In Vivo Brain Changes in Late-Life Depression

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Abstract

Late-life depression (LLD) is common illness, frequently associated with neuropsychological impairment. Disruption of frontal-subcortical and limbic networks may play a key role in LLD and can be examined using magnetic resonance imaging (MRI). Grey matter (GM) can be examined using T_1-weighted MRI, white matter (WM) using diffusion tensor imaging (DTI), and functional connectivity using resting-state functional MRI (fMRI).

To clarify the roles of GM, WM and functional connectivity in LLD, systematic reviews and meta-analyses of T_1-weighted MRI, DTI and resting-state fMRI studies of depression were performed. The literature provided evidence for GM and WM abnormalities within frontal-subcortical and limbic networks, and increased functional connectivity within the default-mode network, in depression. To examine whether results gained from different techniques are complementary, multi-modal MRI was used to compare GM, WM and functional connectivity between thirty-six participants with LLD and twenty-five control participants. WM integrity was widely reduced in LLD, without significant group differences in GM or functional connectivity.

To investigate whether neuropsychological deficits represent independent processes with specific neural correlates, or whether they can be explained by a core deficit, the relationships between neuropsychological and MRI measures were explored. Executive function and processing speed were found to represent core deficits that contribute to impairment in other domains; and impaired performance was correlated with reduced frontal WM integrity. Episodic memory deficits were dependent on executive function and processing speed; and associated with reduced frontal and hippocampal WM integrity.

The relationships between age at onset, severity and MRI measures of GM, WM and functional connectivity were also investigated. Later onset was associated with reduced WM integrity, in line with the vascular hypothesis. Earlier onset was associated with greater duration of illness and reduced hippocampal volume, consistent with the glucocorticoid cascade hypothesis. Severity was not associated with any MRI measure.

This thesis strongly supports the hypothesis that WM abnormalities in frontal-subcortical and limbic networks play a key role in LLD, with abnormalities related to neuropsychological impairment and compatible with the vascular hypothesis.

This thesis contains approximately 33 000 words
A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in the University of Oxford
Hilary Term 2011

Contents

Acknowledgements

Firstly, I would like to acknowledge all of the participants who volunteered for this project, without whom this research simply would not be possible, and the Gordon Small Charitable Trust, who provided funding.

I am extremely grateful to many colleagues who have helped with this study:

- Lucie Herrmann, Lisa McDermott and Ukwuori Kalu helped greatly with recruitment and data acquisition;
- Dr Marisa Le Masurier and Dr Charlotte Allan assisted with recruitment and performed clinical assessments;
- Dr Danilo Arnone, Caroline Buttolph, Dr Alessia Gargiulo, Dr Lillian Hickey, Dr Rebecca Mather, Dr Jenny McCleery, Dr Jane Pearce, Dr Hugh Series, Dr Martina Stoeffels, Dr Philip Wilkinson and others at OBMH referred participants.
- Steve Knight operated the majority of MRI scans;
- Dr Kevin Bradley checked MRI scans for abnormalities;
- Matthias Muller performed white matter hyperintensity ratings;
- Dr Nico Filippini generously taught resting-state analysis techniques;
- Louisa Coulson carried out detailed proof reading.

Special thanks go to my supervisors, Dr Clare Mackay and Prof Klaus Ebmeier, who have provided invaluable guidance and support throughout my time in Oxford.

Finally, to my family and Philip for all their support, I cannot thank you enough.

Abbreviations

ACC	Anterior Cingulate Cortex
ACE-R	Addenbrooke's Cognitive Examination Revised
AN	Affective Network
BOLD	Blood Oxygen Level Dependent
CSF	Corticospinal Fluid
DA	Axial Diffusivity
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DMPFC	Dorsomedial Prefrontal Cortex
DR	Radial Diffusivity
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DTI	Diffusion Tensor Imaging
ECN	Executive Control Network
EOD	Early-Onset Depression
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full-Scale IQ
FSL	FMRIB's Software Library
GDS	Geriatric Depression Scale
GLM	General Linear Model
GM	Grey Matter
HAM-D	Hamilton Depression Rating Scale
HPA	Hippocampal-Pituitary-Adrenal
ICA	Independent Components Analysis
LOD	Late-Onset Depression
LLD	Late-Life Depression
LPFC	Lateral Prefrontal Cortex
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Mean Diffusivity
MNI	Montreal Neurological Institute

MRI	Magnetic Resonance Imaging
MMSE	Mini-Mental State Examination
MPFC	Medial Prefrontal Cortex
OCMR	University of Oxford Centre for Clinical Magnetic Resonance Imaging
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
RCF	Rey-Osterrieth Complex Figure
ROI	Region of Interest
RSN	Resting-State Network
SPECT	Single Photon Emission Computed Tomography
TBSS	Tract-Based Spatial Statistics
TE	Echo Time
TMT	Trail Making Test
TOI	Tract of Interest
TR	Repetition Time
VBA	Voxel-Based Analysis
VBM	Voxel-Based Morphometry
WB	Whole Brain
WM	White Matter
WMH	White Matter Hyperintensities

List of Figures

List of Tables

Publications

Papers

Sexton CE, Mackay CE, Ebmeier KP.

A systematic review of diffusion tensor imaging studies in affective disorders.

Biol Psychiatry. 2009; 66(9):814-823 (Sexton et al 2009)

Conference Abstracts

Sexton CE, Kalu UG, McDermott LM, Allan CL, Mackay CE, Ebmeier KP

Network Dysfunction in Late-Life Depression

Society for Biological Psychiatry, New Orleans USA, 2010

Preface

Late-life depression (LLD) is a common and heterogeneous illness, frequently associated with neuropsychological impairment. Disruption of frontal-subcortical and limbic networks is hypothesised to play a key role in the pathophysiology of LLD, and may involve both structural and functional abnormalities. Structural abnormalities may involve differences in the volume or shape of grey matter (GM) regions, and also in the integrity of the connecting white matter (WM) tracts. Functional abnormalities may involve differences in the amplitude and coherence of neuronal activity within networks during exposure to emotional stimuli, participation in cognitive tasks, and at rest.

Magnetic resonance imaging (MRI) is an ideal tool to investigate network disruption in LLD in vivo and different MRI sequences allow various aspects of network disruption to be investigated. GM is most commonly studied using T_1-weighted MRI, white matter hyperintensities using T_2-weighted MRI, and WM integrity using diffusion tensor imaging (DTI). Resting-state functional MRI (fMRI) is able to examine functional connectivity (coherence) within neural networks. The overall aim of this thesis is to examine network disruption in LLD using multi-modal MRI techniques.

Chapter 1 aims to provide an introduction to network disruption in LLD. It contains a description of the epidemiology and symptomatology of LLD, an overview of frontal-subcortical and limbic circuitry, and summaries of three hypotheses regarding the nature and aetiology of network disruption in depression (the vascular depression hypothesis, the glucocorticoid cascade hypothesis and the limbic-cortical hypothesis).

Chapter 2 aims to clarify the role of GM abnormalities in the pathophysiology of LLD. It contains a systematic review and meta-analysis of T_1-weighted MRI studies of LLD as well as an

original study comparing subcortical GM structures, using both volumetric and shape analysis, and GM globally, using voxel-based morphometry, between thirty-six participants with LLD and twenty-five control participants.

Chapter 3 aims to clarify the role of WM abnormalities in the pathophysiology of LLD. It includes a systematic review and meta-analysis of DTI studies of depression and a tract-based spatial statistics study comparing WM integrity between LLD and control groups.

Chapter 4 aims to clarify the role of abnormalities in functional connectivity in the pathophysiology of LLD. It contains a systematic review of resting-state fMRI studies of depression and an independent components analysis study comparing functional connectivity within the default-mode network, the executive control network and the affective network between LLD and control groups.

Chapter 5 aims to examine the pattern of neuropsychological impairment in LLD and investigate the relationships between neuropsychological impairment and MRI measures. Group differences between LLD and control groups are examined across five domains: episodic memory, executive function, language skills, processing speed and visuospatial skills. The influence of executive function and processing speed deficits on other neuropsychological domains are investigated and MRI correlates of executive function, processing speed and episodic memory are explored in the LLD group.

Chapter 6 aims to explore the aetiology of LLD by examining the relationships between age at onset, current severity and MRI measures of GM, WM and functional connectivity in LLD.

Chapter 7 aims to summarise the main findings of this thesis and provides suggestions for future research.

Chapter 1: Introduction

1.1 Late-Life Depression

Late-life depression (LLD) is typically defined as depression in adults aged sixty years or over. Estimates of the prevalence of LLD within the United Kingdom range from 3.5% to 17.3% (Copeland et al 1999; McDougall et al 2007). Symptoms are more common in women compared with men, and are associated with functional disability, medical co-morbidity, and social deprivation (Copeland et al 1999; McDougall et al 2007; Prince et al 1999). With the number of people aged sixty-five and over in the UK predicted to increase from 9.9 million in 2008 to 16.4 million in 2033, the number of older adults with depression is set to rise to unprecedented levels (Office-for-National-Statistics 2008).

The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (2000) criteria for a diagnosis of major depression are summarised in table 1.1. For a diagnosis to be made, five or more of the listed symptoms must be present for at least two weeks, with at least one of the symptoms being either depressed mood or diminished interest or pleasure. The symptoms should cause distress or functional impairment, and not be a direct effect of substance use, a medical condition, or bereavement.

Table 1.1: DSM-IV-TR criteria for major depression

DSM-IV-TR Criteria for Major Depression	
Depressed mood	**Diminished interest or pleasures in all or almost all activities**
Fatigue	Weight loss or gain (a change of more than 5% in bodyweight)
Insomnia or hypersomnia	Feelings of worthlessness or inappropriate guilt
Psychomotor agitation or retardation	Recurrent thoughts of death or suicide
Reduced ability to concentrate	

Although the core symptoms of major depression are consistent across ages, LLD is associated with a greater degree of neuropsychological impairment compared with depression earlier in life, which cannot be explained by ageing alone (Lockwood et al 2002; Tarbuck & Paykel 1995; Thomas et al 2009). Deficits typically persist after clinical recovery (Bhalla et al 2006; Butters et al 2000; Kohler et al 2010; Murphy & Alexopoulos 2004; Nebes et al 2003) and are present across multiple domains, including executive function, episodic memory, processing speed, language skills and visuospatial skills (Butters et al 2004; Dillon et al 2009; Elderkin-Thompson et al 2007; Herrmann et al 2007; Kohler et al 2010). However, it is unclear whether deficits in multiple domains represent relatively independent processes, or whether they can be explained by a core cognitive deficit, for example in executive function or processing speed (Butters et al 2004; Elderkin-Thompson et al 2007; Kohler et al 2010; Sheline et al 2006).

1.2 Pathophysiology of Depression

Depression is a multi-factorial illness that is associated with neurobiological, psychological and social factors. With regard to the neurobiological factors, it is unlikely that depression is simply associated with abnormalities of a single brain region. Rather, it is postulated that depression is associated with disruption of the neural networks that regulate mood and behaviour. In particular, disruption of frontal-subcortical and limbic circuitry is hypothesised to play a key role in the pathophysiology of LLD (Alexopoulos 2002).

In this section, a brief overview of the anatomy and function of frontal-subcortical and limbic circuits will be provided. Then, three prominent theories regarding the nature and aetiology of network disruption in LLD will be detailed.

1.2.1 Frontal-Subcortical Circuitry

Five anatomically and functionally discrete parallel loops connect specific areas of the prefrontal cortex (PFC), through the basal ganglia and thalamus, back to the PFC (Alexander et al 1986). These frontal-subcortical circuits play a key role in the regulation of motor, cognitive, and motivational processes. Two of the circuits are primarily related to motor function and originate from the supplementary motor area and the frontal eye field. The remaining three circuits originate from the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the lateral orbitofrontal cortex (OFC). The DLPFC circuit allows the organisation of information to facilitate a response; the ACC circuit is required for motivated behaviour; and the OFC circuit allows the integration of emotional information into behavioural responses. Executive dysfunction, apathy and disinhibition are characteristics of disruption within the DLPFC, ACC and OFC circuits, respectively (Bonelli & Cummings 2007; Tekin & Cummings 2002). These circuits are also interconnected with each other (Joel & Weiner 1994), and functionally related brain areas (Tekin & Cummings 2002). For example, the DLPFC circuit receives afferents from dorsofrontal, parietal and limbic regions, and projects efferents to dorsofrontal and anterior frontal regions. Major afferents to the ACC circuit include the hippocampus and entorhinal cortex, and major efferents include the substantia nigra, subthalamic nucleus and hypothalamus. The OFC circuit receives major afferents from superior temporal and orbitofrontal regions, and projects efferents to orbitofrontal and mediofrontal regions.

