode Network (DMN)	Glucocorticoid receptor (GR)
Blood brain barrier (BBB)	Diagnostic and Statistical Manual (DSM)	Hamilton Anxiety Scale (HAS or HAM-A)
Body mass index (BMI)	Diffusion tensor imaging (DTI)	Hamilton Depression Rating Scale (HDRS or HAM-D)
cAMP responsive element binding protein (CREB)	Dopamine (DA)	Hypothalamus-pituitary-adrenal (HPA)
Central nervous system (CNS)	Dorsal anterior cingulate cortex (dACC)	Hypoxia-inducible factors (HIF)
Cerebrospinal fluid (CSF)	Dorsolateral prefrontal cortex (DLPFC)	Independent components analysis (ICA)
Chronic traumatic encephalopathy (CTE)	Echo-planar imaging (EPI)	Indoleamine 2,3 dioxygenase (IDO)
Citalopram (CIT)	Effect size (ES)	Induced pluripotent stem cells (iPS)
Clinical Global Impression (CGI)	Electrocardiogram (ECG)	Institutional Review Board (IRB)
Cognitive control network (CCN)		

Interferon (IFN)	Mini-Mental State Examination (MMSE)	Posterior superior temporal sulcus (pSTS)
Interferon $\gamma$ -induced protein (IP)	Mitogen-activated protein kinase (MAPK)	Preferred reporting items for systematic reviews and meta-analyses (PRISMA)
Interleukin (IL)	Monocyte chemotactic protein (MCP)	Reactive oxygen species (ROS)
International Classification of Diseases (ICD)	Montgomery-Asberg Depression Rating Scale (MADRS)	Regions of interest (ROIs)
Janus kinase (JNK)	Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC)	Relative distribution volume (DVR)
Late-life depression (LLD)	Neural stem cells (NSCs)	Relative risk (RR)
Macrophage inflammatory protein (MIP)	Neurofibrillary tangles (NFTs)	Resting-state functional magnetic resonance imaging (rs-fMRI)
Macrophages migration inhibitory factor (MIF)	Noradrenaline (NA)	Selective serotonin reuptake inhibitors (SSRIs)
Major depressive disorder (MDD)	Nuclear factor- $\kappa$ B (NF- $\kappa$ B)	Selenium binding protein 1 (SELENBP1)
Major histocompatibility complex, class II, DR $\beta$ 5 (HLA-DRB5)	Nucleus accumbens (NAcc)	Serotonin (5-HT)
Medial prefrontal cortex (mPFC)	Peripheral blood mononuclear cells (PBMC)	Serotonin noradrenaline reuptake inhibitors (SNRIs)
Medial temporal lobe (MTL)	Pittsburgh Compound B (PiB)	Sialic acid binding immunoglobulin-like lectin, pseudogene 3 (SIGLECP3)
Medical Outcomes Study Short Form 36-Item Health Survey (SF-36)	Positron emission tomography (PET)	Signal transducer and activator of transcription (STAT)
Methylphenidate (MPH)	Posterior cingulate cortex (PCC)	
Mild cognitive impairment (MCI)		

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

Standard deviation  
(SD)

Statistical parametric  
mapping (SPM)

Stress-activated  
protein kinase (SAPK)

TGF $\beta$  activated kinase-  
1 (TAK-1)

T-helper (T<sub>h</sub>)

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

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