1.2.2 Limbic Circuitry

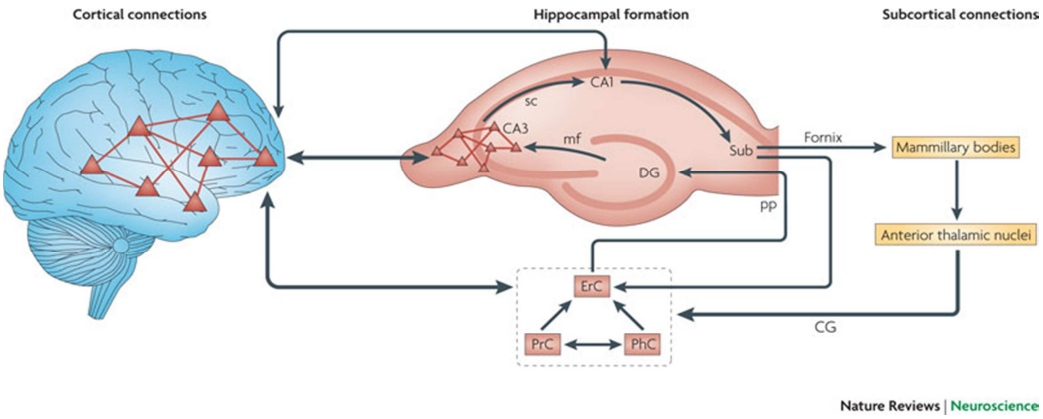
The limbic system includes the hippocampus, amygdala, hypothalamus, anterior thalamic nucleus, parahippocampal gyrus and cingulate gyrus and plays a key role in emotional and

cognitive processes. A full consideration of the circuitry of the limbic system is beyond the scope of this thesis. Instead the basic circuitry of the hippocampus, amygdala, and ACC, regions commonly implicated in the pathophysiology of depression, are summarised.

The hippocampus consists of the dentate gyrus, the hippocampus proper (cornu Ammonis; CA1-CA4), and the subiculum, and plays a key role in the formation and retrieval of episodic memory. The hippocampus is reciprocally connected with neocortical association areas either directly or via the entorhinal cortex. From the entorhinal cortex, the perforant path extends to the dentate gyrus; the mossy fibres connect the DG to the CA3 subfield; and the Schaffer collaterals project from the CA3 subfield to the CA1 subfield. CA1 neurons then project onto the subiculum. The subiculum projects back to the entorhinal cortex either directly or indirectly via the fornix and cingulum, which connect the mammillary bodies of the hypothalamus, the anterior thalamic nuclei and the entorhinal cortex. Finally, the entorhinal cortex projects back to neocortical association areas (figure 1.1: (Henke 2010)).

Figure 1.1: Hippocampal circuitry

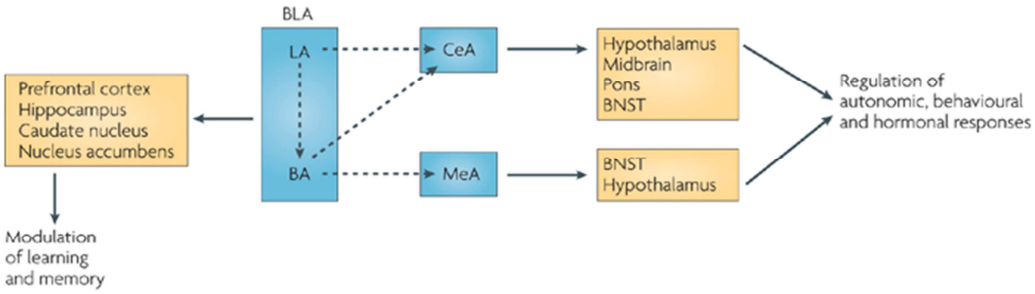
Abbreviations – CG: cingulum; DG: dentate gyrus; ErC: entorhinal cortex; mf: mossy fibres; PhC: parahippocampal cortex; pp: perforant path; PrC: perirhinal cortex; sc: Schaffer collaterals; Sub: subiculum. Reprinted with permission from Macmillan Published Ltd: Nature Reviews Neuroscience (Henke 2010), copyright 2010.



The amygdala consists of the basolateral nuclei, the central nuclei, and the corticomedial nuclei and plays a key role in emotional processing. The amygdala receives afferents from cortical regions, the thalamus, hypothalamus and brainstem (Sah et al 2003). Following internal processing, the basolateral nuclei project efferents to brain regions implicated in learning and memory, including the PFC, hippocampus and striatum. The central and medial amygdala project efferents to regions involved in autonomic, behavioural and hormonal processes, including the hypothalamus, midbrain, pons and bed nucleus of the stria terminus (figure 1.2: (Roozendaal et al 2009)).

Figure 1.2: Amygdala circuitry

Abbreviations – BA: basal amygdala; BLA: basolateral amygdala; BNST: bed nucleus of the stria terminals; CeA: central amygdala; LA: lateral amygdala; MeA: medial amygdala. Reprinted with permission from Macmillan Published Ltd: Nature Reviews Neuroscience (Roozendaal et al 2009), copyright 2009.



The ACC plays a key role in both cognition and emotion. Indeed, the ACC is commonly subdivided into a dorsal cognitive division, and a ventral affective division that includes rostral, subcallosal, and subgenual regions (Devinsky et al 1995). In addition to being functionally distinct, these subregions also have unique connectivity patterns. The dorsal ACC is interconnected with prefrontal, precentral and parietal cortex (Beckmann et al 2009; Devinsky et al 1995). In contrast, the ventral ACC is interconnected with the amygdala,

hippocampus, striatum, hypothalamus, anterior insula, and OFC (Beckmann et al 2009; Devinsky et al 1995).

Disruption of frontal-subcortical and limbic circuitry in depression may involve both structural and functional abnormalities. With regard to structural abnormalities, there may be differences in the volume or shape of grey matter (GM) regions, and also in the integrity of the connecting white matter (WM) tracts. Functional abnormalities may involve differences in the amplitude and coherence of neuronal activity within networks during exposure to emotional stimuli, participation in cognitive tasks, and at rest.

1.3 Aetiology of Late-Life Depression

There are many hypotheses concerning the nature and aetiology of network disruption in LLD. These include, but are not limited to, the vascular depression hypothesis, the glucocorticoid cascade hypothesis and the limbic-cortical network hypothesis. Each hypothesis is associated with a distinct profile of clinical factors and neuropsychological impairment. For example, the nature and aetiology of network disruption is hypothesised to vary with age at onset, with LLD participants commonly divided into early-onset depression (EOD, typically age at onset younger than sixty years) and late-onset depression (LOD, typically age at onset older than sixty years), and also current symptom severity. However, it is important to note that hypotheses are neither exclusive nor independent. Indeed, the heterogeneity of depression indicates that multiple neural mechanisms may be implicated.

1.3.1 Vascular Depression Hypothesis

The vascular depression hypothesis proposes that cardiovascular factors may 'predispose, precipitate, or perpetuate' LOD (Alexopoulos et al 1997). Specifically, vascular factors are hypothesised to cause WM damage within frontal-subcortical circuits, and result in deficits in executive function (Alexopoulos 2002; Alexopoulos et al 1997).

There are several lines of support for the vascular depression hypothesis. Compared with EOD, LOD is associated with increased co-morbidity with vascular risk factors (Baldwin & Tomenson 1995; Miller et al 2002), increased prevalence of white matter hyperintensities (WMH) (Herrmann et al 2008) combined with evidence supporting a vascular basis for WMH (Chen et al 2006; Smith et al 2009b; Thomas et al 2002; Thomas et al 2003), greater impairments in executive function (Herrmann et al 2007), lower rates of family history of major depression (Baldwin & Tomenson 1995; Brodaty et al 2001; Conwell et al 1989; Devanand et al 2004; Gallagher et al 2010; Kendler et al 2009), and higher rates of family history of vascular disease (Kendler et al 2009). However, results from prospective population-based studies have posed challenges to the vascular hypothesis. For example, Newson et al (2010) found that atherosclerosis did not increase the risk of depression in a study of 3564 older adults. Also, Vinkers et al (2005) found that a higher rating of generalised atherosclerosis was not associated with depressive symptoms in a study of 599 adults aged 85 and older.

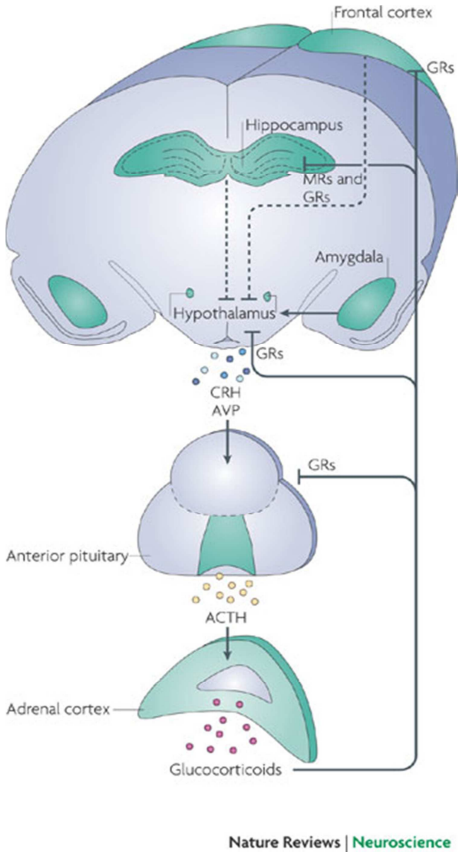
1.3.2 Glucocorticoid Cascade Hypothesis

The glucocorticoid cascade hypothesis proposes that stress-induced increases in glucocorticoid levels in depression lead to disruption of hippocampal circuitry (Sapolsky 2000). Specifically, regression of dendritic processes, inhibition of neurogenesis, and neurotoxic effects in the hippocampus are hypothesised to cause reductions in hippocampal volume, and result in deficits in episodic memory (McEwen & Sapolsky 1995; Sapolsky 2000). In line with this theory, it follows that greater duration of illness will result in greater hippocampal damage due to repeated exposure to elevated glucocorticoid levels.

The hypothalamus-pituitary-adrenal (HPA) axis is a key system involved in the neuroendocrine response to stress. Briefly, stress-induced activation of the HPA axis results in the secretion of corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus, which stimulates the production and release of adrenocorticotrophin from the anterior pituitary. Adrenocorticotrophin then stimulates the synthesis and release of glucocorticoids (cortisol in humans, corticosterone in rodents) from the adrenal cortex. As the hippocampus is a major site in the glucocorticoid negative feedback circuit on the HPA axis, hippocampal damage resulting from elevated glucocorticoid levels, in turn, results in further increases in glucocorticoid levels (figure 1.3: (Lupien et al 2009)) (Sapolsky et al 1986).

Figure 1.3: Hypothalamus-pituitary-adrenal axis

Abbreviations – AVP: arginine vasopressin; ACTH: adrenocorticotrophin; CRH: corticotropin-releasing hormone; GR: glucocorticoid receptor; MR: mineralocorticoid receptor. Reprinted with permission from Macmillan Published Ltd: Nature Reviews Neuroscience (Lupien et al 2009), copyright 2009.



In support of the glucocorticoid cascade hypothesis, hyperactivity of the HPA axis has been consistently observed in depression. For example, studies have found increased concentrations of corticotropin-releasing hormone in the cerebrospinal fluid (CSF), increased levels of cortisol, non-suppression of adrenocorticotrophin and cortisol production following administration of the synthetic glucocorticoid dexamethasone, and blunted adrenocorticotrophin response to corticotropin-releasing hormone administration in depression (Holsboer 2000). Studies directly examining the relationship between HPA axis dysfunction and hippocampal volume, however, are few and provide discordant results. For

example, a study directly examining the relationship between hippocampal volume and cortisol levels in LLD found that hippocampal volume reduction was not associated with increased cortisol levels (O'Brien et al 2004). Similarly, Gerritsen et al (2011) found that while EOD was associated with reduced hippocampal volumes compared with control participants, it was not associated with alterations in basal HPA axis regulation.

1.3.3 Limbic-Cortical Network Hypothesis

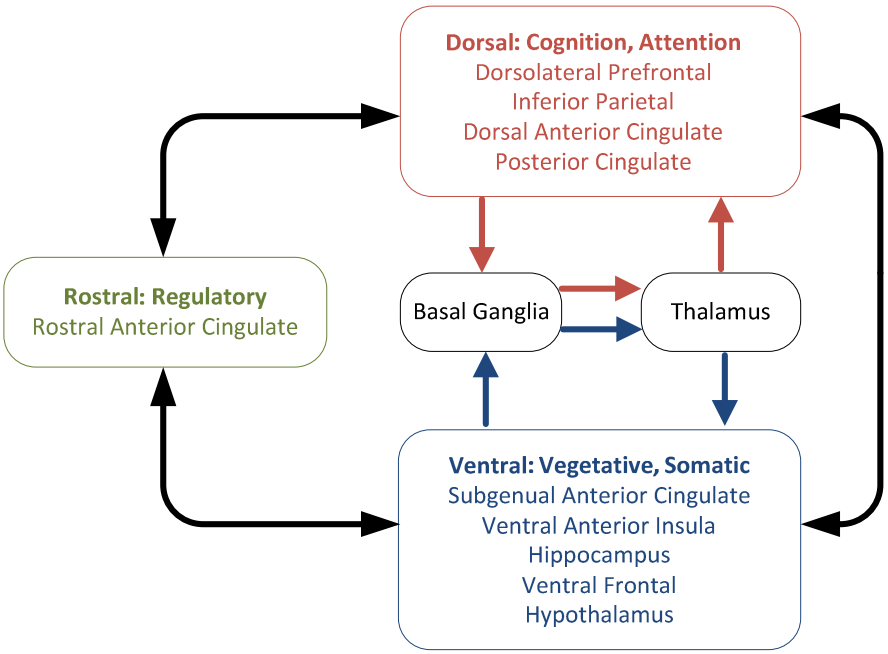
The limbic-cortical network hypothesis proposes that depressive episodes are associated with abnormal patterns of functional activation within limbic-cortical networks, which normalise upon remission (Mayberg 1997; Phillips et al 2003).

While abnormal patterns of functional activation have been included in several models of depression (Mayberg 1997; Phillips et al 2003; Seminowicz et al 2004), for simplicity only the core elements of Mayberg's limbic-cortical network model of depression will be outlined (figure 1.4: (Mayberg 1997)). In this model regions with known anatomical interconnections are grouped into dorsal, ventral, and rostral components. The dorsal component is composed of neocortical and superior limbic structures including the DLPFC, inferior parietal, dorsal ACC and posterior cingulate cortex (PCC). This component is hypothesised to regulate cognitive-attention functions including cognitive aspects of negative emotion such as apathy, psychomotor slowing, impaired attention and executive function. The ventral component is composed of limbic, paralimbic and subcortical structures including the subgenual ACC, ventral anterior insula, hippocampus, ventral frontal cortex, and hypothalamus. This component is hypothesised to mediate vegetative circadian functions including sleep, appetite, libidinal, and endocrine disturbances. The rostral component consists of the rostral ACC, isolated based on its cytoarchitectural characteristics and

reciprocal connections to both dorsal and ventral ACC, and is proposed to play a regulatory role in the interactions between the two components. Dysfunction of this coordinating area may result in disintegrated mood, cognitive, somatic and autonomic responses.

Figure 1.4: Limbic-cortical network hypothesis

Summary of dorsal, ventral and rostral divisions included within the limbic-cortical network hypothesis. Red and blue arrows indicate connections with frontal-striatal circuitry; black arrows indicate reciprocal connections through the cingulum. Reprinted with permission from the Journal of Neuropsychiatry and Clinical Neurosciences, American Psychiatric Association (Mayberg 1997), copyright 1997.



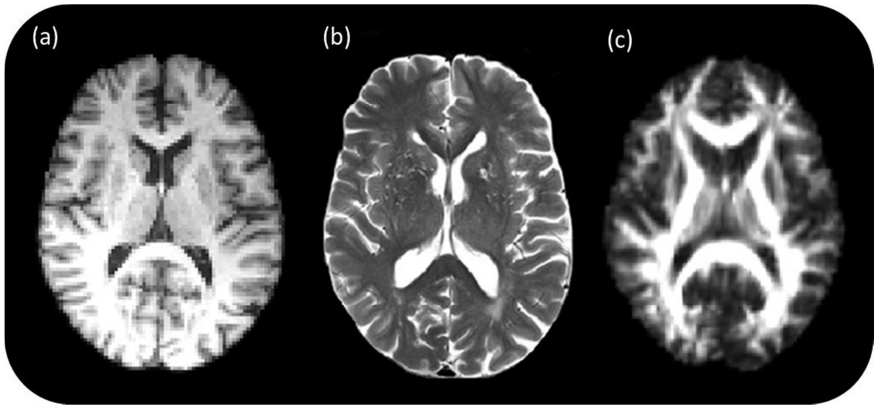
The limbic-cortical network hypothesis is primarily supported by studies utilising Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) which have revealed that sadness and depressive illness are associated with decreases in activation in dorsal areas and relative increases in ventral areas, and that following pharmacological or psychological treatment there is a reversal of these findings (Brody et al 2001; Fitzgerald et al 2008; Goldapple et al 2004).

1.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-invasive technique that can provide high resolution in vivo images of the brain, and is thus an ideal tool to investigate disruption of networks in depression. Different MRI sequences allow various aspects of network disruption to be investigated. GM is most commonly studied using T_1-weighted MRI, WMH using T_2-weighted MRI, and WM integrity using diffusion tensor imaging (DTI) (figure 1.5). Resting-state functional MRI (fMRI) is able to examine functional connectivity (coherence) within networks. A full description of the theory of T_1 and T_2-weighted MRI, DTI and resting-state fMRI is provided in chapters 2, 3, and 4, respectively.

Figure 1.5: Structural MRI scans

Examples of (a) a T_1-weighted image, (b) a T_2-weighted image and (c) a fractional anisotropy (FA) map derived from DTI data.



1.6 Aims

The overall aim of this thesis is to examine network disruption in LLD using MRI techniques. In detail, the specific aims are:

To clarify the roles of grey matter, white matter and functional connectivity in the pathophysiology of late-life depression

Abnormalities in GM, WM and functional connectivity have all been hypothesised to play key roles in the pathophysiology of LLD. To investigate these hypotheses, many studies have used MRI techniques to extract measures of GM, WM or functional connectivity, and compared measures between depressed and control groups. However, there is great heterogeneity within the literature in terms of participant details, data acquisition, data analysis and results. Therefore, in order to clarify the literature to date, studies examining group differences in GM, WM or functional connectivity, using structural MRI, DTI and resting-state fMRI, respectively, will be systematically reviewed.

While the systematic reviews will summarise studies that have examined GM, WM or functional connectivity individually, no study to date has concurrently examined GM, WM and functional connectivity. In order to directly examine which MRI technique is the most sensitive in detecting group differences, and consider whether results gained from different techniques are complementary, multi-modal MRI will be used to examine group differences in GM, WM and functional connectivity between thirty-six participants with LLD and twenty-five control participants. To distinguish the results of this original study from results of previous studies, this study will be referred to as the Oxford study.

To examine the pattern of neuropsychological impairment in late-life depression and the relationships between neuropsychological impairment and MRI measures

Neuropsychological impairment is a key feature of LLD, with deficits observed across multiple domains, including executive function, episodic memory, processing speed, language skills and visuospatial skills. However, it is unclear whether deficits in multiple domains represent relatively independent processes with specific neural correlates, or whether they can be explained by a core cognitive deficit, for example in executive function or processing speed.

In order to examine the pattern of neuropsychological impairment in LLD, group differences will be examined across five domains: episodic memory, executive function, language skills, processing speed and visuospatial skills, and the influence of deficits in executive function and processing speed on other neuropsychological domains investigated. Next, the relationships between neuropsychological impairment and MRI measures in the LLD group will be explored by examining MRI correlates of executive function, processing speed and episodic memory.

To explore the aetiology of depression by examining the relationships between age at onset, symptom severity and MRI measures of grey matter, white matter and functional connectivity

There are many hypotheses concerning the nature and aetiology of network disruption in depression including the vascular depression hypothesis, the glucocorticoid hypothesis, and the limbic-cortical network hypothesis of depression. Clinical factors including age at onset and current severity may be associated with the nature and aetiology of network

dysfunction in LLD. For example, a negative correlation between age at onset and WM deficits would be compatible with the vascular depression hypothesis. A positive association between age at onset and hippocampal volume would provide support for the glucocorticoid cascade hypothesis. Variation in functional connectivity may be state dependent and associated with current severity, in line with the limbic-cortical network hypothesis. Thus, in order to explore the aetiology of depression, the relationships between age at onset, current severity and MRI measures of GM, WM and functional connectivity will be examined in thirty-six participants with LLD.

Chapter 2: The Role of Grey Matter in Late-Life Depression

2.1 Abstract

Along with white matter and functional abnormalities, grey matter abnormalities within frontal-subcortical and limbic networks are hypothesised to play a key role in the pathophysiology of depression.

In this chapter, grey matter abnormalities in late-life depression are examined first in a systematic review and meta-analyses of T_1-weighted magnetic resonance imaging studies and second in a study comparing the volume and shape of subcortical grey matter structures and also grey matter globally between participants with late-life depression and control participants.

In the systematic review twenty-nine articles were identified that compared participants with late-life depression with control participants and nineteen studies were included in meta-analyses of volumes of the whole brain, orbito-frontal cortex, amygdala, caudate, hippocampus, putamen and thalamus. Volume reductions were detected in seven of fifteen comparisons of the hippocampus and a meta-analysis revealed a significant, but small, effect size. Although examined by fewer studies, meta-analyses also revealed significant volume reductions in the orbito-frontal cortex, caudate, putamen and thalamus. Clarification of the global picture of grey matter abnormalities and examination of the localisation of subcortical abnormalities were identified as key areas for future research.

Next, FMRIB's integrated registration and segmentation tool was employed to examine group differences in the volume and shape of the amygdala, caudate, hippocampus, pallidum, putamen and thalamus in thirty-six participants with late-life depression and twenty-five control participants. Voxel-based morphometry was also employed to examine group differences in grey matter globally. Whole brain volume was significantly reduced in the late-life depression group. Analyses covarying for age, gender and whole brain volume did not detect any significant differences between late-life depression and control groups in either subcortical volumes or shape. Voxel-based morphometry did not detect any group differences in grey matter between late-life depression and control groups.

Overall, while the literature provided moderate support for the hypothesis that grey matter abnormalities play a role in the pathophysiology of late-life depression, no differences in grey matter were detected in the Oxford study.

2.2 Background

Along with functional abnormalities, structural abnormalities are hypothesised to contribute to frontal-subcortical and limbic network disruption in depression. To date, grey matter (GM) has been the subject of the majority of research examining structural abnormalities in depression. While post-mortem studies have provided support for GM differences in frontal, subcortical and limbic regions (Rajkowska 2003), T_1-weighted MRI has proved to be an ideal tool to examine cortical and subcortical GM abnormalities in vivo. Furthermore, recent methodological advances now allow unique assessment of the anatomy of GM differences in depression.

2.2.1 T_1-weighted MRI

The physical principles of T_1-weighted MRI are based upon the nuclear magnetic resonance of protons. Briefly, protons possess magnetic spins that, in the absence of a magnetic field, are randomly oriented. A MRI scanner consists of a large magnet that exerts a powerful external magnetic field (B_0) in which spins align to create net magnetisation in the direction of the magnetic field. During an MRI scan, application of a radio-frequency pulse tilts the net magnetisation away from B_0. The spins then realign with B_0, with the rate of recovery of magnetisation along the longitudinal axis, and the loss of magnetisation in the transverse plane, defined by the time constants T_1 and T_2, respectively. The precessing magnetisation can be detected with a radio-frequency-tuned coil, with the signal dependent upon the proton density, the T_1 and T_2 relaxation constants, and the relative timing of external radio-frequency pulses and field gradients. Since proton-density, T_1 and T_2 are tissue-specific properties, it is possible to vary the scan repeat time (repetition time, TR) and the time between transmitting an RF pulse and measuring a signal (echo time, TE) in a MRI pulse sequence in order to be sensitive to proton-density, T_1 or T_2 and create the relevant image contrast. T_1-weighted MRI provides particularly good GM / WM contrast and is thus the preferred modality to examine GM.

T_1-weighted MRI can be used to study the volumes of a-priori defined cortical regions and subcortical structures using region of interest (ROI) analysis, the location and pattern of structural changes in subcortical structures using shape analysis (Patenaude 2007), or GM across the entire brain using voxel-based morphometry (VBM) (Ashburner & Friston 2000; Good et al 2001).

ROI analyses have recently progressed from manual tracing of individual GM regions to fully automated segmentation of GM structures (Babalola et al 2009). Whilst automated

segmentation methods overcome some of the limitations associated with manual techniques, including inter- and intra-rater reliability issues, there remains a possibility of type II error with ROI analysis; that is, important differences occurring outside of or overlapping the ROIs may go unobserved.

Shape analysis techniques can provide greater detail of the location and pattern of structural changes in subcortical structures, even in the absence of significant volumetric differences (Patenaude 2007; Patenaude et al 2007; 2008; Styner et al 2003). However, such techniques have not yet been widely employed in studies of depression.

In contrast to ROI analysis and shape analysis, which are used to examine a limited number of a priori defined GM regions, VBM can provide a global assessment of GM. VBM typically involves: segmentation of T_1-weighted images into GM, WM and CSF; registration of images into a standard space; optional modulation of images to compensate for the effects of registration; and spatial smoothing of images to result in each voxel representing the average of itself and its neighbours (Ashburner & Friston 2000; Good et al 2001). A voxel-by-voxel whole brain statistical comparison of GM can then be made between groups. However, VBM is limited by the quality of inter-participant image registration and the amount of spatial smoothing of data (Bookstein 2001).

2.2.2 Literature Review

Introduction

Koolschijn et al (2009) and Arnone et al (2011) have recently performed meta-analyses of sixty-four and ninety-seven structural MRI studies of major depression, respectively. Both found that depression was characterised by volume reductions in frontal regions, especially

in the OFC and ACC, the hippocampus, and basal ganglia. GM volume reductions are also well documented in ageing (Good et al 2001; Resnick et al 2003), and a recent review examining inconsistency among volumetric studies of the hippocampus in depression suggested that depressed groups with a mean age older than 40 years are more likely to demonstrate hippocampal volume reductions compared with younger depressed groups (Eker & Gonul 2010).

This section aims to provide an overview of structural MRI studies specifically of LLD through first conducting a systematic review of studies to date, and second conducting meta-analyses of ROI studies.

Methods

Online searches of the databases EMBASE and MEDLINE were performed in August 2010, using the keywords ([“magnetic resonance imaging” or “MRI”] and [“depress*”] and [“elderly” or “geriatric” or “late life” or “late onset” or “old age” or “older”]). Reference lists of included studies and relevant reviews were also searched for additional studies.

For the systematic review, studies were screened for journal articles published in English that used MRI to analyse group differences in the volumes of brain regions between participants with major depression and an average age of over sixty, and healthy control participants. Studies that used manual ratings to assess atrophy were excluded in order to ensure sufficient reliability. Cohort studies that examined depressive symptoms, but in which a diagnosis of major depression was absent, were also excluded. When two or more studies had similar authors, methods and regions studied, preference was first given to the study with the greater number of LLD participants, and then to the study that divided LLD

participants into LOD and EOD. When studies with overlapping participants utilised different methods of data analysis (e.g. VBM and ROI) both studies were included.

Key details regarding the participants, data acquisition, data analysis and results were recorded for all studies. If not stated, age at onset was calculated by subtracting duration of illness from mean age, or assumed to equal mean age if first-episode. Current medication status was divided into medicated or medication free; medicated state was assumed if not specifically stated otherwise. If 17-item Hamilton depression rating scale (HAM-D) score was not available, HAM-D was converted from alternative HAM-D scores or from Montgomery-Asberg depression rating scale (MADRS) scores (Heo et al 2007). Voxel size was calculated from the field of view, matrix size, slice thickness and gap. As the method for labelling anatomy differed considerably between studies, regions were grouped according to cerebral lobe (frontal, temporal, parietal and occipital) or structure (hippocampus, thalamus, etc.). To provide an overview of the anatomy of significant differences, the lobe or structure that contained a minimum of one region that was significantly different in volume ($p < 0.05$, unless a stricter limit was imposed by the authors) between participants with LLD and control participants, after corrections and covarying, was recorded. The results of included studies that utilised shape analysis were also summarised. For VBM studies, Montreal neurological institute (MNI) co-ordinates of regions that were significantly different between groups were recorded.

For the meta-analyses, articles included in the systematic review were screened for ROI studies that presented raw or adjusted volumes as means and standard deviations, or *p*-values from two-sample tests. Studies that assessed GM using VBM were excluded from the meta-analysis. Such studies would add a considerable source of bias to the analysis as they typically only provide details of areas that are significantly different between groups, and are

better examined separately using co-ordinate based or image-based meta-analysis methods (Salimi-Khorshidi et al 2009). Regions that were reported by a minimum of three studies were included in the meta-analysis, a threshold employed by previous meta-analyses (Kempton et al 2008; Sexton et al 2010). Depression subgroups of EOD and LOD, and remitted and non-remitted participants were entered as if they were separate studies with the number of participants in the control group (degrees of freedom) divided by the number of subgroups, as in previous meta-analyses (Kempton et al 2008; Sexton et al 2010).

Data were analysed using Comprehensive Meta-Analysis [version 2.2.048, ©2006, Biostat, Inc., Englewood, NJ, USA]. Effect size was measured using Hedges' g in order to correct for small sample size (Hedges & Olkin 1985). A random-effects model was used to calculate the pooled mean effect size, in order to allow unconditional inferences beyond the included studies (Hedges & Vevea 1998). In studies that used multiple ROIs in a single region, the total effect size was calculated. In order to maximize the number of studies included in the meta-analysis, volumes were summed across the left and right hemispheres. Effect sizes between 0.2 and 0.5 were classified as small, between 0.5 and 0.8 as medium, and over 0.8 as large.

Heterogeneity was assessed using Cochrane's Q and I^2, the percentage of the total variability due to between-studies variability (Higgins et al 2003). When heterogeneity was significant, fixed effect regression with Hedges' g was performed with the LLD group's mean age, percentage of female participants, age at onset, current medication status, symptom severity (HAM-D score), and voxel volume.

Publication bias was considered using Begg and Mazumdar rank correlations (Begg & Mazumdar 1994) and Egger's regression intercept test (Egger et al 1997).

Results

Titles and abstracts of seven-hundred and forty-three identified citations were screened, of which twenty-seven met the inclusion criteria for the systematic review and nineteen met the inclusion criteria for the meta-analyses. A flow diagram of the identification and attrition of studies is provided in figure 2.1.

The participant details and data acquisition parameters of included studies are outlined in table 2.1. Results of twenty-eight ROI comparisons are detailed in table 2.2, results of five VBM comparisons in table 2.3 and results of the meta-analyses in table 2.4.

Figure 2.1: Identification and attrition of studies

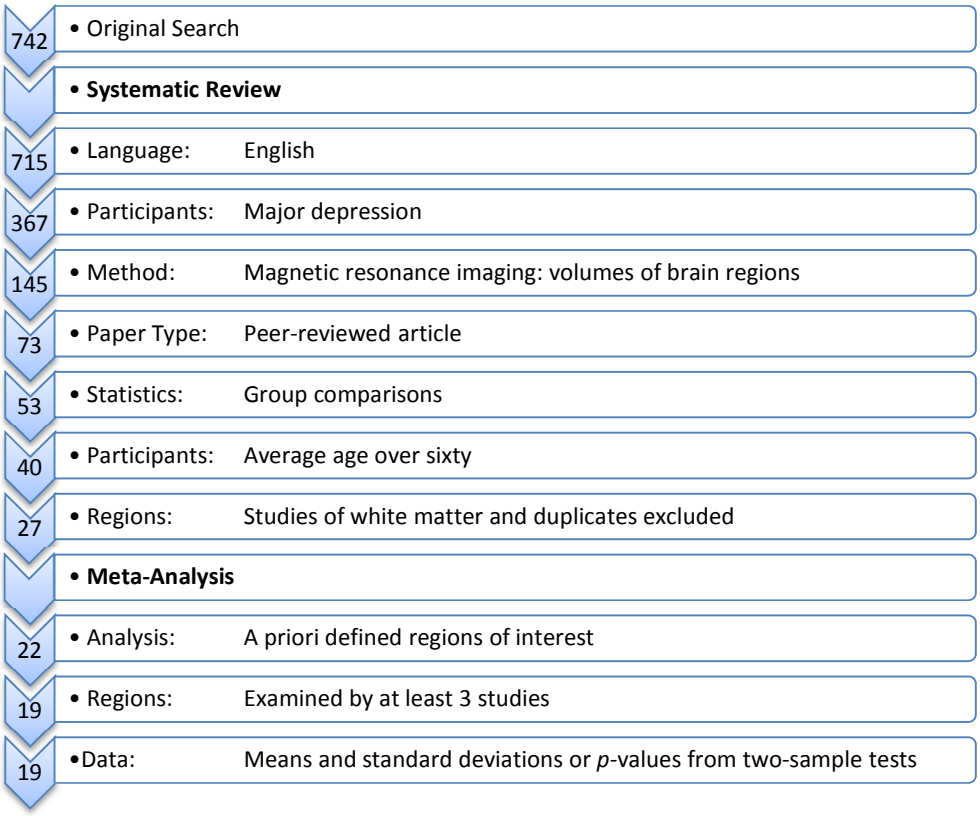


Table 2.1: Participant details and data acquisition

Abbreviations – AD: antidepressants; AP: antipsychotics; AX: anxiolytics; C: control; D: depression; EOD: early-onset depression; LOD: late-onset depression; LS: lithium salts; NR: non-remitted; R: remitted.

Study	Group	Number of Participants	% of Females	Mean Age	Age at Onset	HAM-D	Medication	Field Strength (T)	Acquisition Voxel Size (mm)
Almeida et al (2003)	EOD LOD C	24 27 37	96 67 73	72.8 75.5 72.9	39.2 72.4	24.4 24.9	Not stated	1.0	1.0 thickness
Andreescu et al (2008)	D C	71 32	69 53	72.2 ± 6.2 71.0 ± 6.7	52.3 ± 20 <60 (38); ≥60 (31)	18.3 ± 3.0	Yes - AD (12); AP (1); AX (19)	1.5	1.0 x 1.0 x 1.5
Ashtari et al (1999)	D C	40 46	71 60	74.3 ± 6.0 71.4 ± 0.3	61.5 ± 5.5 ≤60 (16); >60 (24)	26.1 ± 0.5	Not stated	1.0	1.0 x 1.0 x 3.1
Avila et al (2009)	D C	48 31	71 74	70.0 ± 6.7 70.3 ± 7.2	≤65 (20); >65 (28)	18.6 ± 5.9	Yes – AD (8); AX (10)	1.5	0.9 x 0.9 x 1.2
Ballmaier et al (2008)	EOD LOD C	24 22 34	83 64 56	68.0 ± 5.8 74.5 ± 8.1 72.4 ± 6.9	33.1 ± 16.1 71.3 ± 7.2	17.3 ± 2.6 18.1 ± 3.8	No - medication free ≥ 2 weeks No - medication free ≥ 2 weeks	1.5	0.9 x 0.9 x 1.4
Bell-McGinty et al (2002)	D C	30 47	43 57	69.3 ± 5.7 66.9 ± 7.3	Not stated	15.6 ± 7.1	Not stated	1.5	Not stated
Butters et al (2009)	D C	23 15	61 40	70.5 ± 5.7 69.4 ± 6.4	46.4 ± 19.9 <60 (16); ≥60 (7)	19.0 ± 4.5	Not stated	1.5	1.5 thickness
Egger et al (2008)	D C	14 20	71 65	71.4 ± 7.5 72.3 ± 7.8	≥ 60	N/A	Yes - AD (10), AP (4)	1.5	0.9 x 0.9 x 1.5
Hannestad et al (2006)	D C	182 64	71 64	70.2 ± 5.8 70.0 ± 7.7	43.7 ± 20.8	22.2 ± 5.6	Not stated	1.5	0.8 x 0.8 x 3.0
Janssen et al (2004)	D C	28 41	100 100	64.0 ± 10.9 62.4 ± 11.4	33.0 ± 9.5	14.2 ± 9.6	Yes (22) – AD (16), AP (4), AX (1), LS (3)	1.5	1.0 x 1.0 x 1.2
Janssen et al (2007a)	LOD C	15 22	100 100	72.7 ± 6.7 71.1 ± 7.5	69.9 ± 6.4	27.6 ± 4.8	Yes – LS (4)	1.5	1.0 x 1.0 x 1.2
Koolschijin et al (2010)	D C	28 38	100 100	64.0 ± 10.9 61.9 ± 11.0	33.0 ± 9.5	14.2 ± 9.6	Yes (22) – AD (16), AP (4), AX (1), LS (3)	1.5	1.0 x 1.0 x 1.2
Krishnan et al (1993)	EOD LOD C	11 14 20	73 64 55	70.6 ± 4.9 76.9 ± 6.5 72.5 ± 3.6	<60 ≥60	N/A	Not stated	1.5	7.5 thickness
Kumar et al (2000)	D C	51 30	71 77	74.3 ± 6.6 69.4 ± 6.1	<60 (16); ≥60 (35)	19.8 ± 3.9	Yes - some AD, AX	1.5	0.9 x 0.9 x 5.0

Lavretsky et al (2007)	D C	43 41	77 49	70.7 ± 7.8 72.2 ± 7.3	49.6 ± 23.1	17.7 ± 2.9	Medication free ≥ 2 weeks	1.5	0.9 x 0.9 x 1.4
Lehmbeck et al (2008)	D C	21 13	100 100	66.1 ± 6.3 65.2 ± 3.2	LOD	12.2 ± 3.8	Not stated	3.0	1.0 x 1.0 x 1.0
Lloyd et al (2004)	EOD LOD C	23 28 39	96 68 74	72.7 ± 6.7 75.1 ± 5.8 73.1 ± 6.7	38.7 72.0	24.0 ± 5.4 25.3 ± 3.8	Yes - including AD, LS	1.0	1.0 x 1.0 x 1.0
Pan et al (2009)	D C	170 83	66 73	69.4 ± 7.5 69.8 ± 5.6	Not stated	21.6 ± 5.2	Not stated	1.5	0.8 x 0.8 x 3.0
Pantel et al (1997)	D C	19 13	79 77	72.4 ± 8.8 68.2 ± 5.3	>50	26.7 ± 6.6	Not stated	1.5	1.0 x 1.0 x 1.3
Sheline et al (1996)	D C	10 10	100 100	68.5 ± 10.4 68.0 ± 9.5	Not stated	6.0 ± 5.4	Yes - including AD (8); previous AP (2)	1.5	1.0 x 1.0 x 1.3
Smith et al (2009a)	D C	16 13	63 62	65.3 ± 9.1 67.4 ± 7.4	Not stated	18.4 ± 2.5	Medication free ≥ 2 weeks	1.5	1.5 thickness
Tamburo et al (2009)	D C	14 11	36 36	69.8 ± 5.1 67.2 ± 6.8	Not stated	13.8 ± 4.2	History of AD (14)	1.5	0.9 x 0.9 x 1.5
Taylor et al (2005)	EOD LOD C	72 63 83	71 62 77	68.7 ± 6.4 71.5 ± 7.9 69.4 ± 6.3	30.2 ± 12.8 70.0 ± 8.7	20.3 ± 4.8 21.4 ± 4.3	Not stated	1.5	0.8 x 0.8 x 3.0
Taylor et al (2007b)	D C	226 144	88 83	70.0 ± 7.4 70.3 ± 6.5	45.2 ± 20.9	21.8 ± 5.0	Yes - some AD	1.5	0.8 x 0.8 x 3.0
Weber et al (2010)	D C	38 62	81 77	66.1 ± 6.2 71.1 ± 7.3	37.8 ± 14.8	Euthymic	Yes (34) – AD (18); AX (14)	3.0	0.9 x 0.9 x 0.9
Yuan et al (2008)	D C	19 16	53 50	67.1 ± 7.2 67.7 ± 3.8	64.6 ± 5.8	3.1 ± 2.3	Yes - AD (19)	1.5	0.9 x 1.3 x 2
Zhao et al (2008)	R NR C	24 37 43	63 60 67	65.9 ± 5.7 65.1 ± 5.3 69.0 ± 5.5	41.5 ± 21.7 38.1 ± 19.1	0.1 ± 0.6 17.6 ± 3.9	Yes - AD (23) Yes - AD (33)	3.0	1.0 x 1.0 x 1.0

Table 2.2: Results of ROI studies

WB excluded as possible overlap with [1](Lloyd et al 2004) [2](Taylor et al 2007b). Abbreviations - ACC: anterior cingulate cortex; EOD: early-onset depression; LOD: late-onset depression; OFC: orbitofrontal cortex; ROI: region of interest; VBM: voxel-based morphometry; WB: whole brain.

Study	Method	Regions	Significant Difference Compared With Controls
Almeida et al (2003) EOD	ROI	Frontal [1]	No significant differences
Almeida et al (2003) LOD	ROI	Frontal [1]	No significant differences
Andreescu et al (2008)	ROI	WB, Frontal (including OFC) , Temporal, Parietal Amygdala, Caudate, Hippocampus, Pallidum, Putamen, Thalamus	↓ Frontal (including OFC), Temporal, Parietal ↓ Amygdala, Hippocampus, Pallidum, Putamen, Thalamus
Ashtari et al (1999)	ROI	WB, Hippocampus, Hippocampus-Amygdala	No significant differences
Avila et al (2009)	ROI	Hippocampus, Temporal	No significant differences
Ballmaier et al (2008) EOD	ROI	WB, Hippocampus	↓ Hippocampus (L)
Ballmaier et al (2008) LOD	ROI	WB, Hippocampus	↓ Hippocampus (L, R)
Butters et al (2009)	ROI	Caudate	↓ Caudate (L)
Hannestad et al (2006)	ROI	Caudate [2]	No significant differences
Janssen et all (2004)	ROI	WB, Frontal (OFC), Temporal, Hippocampus	↓ Hippocampus (R)
Janssen et al (2007a) LOD	ROI	WB, Hippocampus	↓ WB
Krishnan et al (1993) EOD	ROI	Caudate, Putamen, Thalamus	No significant differences
Krishnan et al (1993) LOD	ROI	Caudate, Putamen, Thalamus	↓ Caudate, Putamen
Kumar et al (2000)	ROI	WB, Frontal, Temporal	↓ WB, Frontal
Lavretsky et al (2007)	ROI	Frontal (ACC, OFC)	↓ Frontal (OFC) (L, R)
Lehmbeck et al (2008)	VBM within ROI	Frontal (ACC)	↓ Frontal (ACC) (L)
Lloyd et al (2004) EOD	ROI	WB, Temporal, Hippocampus	No significant differences
Lloyd et al (2004) LOD	ROI	WB. Temporal, Hippocampus	↓ Hippocampus (L, R)
Pan et al (2009)	ROI	Putamen	No significant differences
Pantel et al (1997)	ROI	WB, Frontal, Temporal, Amygdala-Hippocampus	No significant differences
Sheline et al (1996)	ROI	WB, Hippocampus	↓ Hippocampus (L, R)
Tamburo et al (2009)	ROI	Amygdala	No significant differences
Taylor et al (2005) EOD	ROI	Hippocampus	No significant differences
Taylor et al (2005) LOD	ROI	Hippocampus	No significant differences
Taylor et al (2007b)	ROI	WB, Frontal (OFC)	↓ Frontal (OFC) (L, R)
Weber et al (2010)	ROI	Amygdala, Hippocampus, Frontal (ACC), Temporal	No significant differences
Zhao et al (2008) R	ROI	WB, Hippocampus	No significant differences
Zhao et al (2008) NR	ROI	WB, Hippocampus	↓ Hippocampus (L)

Table 2.3: Results of VBM studies

Abbreviations – OFC: orbitofrontal cortex; VBM: voxel-based morphometry.

Study	Method	Significant Difference Compared With Controls	MNI Co-Ordinates
Bell-McGinty et al (2002)	VBM	↓ Frontal (L, R) ↓ Hippocampus (R)	Not stated
Egger et al (2008)	VBM	↓ Frontal (OFC) (L, R) ↓ Amygdala (R) ↓ Hippocampus (R)	(-21, 14, -24), (6, 13, -21) (22, -9, -18) (25, -14, -20)
Koolschijin et al (2010)	VBM	No significant differences	N/A
Smith et al (2009a)	VBM	↓ Parietal (L) ↓ Occipital (L) ↓ Caudate (L, R) ↓ Thalamus (R)	(-37, -71, 42), (-57, -49, 27) (-22, -97, 13) (-14, 9, 10), (14, 6, 18) (21, -31, 11)
Yuan et al (2008)	VBM	↑ Frontal (ACC) (L) ↓ Frontal (R) ↓ Temporal (R) ↓ Parietal (L)	(-3, 15, 29) (8, -19, 70) (41, -12, -12) (-32, -24, 49)

Table 2.4: Meta-analysis results

Data shown in red indicate statistical significance ($p < 0.05$).

Region	Number of Studies	Total Number of Participants	Effect Size		Variability		Variability	Begg and Mazumdar		Egger	
			Hedges's g	*p*-value	Cohrane's Q	*p*-value	I^2	Kendall's Tau	*p*-value	t	*p*-value
Whole Brain	14	1073	0.03	0.674	11.52	0.567	0	0.31	0.125	1.55	0.148
Orbitofrontal Cortex	4	626	0.42	0.003	6.51	0.089	54	0.17	0.734	0.85	0.486
Amygdala	3	228	0.51	0.127	10.00	0.007	80	0.00	1.000	0.18	0.890
Caudate	5	432	0.59	0.035	20.08	<0.001	80	0.70	0.086	3.69	0.035
Hippocampus	15	931	0.31	<0.001	20.52	0.115	32	0.34	0.075	2.24	0.043
Putamen	4	401	0.49	0.038	9.42	0.024	68	0.50	0.308	1.79	0.216
Thalamus	3	148	0.59	0.001	1.68	0.432	0	-0.67	0.296	1.09	0.473

Of the twenty-eight ROI and five VBM group comparisons included in the systematic review, thirteen ROI and four VBM comparisons detected decreases in GM volume in LLD. An increase in GM volume in LLD was detected by one VBM study, but not by any ROI study. Fourteen ROI group comparisons and one VBM group comparison did not detect significant differences between LLD and control groups in GM.

Results of the systematic review and meta-analyses will now be detailed in order of whole brain (WB) volume, cerebral lobe then subcortical structure.

Whole Brain Volume

Only two of fourteen comparisons of WB volume detected a significant volume reduction in LLD. A meta-analysis of WB volumes resulted in a non-significant pooled effect size of 0.03 (p = 0.674). Studies did not display a significant level of heterogeneity or publication bias.

Frontal Lobe

Six of nine ROI comparisons examining the frontal lobe detected a significant reduction in volume in LLD. The most frequently studied frontal sub-region was the OFC, with three of four studies detecting a significant reduction in volume. A meta-analysis of OFC ROI results resulted in a significant pooled effect size of 0.42 (p = 0.003). Studies did not display a significant level of heterogeneity or publication bias.

In line with the ROI studies, three of five VBM studies detected a decrease in GM volume in a frontal region in LLD, including one in the OFC. However, one VBM study also detected an increase in GM volume in the ACC.

Temporal Lobe

Only one of eight comparisons of temporal ROI detected a significant decrease in volume in LLD. The anatomy of temporal ROI was diverse and included parahippocampal (Andreescu et al 2008; Avila et al 2009; Janssen et al 2004), entorhinal (Weber et al 2010), superior temporal (Andreescu et al 2008), middle temporal (Andreescu et al 2008), inferior temporal (Andreescu et al 2008), temporal pole (Andreescu et al 2008) and temporal horn (Lloyd et al 2004) ROI, as well as the whole of the temporal lobe (Kumar et al 2000; Pantel et al 1997). For this reason, a meta-analysis of temporal ROI was not performed. One VBM study detected a decrease in GM volume in the middle temporal gyrus.

Parietal Lobe

Only one ROI study placed a parietal ROI, and found a significant decrease in volume in LLD. Two VBM studies also detected decreases in GM volume in parietal regions.

Occipital Lobe

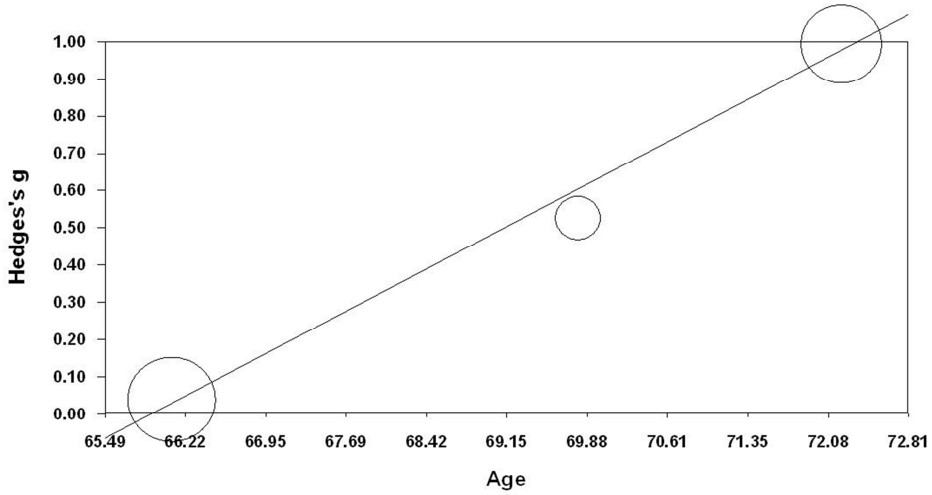
Occipital regions were not studied by any ROI study. However, one VBM study did identify a decrease in GM volume in the cuneus in LLD.

Amygdala

The amygdala was examined by three ROI studies, with one study detecting a significant decrease in volume in LLD. A meta-analysis resulted in a non-significant pooled effect size of 0.51 ($p = 0.127$). Studies were significantly heterogeneous ($Q = 10.00$, $p = 0.007$, $I^2 = 80$). Meta-regression was possible for mean age, percentage of female participants and voxel size. Greater effect size was associated with increased age (slope = 0.155, $p = 0.002$, figure

2.2) and increased voxel size (slope = 1.226, p = 0.002). Measures of publication bias were not significant.

Figure 2.2: Regression of age on effect sizes for the amygdala



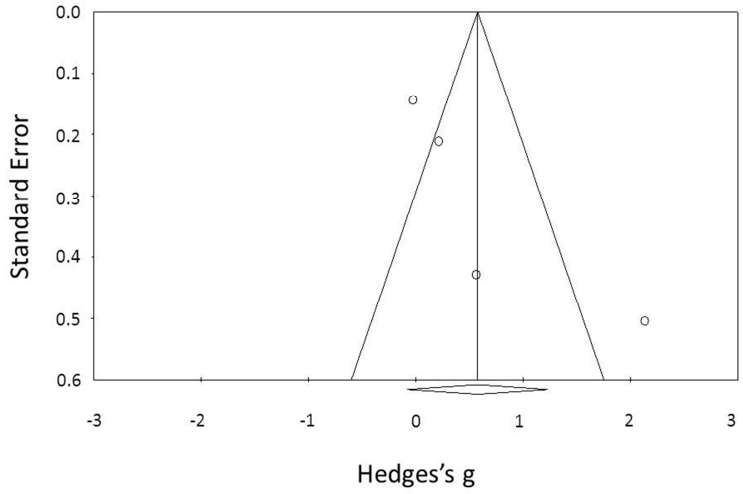
One VBM study found a significant decrease in amygdala volume in LLD. Also, despite an absence of significant differences in overall volume size, contractions of the basolateral nuclei bilaterally, and contraction or expansion of multiple, dispersed regions, were detected using shape analysis in one study (Tamburo et al 2009).

Caudate

Two of five ROI comparisons of caudate volume detected a significant decrease in volume in LLD. A meta-analysis found a significant pooled effect size of 0.59 (p = 0.035). Studies were significantly heterogeneous (Q = 20.08, p < 0.001, I^2 = 80). Meta-regression was performed with the LLD group's mean age, percentage of female participants, age at onset, and depression severity. Greater effect size was associated with increased age (slope = 0.250, p < 0.001) and smaller percentage of female participants (slope = -0.096, p = 0.003). Begg and Mazumdar rank correlations were not significant (τ = 0.70, two-tailed p = 0.09), while Egger's

regression intercept was significant (t = 3.69, p = 0.035), indicating a significant level of publication bias (figure 2.3).

Figure 2.3: Funnel plot of standard errors plotted against effect sizes for the caudate



Caudate volume was significantly reduced in LLD in one VBM study. Analysis of mean radial size indicated that volume reductions may be localised in the caudate head (Butters et al 2009). However, this pattern of radial reduction did not survive correction for multiple comparisons.

Hippocampus

The hippocampus was the most frequently studied ROI. Volume reductions were detected in LLD in seven of fifteen comparisons. A meta-analysis of all fifteen comparisons resulted in a significant pooled effect size of 0.31 (p < 0.001, figure 2.4). Measures of variability were not significant. Begg and Mazumdar rank correlations were not significant (τ = 0.34, two-

tailed $p = 0.075$), while Egger's regression intercept was significant (t = 2.24, $p = 0.043$), indicating a significant level of publication bias (figure 2.5).

Two VBM studies also detected a significant decrease in GM volume in the hippocampus in LLD. Furthermore, two ROI studies performed shape analysis of the hippocampus. Ballmaier et al (2008) detected contractions bilaterally in the anterior CA1-CA3 subfields and in the subiculum, in both EOD and LOD. Zhao et al (2008) localised contractions to the dentate gyrus, and possibly the CA4 region, in the left hippocampus. Areas of expansion were noted in the subiculum and CA2-CA3 subfields.

Figure 2.4: Forest plot of effect sizes for the hippocampus

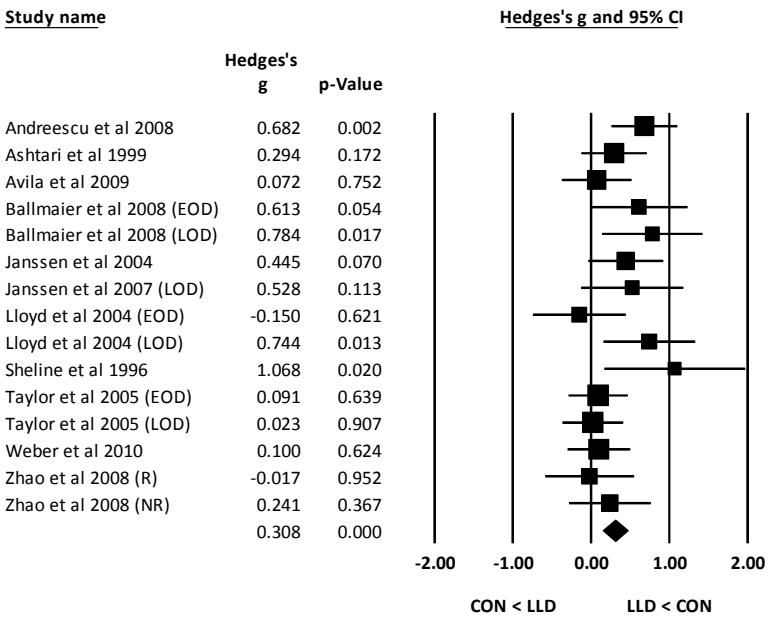
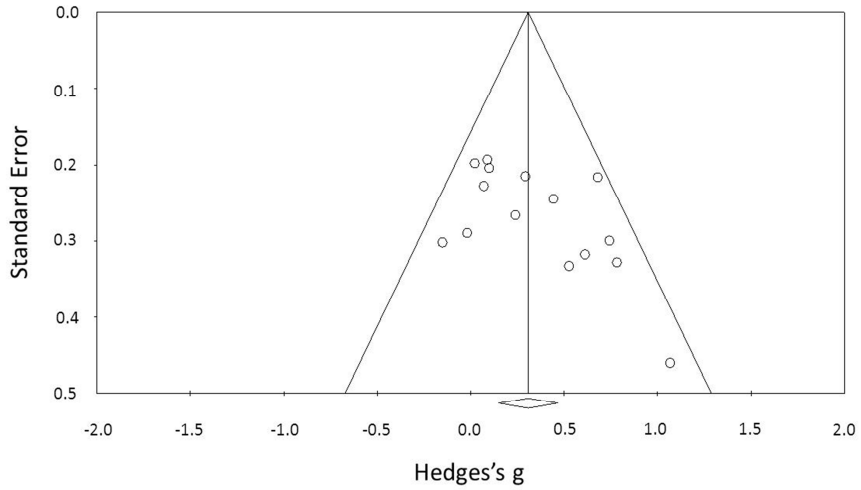


Figure 2.5: Funnel plot of standard errors plotted against effect sizes for the hippocampus



Pallidum

There has only been one ROI study of the pallidum, which detected a significant reduction in volume in LLD. The pallidum was not identified as significantly different in any VBM study.

Putamen

Of four ROI comparisons of the putamen, two detected a significant reduction in volume in LLD. A meta-analysis resulted in a significant pooled effect size of 0.49 (p = 0.038). Studies were significantly heterogeneous (Q = 9.42, p = 0.02, I^2 = 68). Meta-regression was only possible with mean age and percentage of females of the LLD group. Greater effect size was associated with increased age (slope = 0.159, p = 0.003). Measures of publication bias were not significant. The putamen was not identified as significantly different in any VBM study.

Thalamus

One of three ROI comparisons detected a significant decrease in thalamic volume in LLD. A meta-analysis resulted in a significant pooled effect size of 0.59 (p = 0.001). Measures of variability and publication bias were not significant. One VBM study also found a decrease in thalamic GM volume.

Discussion

In this section, GM abnormalities in LLD were examined in a systematic review and meta-analyses of MRI studies. With regard to ROI studies, the hippocampus was the most frequently studied structure. Volume reductions were detected in LLD in seven of fifteen comparisons and a meta-analysis of hippocampal ROI revealed a significant, but small, effect size. Although examined by fewer studies, meta-analyses also revealed significant volume reductions in the OFC, caudate, putamen and thalamus in LLD. The anatomy and effect sizes of significant regions were comparable to those stated by previous meta-analyses that spanned a greater age range (Koolschijn et al 2009). Increased mean age of the LLD group was associated with a greater effect size in all three regions in which the meta-analysis was associated with a significant amount of heterogeneity, though, indicating that there may be an age by diagnosis interaction within LLD.

VBM studies supported ROI findings, but also identified differences in occipital and parietal regions infrequently studied using ROI analysis. Shape analysis has shown potential at detecting subtle differences between groups, even in the absence of volumetric differences, but is yet to produce consistent results.

Methodological Considerations

Important methodological considerations arise as a result of grouping together studies that are heterogeneous in terms of participant details, data acquisition and data analysis, and are often limited in study size. Indeed, amygdala, caudate and putamen meta-analyses were associated with a significant amount of heterogeneity. Also, although Begg and Mazumdar's rank correlation was not significant for any region, Egger's regression intercept was significant for meta-analyses of the caudate and hippocampus. It is therefore possible that publication bias (selective reporting of publication of positive results) influenced results in these regions.

With regard to participant characteristics, meta-regression with potential confound regressors identified increased mean age of the LLD group as associated with a greater effect size in all three regions in which the meta-analysis was associated with a significant amount of heterogeneity. In addition, decreased percentage of female participants in the LLD group was associated with greater effect size in the caudate. No study has examined the effect of gender in the caudate, but Lavretsky et al (2004) found that depressed men may be particularly susceptible to atrophy in frontal subregions. While age and gender may indeed contribute to the heterogeneity observed, there are several limitations associated with using meta-regression to identify potential confound regressors. First, only a limited number of studies were included in each meta-analysis, and not all confound regressors were available for each study. Second, the meta-regression analyses did not incorporate a measure of confounder variance within each study. For example, the standard deviation associated with mean age varied from 4.9 (Krishnan et al 1993) to 10.9 (Janssen et al 2004; Koolschijn et al 2010), for age at onset from 2.6 (Ballmaier et al 2008) to 23.1 (Lavretsky et al 2007), and HAM-D from 0.5 (Ashtari et al 1999) to 9.6 (Janssen et al 2004; Koolschijn et al

2010). Third, the meta-regression used age and percentage female of the LLD group as confound regressors, but studies varied in how well matched LLD and control groups were for age and gender. Fourth, each variable was examined independently, but it may be that a combination of variables influences effect size.

With regard to data analysis, it is important to note that the studies included in the meta-analyses typically only assessed one or two GM regions. Thus, while the results of the meta-analyses supported reduced GM volume in several regions, the global picture of GM abnormalities needs to be clarified by further ROI studies examining GM volume in multiple regions or VBM studies examining GM across the whole brain.

Conclusion

In summary, the systematic review and meta-analyses indicated that LLD is associated with volume reductions localised in several brain regions including the OFC, caudate, hippocampus, putamen and thalamus. However, several negative reports exist and the global picture of GM needs clarification. Also, further studies examining differences in the shape of subcortical structures are warranted.

2.3 Aims

In the following sections, GM will be investigated in LLD and control groups. First, subcortical GM structures will be automatically segmented and volumetric and shape analysis performed. Second, VBM will be performed in order to examine GM globally. In line with the results of the systematic review and meta-analyses, it is hypothesised that there will be volumetric reductions in LLD, particularly within the frontal cortex and the hippocampus.

2.4 Methods

2.4.1 Participants

Recruitment

The study was conducted with approval from the Mid and South Buckinghamshire Local Research Ethics Committee, which during the course of the study was consolidated within the Berkshire Local Research Ethics Committee (Ref: 06/Q160/90). Informed written consent was obtained from all participants.

Two groups of participants were enrolled in this study: participants with LLD and control participants. Participants with LLD were identified from the general adult and old age psychiatric services of Oxfordshire and Buckinghamshire Mental Health National Health Service Trust and also from the community. Control participants were identified from the community.

Inclusion and Exclusion Criteria

Eligible participants were over the age of sixty, with no potentially confounding co-morbid medical, psychiatric or neurological conditions, and no implanted metallic devices, as required by standard MRI protocols.

Participants with LLD had met the DSM-IV-TR (2000) criteria for major depression, assessed by a psychiatrist, but were not necessarily currently depressed.

Control volunteers with a history of memory impairment or psychiatric illness were excluded, using the Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders Non-Patient Edition (January 2007) (First et al 2007).

2.4.2 Data Acquisition

Clinical Assessment

Participants underwent a clinical assessment to determine:

Age at Onset

Age at onset was defined as the age at which an individual experienced their first episode of major depression and was determined for LLD participants from personal testimony and hospital notes.

Cognitive Impairment

Cognitive impairment was assessed in all participants using the Addenbrooke's cognitive examination revised (ACE-R) and the mini-mental state examination (MMSE). The ACE-R has a maximum score of 100 and covers the domains of attention / orientation, memory, verbal fluency, language and visuospatial skills (Mioshi et al 2006). The MMSE is contained within the ACE-R and assesses attention / orientation, memory, language and visuospatial skills (Folstein et al 1975).

Depression Severity

Severity of depressive symptoms was assessed in LLD participants using the 17-item HAM-D (Hamilton 1967) and the 15-item geriatric depression scale (GDS) (Yesavage et al 1982).

HAM-D scores between 0 and 7 are classified as within the normal range, scores between 8 and 13 indicate mild depression, 14 and 18 moderate depression, 19 and 22 severe depression, and scores of 23 and over indicate very severe depression. GDS scores between 0 and 4 are within the normal range, scores between 5 and 8 indicate mild depression, 8 and 11 moderate depression, and 12 and 15 severe depression.

Duration of Illness

Duration of illness was estimated for LLD participants by subtracting age at onset from current age.

Education

For all participants, the number of years of full time education was determined from personal testimony.

Full-Scale Intelligence Quotient (FSIQ)

Full-scale intelligence quotient (FSIQ) was estimated from the number of errors on the national adult reading test for all participants (McGurn et al 2004). The national adult reading test consists of a list of fifty irregularly pronounced words that the participant is asked to read aloud. 'Irregular' words do not follow the normal rules of pronunciation, and therefore their correct pronunciation cannot be guessed.

Handedness

Handedness was assessed using Briggs and Nebes' twelve-item handedness questionnaire (Briggs & Nebes 1975) for all participants. Scores between -24 and -9 indicate left-handedness, between -8 and 8 mixed handedness, and between 9 and 24 right-handedness.

Medication Status

Medication status was determined for LLD participants from personal testimony and hospital notes. Medication was classified into the following categories: anticonvulsant, antidepressant, antipsychotic, anxiolytic, and lithium salts.

Framingham Stroke Risk

Framingham Stroke Risk was calculated for all participants based upon the following predictors: age, systolic blood pressure, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy (ascertained from personal testimony and hospital notes) and use of hypertensive medication (D'Agostino et al 1994).

MRI Acquisition

All participants underwent a MRI scan at the University of Oxford Centre for Clinical Magnetic Resonance Imaging (OCMR) using a 3.0 Tesla Trio Siemens scanner with a 12-channel head-coil. High-resolution 3D T_1-weighted MRI scans were acquired using a magnetization-prepared rapid gradient echo sequence (TR = 2040 ms, TE = 4.7 ms, flip angle = 8°, field of view = 192 mm, voxel dimension = 1 mm isotropic).

2.4.3 Data Analysis

Demographic Data

Statistical analysis was performed using PASW Statistics version 18 (IBM Corporation, Route 100, Somers, NY 10589, U.S.A.).

Continuous demographic variables were compared between groups using independent samples t-tests and categorical demographic data compared using χ^2 tests.

Image Analysis

Image analysis was performed using tools from the FMRIB software library (FSL, (Smith et al 2004), www.fmrib.ox.ac.uk/fsl).

Whole Brain Volume and Tissue-Type Percentages

T_1-weighted images were brain-extracted using the brain extraction tool (BET) (Smith 2002) and partial volume tissue segmentation carried out using FMRIB's automated segmentation tool v4.1 (FAST) (Zhang et al 2001). FAST creates a partial volume image for each class (GM, WM and CSF), where each voxel contains a value between 0 and 1 that represents the proportion of that class present in that voxel, based upon both the intensity of the voxel and spatial neighbourhood information. FAST is fully-automated, corrects for spatial intensity variations (also known as bias field or radio-frequency inhomogeneities) and is more accurate and robust than most finite mixture model-based methods. WB volume and GM, WM and CSF percentages were calculated and compared between LLD and control groups using a multi-variate general linear model (GLM) with age and gender as covariates.

Subcortical Structures

Subcortical brain segmentation and shape (vertex) analysis of the amygdala, caudate, pallidum, putamen and thalamus was performed using FMRIB's integrated registration and segmentation tool (FIRST) (Patenaude 2007; Patenaude et al 2007; 2008). FIRST is an automated model-based subcortical segmentation tool, trained using manually labelled

images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston.

First, T_1-weighted images were aligned to MNI152 space at 1mm resolution using two-stage (amygdala, caudate, pallidum, putamen, thalamus) or three-stage (hippocampus) affine registration. Second, based on the learned models, linear combinations of shape modes of variation were searched through for the most probable shape instance given the observed intensities in the T_1-weighted image. This results in a mesh composed of a set of triangles, with the apex of adjoining triangles called a vertex. Each mesh is composed of a fixed number of connected vertices for each structure so that the spatial location of corresponding vertices can be compared between groups. Third, boundary correction classified boundary voxels in the volumetric output for each structure. Both the registrations and subsequent segmentations were manually checked for errors and none were found.

Volumes of each of the subcortical structures were extracted and compared using a multi-variate GLM with age, gender and WB volume as covariates.

Vertex-wise statistics were performed using 'first_utils', with age, gender and WB volume included as confound regressors. First_utils employs a multi-variate GLM to test differences in mean vertex location between groups, using Pillai's trace to derive F-statistic values. False Discovery Rate correction for multiple comparisons was then applied to obtain thresholded F statistics.

Voxel-Based Morphometry

VBM analysis was performed using FSL-VBM (Ashburner & Friston 2000; Good et al 2001). GM partial volume images were aligned to MNI152 standard space using the affine

registration tool FMRIB's linear image registration tool (FLIRT) (Jenkinson et al 2002; Jenkinson & Smith 2001), followed by non-linear registration using FMRIB's non-linear image registration tool (FNIRT) (Andersson et al 2007a; Andersson et al 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al 1999). The resulting images were averaged to create a study-specific template, to which the native GM images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3mm. Finally, voxelwise statistics were performed using 'randomise', a permutation-based inference tool for non-parametric statistical thresholding that corrects for multiple comparisons across space (Nichols & Holmes 2002). The significance threshold for between-group differences was set at $p < 0.05$, using the threshold-free cluster enhancement option in 'randomise', with age and gender included as confound regressors (Smith & Nichols 2009). As modulation in FSL-VBM is based only on the non-linear registration stage, rather than both the affine and non-linear stages of registration, it was not necessary to also include WB volume as a confound regressor.

2.5 Results

Group demographics are included in table 2.5. There were no significant differences between the LLD and control groups in gender, age, education, FSIQ, MMSE, Framingham Stroke Risk or handedness. The LLD group had significantly lower ACE-R scores compared with the control group. The majority of LLD participants had HAM-D scores indicative of remission (HAM-D ≤ 7) or mild depression (HAM-D 8-13) and were currently receiving antidepressant treatment.

Table 2.5: Demographic Data

Values presented are: mean ± standard deviation (range). Data shown in red indicate statistical significance ($p < 0.05$).

	Control	LLD	*p*-value
Number of Participants	25	36	
Gender (F: M)	16 : 9	24 : 12	0.829
Age	71.76 ± 7.30 (60 – 89)	71.83 ± 7.71 (61 – 89)	0.970
Years of Education	14.56 ± 3.08 (10 – 22)	13.94 ± 3.74 (9 – 24)	0.558
FSIQ	122.35 ± 5.08 (103 – 128)	119.85 ± 7.91 (88 – 128)	0.170
Cognitive Impairment			
- **ACE-R**	95.20 ± 5.04 (77 – 100)	91.50 ± 6.26 (71 – 100)	0.017
- **MMSE**	29.48 ± 0.71 (28 – 30)	28.97 ± 1.36 (25 – 30)	0.093
Framingham Stroke Risk	10.08 ± 7.74 (2 – 32)	10.33 ± 7.64 (2 – 32)	0.900
Handedness	21.32 ± 9.59 (-24 – 24)	20.33 ± 9.86 (-24 – 24)	0.699
Age at Onset	N/A	45.39 ± 18.97 (10 – 78)	N/A
Duration of Illness	N/A	26.44 ± 18.70 (2 – 32)	N/A
Severity			
- **HAM-D**	N/A	4.19 ± 4.77 (0 – 18)	N/A
- **GDS**		3.83 ± 3.47 (0 – 11)	
Current Medication			
- **Number of Medications**	N/A	1.44 ± 0.77 (0 – 3)	N/A
- **Medication Free**		2	
- **Anticonvulsants**		1	
- **Antidepressants**		33	
- **Antipsychotics**		7	
- **Anxiolytic**		5	
- **Lithium Salts**		4	

Volumetric results are detailed in table 2.6. WB volume was significantly reduced in the LLD group. There were no significant differences between groups in the percentage of GM, WM or CSF, or in the volume of any subcortical structure. No differences in vertices survived multiple comparison correction in any subcortical structure. No significant differences in GM were detected between LLD and control groups using FSL-VBM.

Table 2.6: Volumetric Results

Values presented are: mean ± standard deviation. Data shown in red indicate statistical significance ($p < 0.05$), with p-values obtained using a multi-variate GLM. Age and gender were included as covariates for comparisons of WB volume, GM %, WM % and CSF %. Age, gender, and WB volume were included as covariates for comparisons of subcortical volumes.

Region	Control	LLD	*p*-value
Whole Brain (cm^3)	1522 ± 140	1457 ± 140	0.033
GM (%)	37.2 ± 1.7	37.3 ± 2.0	0.908
WM (%)	36.0 ± 1.6	35.9 ± 1.9	0.759
CSF (%)	26.8 ± 2.6	26.9 ± 3.1	0.906
Amygdala (mm^3)			
Left	1243 ± 243	1132 ± 184	0.361
Right	1157 ± 338	1088 ± 271	0.863
Caudate (mm^3)			
Left	3375 ± 300	3171 ± 427	0.138
Right	3553 ± 326	3379 ± 493	0.454
Hippocampus (mm^3)			
Left	3640 ± 490	3539 ± 453	0.713
Right	3735 ± 548	3602 ± 494	0.687
Pallidum (mm^3)			
Left	1837 ± 307	1724 ± 435	0.806
Right	1781 ± 254	1740 ± 481	0.687
Putamen (mm^3)			
Left	4470 ± 424	4279 ± 792	0.539
Right	4487 ± 407	4273 ± 708	0.390
Thalamus (mm^3)			
Left	7286 ± 687	6968 ± 827	0.440
Right	7034 ± 702	6721 ± 807	0.476

2.6 Discussion

In this section, subcortical and cortical GM was examined in LLD and control groups. Both volumetric and shape analyses were used to assess subcortical GM structures. Global analysis of GM was performed using FSL-VBM.

The LLD group displayed significantly reduced WB volumes compared with the control group. Reduced WB volume was accompanied by reductions in each tissue-type (GM, WM and CSF). As a result, the percentage of each tissue-type was not significantly different between groups. The finding of reduced WB volume is in contrast to the majority of the literature: in the systematic review, twelve of fourteen studies did not detect significant differences in WB volume. The reduction in WB volume cannot be easily attributed to demographic details, as LLD and control groups were well matched for age and gender.

Differences in subcortical GM structures were not detected with either volumetric or shape analysis. Also, FSL-VBM did not identify any significant differences in GM between LLD and control groups. Although the lack of significant findings is in contrast to the hypotheses of GM reductions in LLD and much of the literature, it is not unprecedented. For example, in the systematic review, eight of fifteen studies did not detect significant differences in hippocampal volume between LLD and control groups. Also, Koolschijin et al (2010) did not detect any regions significantly different in GM between LLD and control groups using VBM.

2.6.1 Methodological Considerations

There are several possible factors that could help explain the lack of significant differences in GM measures in this study. For example, findings may be related to characteristics of the LLD group, in particular, the relatively low HAM-D score of the LLD group compared with

previous studies. Increased severity has been associated with reduced volume in the hippocampus (Ashtari et al 1999) and OFC (Egger et al 2008), although several negative reports exist (Avila et al 2009; Bell-McGinty et al 2002; Janssen et al 2004; Koolschijn et al 2010; Lai et al 2000). Zhao et al (2008) directly compared hippocampal volume and shape between remitted participants, non-remitted participants and controls. The remitted group did not differ from controls in either hippocampal volume or shape. In contrast, the non-remitted group exhibited a significantly smaller left hippocampus than both the control group and the remitted group. This may be due to individuals with increased GM abnormalities being less likely to achieve remission (Frodl et al 2004; Hsieh et al 2002), and thus underrepresented in the Oxford sample. However, Janssen et al (2007b) found no difference in hippocampal or OFC GM volumes between responders and non-responders to treatment. Alternatively, remission may be associated with correction of GM abnormalities, possibly mediated via antidepressant treatment. Indeed, Lavretsky et al (2005) found that depressed participants with prior antidepressant exposure had greater OFC volumes compared with drug-naïve depressed participants. However, in a longitudinal study antidepressant treatment improved depressive symptoms, but did not alter hippocampal volumes (Vythilingam et al 2004). The range of age at onset and duration of illness within the LLD group may also have contributed to GM measures in the LLD group. The influence of severity and age at onset on GM measures in the LLD group will be examined in chapter 6.

Results may have also been influenced by data acquisition and analysis methods. However, the use of multiple techniques to examine GM reduced the likelihood that GM differences could have been detected using different analysis techniques.

2.6.2 Conclusion

Overall, while the literature provided moderate support for the hypothesis that GM abnormalities play a role in the pathophysiology of LLD, no differences in GM were detected in the Oxford study.

Chapter 3: The Role of White Matter in Late-Life Depression

3.1 Abstract

Alongside grey matter and functional abnormalities, white matter abnormalities within frontal-subcortical and limbic networks are hypothesised to play a key role in the pathophysiology of depression. Diffusion tensor imaging can uniquely study the orientation and integrity of white matter tracts and is thus an ideal tool to examine white matter in vivo.

In this chapter, white matter abnormalities are examined first in a systematic review and meta-analysis of diffusion tensor imaging studies of depression and, second, in a tract-based spatial statistics study comparing white matter integrity between participants with late-life depression and control participants.

The systematic review identified seventeen articles that compared participants with depression with control participants, and four studies suitable for a meta-analysis of superior frontal regions. Studies consistently identified reductions in anisotropy in the frontal and temporal white matter of participants with depression relative to control participants. A medium effect size was detected within superior frontal white matter, although heterogeneity and one index of publication bias were significant. Clarification of the extent of white matter abnormalities in depression and investigation of possible factors underlying reductions in anisotropy were identified as key areas for future research.

Next, tract-based spatial statistics was employed to examine group differences in white matter integrity in thirty-six participants with late-life depression and twenty-five control participants. Widespread reductions in anisotropy in late-life depression were identified,

with frontal-subcortical and frontal-temporal tracts particularly affected. Furthermore, reductions in anisotropy were accompanied by increases in radial diffusivity, but no change in axial diffusivity, compatible with decreased myelination.

Overall, the systematic review, meta-analysis and the Oxford tract-based spatial statistics study all strongly supported the hypothesis that white matter abnormalities in frontal-subcortical and limbic networks play a key role in the pathophysiology of depression.

Sections of this chapter have been published within "A systematic review of diffusion tensor imaging studies in affective disorders" (Sexton et al 2009). Compared with the published study, the literature review within this chapter includes more recent studies of depression, but does not include studies of bipolar disorder.

3.2 Background

White matter (WM) comprises up to 50% of the adult brain and its billions of fibres serve to connect GM regions into distributed neural networks (Filley 2010). Results of post-mortem studies have supported a key role for frontal-subcortical and limbic WM abnormalities in the pathophysiology of depression (Tham et al 2010). However, examination of the structure of WM and its role in depression using MRI has been limited by the numerous drawbacks associated with imaging WM with conventional MRI methods. For example, periventricular and deep white matter hyperintensities (WMH) have been typically assessed using visual rating scales on T_2-weighted or fluid attenuation inversion recovery images. While this approach has repeatedly identified more frequent and severe WMH in LLD (Herrmann et al 2008), rating scales suffer from intra- and inter-rater reliability, a lack of anatomical specificity, and may also be insensitive to subtle changes in WM integrity. Greater

characterisation of the nature and anatomy of microstructural WM deficits in depression may instead be gained by using diffusion tensor imaging (DTI).

3.2.1 Diffusion Tensor Imaging

DTI is an MRI technique that can uniquely study the orientation and integrity of WM tracts in vivo by measuring the diffusion of water in neural tissue. If there is unrestricted mobility of water molecules in all directions, diffusion is described as isotropic. In contrast, if there is restricted mobility of water molecules in any direction, diffusion is described as anisotropic. Within WM, a number of structures could potentially restrict perpendicular water diffusion and generate anisotropy, including axonal membranes, myelin sheaths, and neurofibrils (microtubules, neurofilaments). However, it is thought that the parallel arrangement of axonal membranes plays the primary role in generating anisotropy, while myelination can enhance the degree of anisotropy (Beaulieu 2002).

The three-dimensional diffusivity can be modelled as an ellipsoid whose orientation is characterised by the three eigenvectors (ε_1, ε_2, ε_3), which represent the major, medium, and minor principal axes of the ellipsoid, and shape is characterized by the three eigenvalues (λ_1, λ_2, λ_3), which represent the diffusivities in these three directions (figure 3.1). If diffusion is isotropic ($\lambda_1 = \lambda_2 = \lambda_3$), diffusion in all three main axes is equal and the diffusion ellipsoid is a sphere. If diffusion is anisotropic ($\lambda_1 > \lambda_2, \lambda_3$), the major eigenvector reflects the direction of maximum diffusivity, which, in turn, is assumed to reflect the orientation of fibre tracts. DTI can therefore be used to study the orientation and integrity of WM tracts in health and disease by estimating the degree of anisotropy (measures including fractional anisotropy, FA; and relative anisotropy) and the overall displacement of molecules (mean diffusivity, MD; trace; and apparent diffusion coefficient) (table 3.1). In addition, diffusivity can be

examined in greater detail using axial diffusivity (DA, diffusivity parallel to the WM tract) and radial diffusivity (DR, diffusivity perpendicular to the WM tract). Such measurements can be extracted locally in a priori defined regions using region of interest (ROI) analysis or tractography, or globally using voxel-based analysis (VBA) or tract-based spatial statistics (TBSS).

Figure 3.1: Diffusion ellipsoids

In panel (a) isotropic diffusion is modelled as a sphere. In panel (b) anisotropic diffusion is modelled as an ellipsoid.

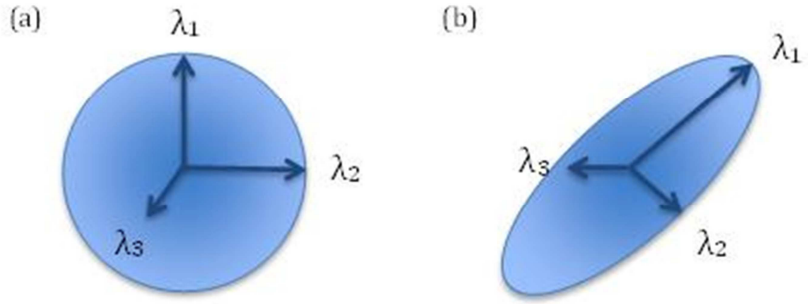


Table 3.1: DTI measures

Measure	Formula
Fractional Anisotropy	$\sqrt{\frac{1}{2}}\frac{\sqrt{[(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2]}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$
Mean Diffusivity	$\frac{\lambda_1+\lambda_2+\lambda_3}{3}$
Axial Diffusivity	λ_1
Radial Diffusivity	$\frac{\lambda_2+\lambda_3}{2}$

With regard to regional analysis techniques, ROI analysis typically involves placing an ROI of a fixed size and shape over a predefined region. Although manual ROI placement avoids registration errors, it is susceptible to user bias. Tractography algorithms can automatically reconstruct WM tracts, although user bias remains a consideration if seed or target regions are manually defined (Mori & van Zijl 2002).

With regard to global analysis techniques, VBA involves spatially registering each scan to a standard space and performing a voxel-by-voxel whole-brain statistical comparison of WM between groups. However, VBA is limited by the quality of inter-participant image registration and the amount of spatial smoothing of data (Smith et al 2006). Tract-based spatial statistics projects all participants' FA data onto an average FA tract skeleton before applying voxelwise cross-participant statistics. TBSS minimizes the effects of misalignment and is more robust and sensitive than VBA (Smith et al 2006). However, as the TBSS skeleton consists of peak FA values, assumed to be the centre of the tract, TBSS may be insensitive to differences that are not uniform throughout the width of the tract.

3.2.2 Literature Review

Introduction

There is great heterogeneity within published DTI studies of depression in terms of participant details, data acquisition, data analysis and results. This section aims to provide an overview of DTI studies of depression through first conducting a systematic review of studies, and second conducting a meta-analysis of ROI studies. As there have been a limited number of DTI studies of LLD, this review includes DTI studies of depression across all ages.

Methods

Online searches of the databases EMBASE and MEDLINE were performed in August 2010, using the keywords ([“diffusion tensor” or “DTI”] and [“depress*”]). Reference lists of included studies were then searched for additional studies.

For the systematic review, studies were screened for journal articles published in English that used DTI, with a minimum of six directions, to analyse group differences in anisotropy

or diffusivity between participants with major depression and healthy control participants. Cohort studies that examined depressive symptoms, but in which a diagnosis of major depression was absent, were excluded.

Key details regarding the participants, data acquisition, data analysis and results were recorded for all studies. If not stated, age at onset was calculated by subtracting duration of illness from mean age, or assumed to equal mean age if first-episode. Current medication status was divided into medication or medication free; medication was assumed if not stated. If 17-item HAM-D was not available, HAM-D was converted from alternative HAM-D scores or from MADRS scores (Heo et al 2007). Voxel size was calculated from the field of view, matrix size, slice thickness and gap. As the method for labelling anatomy differed considerably between studies, regions were grouped according to cerebral lobe (frontal, temporal, parietal and occipital), structure (hippocampus, thalamus, etc.) or tract (corpus callosum, uncinate fasciculus, etc). To provide an overview of the anatomy of significant differences, the lobe, structure or tract that contained a minimum of one region that was significantly different ($p < 0.05$, unless a stricter limit was imposed by the authors) between participants with depression and control participants, after corrections and covarying, was recorded. For VBA and TBSS studies, MNI co-ordinates of regions significantly different between groups were also recorded. Talairach co-ordinates were converted to MNI co-ordinates using Ginger Activation Likelihood Estimate (Lancaster et al 2007).

For the meta-analysis, articles included in the systematic review were screened for ROI studies that presented anisotropy values as means and standard deviations, or *p*-values from two-sample tests. Studies that assessed anisotropy using VBA or TBSS were excluded from the meta-analysis. Such studies would add a considerable source of bias to the analysis as they typically only provide details of areas that are significantly different between groups,

and are better examined separately using co-ordinate based or image-based meta-analysis methods (Salimi-Khorshidi et al 2009). Regions that were reported by a minimum of three studies were included in the meta-analysis, a threshold employed by previous meta-analyses (Kempton et al 2008; Sexton et al 2010).

Data were analysed using Comprehensive Meta-Analysis [version 2.2.048, ©2006, Biostat, Inc., Englewood, NJ, USA]. Effect size was measured using Hedges' g in order to correct for small sample size (Hedges & Olkin 1985). A random-effects model was used to calculate the pooled mean effect size, in order to allow unconditional inferences beyond the included studies (Hedges & Vevea 1998). In studies that used lateralised ROIs, volumes were summed across the left and right hemispheres. Effect sizes between 0.2 and 0.5 were classified as small, between 0.5 and 0.8 as medium, and over 0.8 as large.

Heterogeneity was assessed using Cochrane's Q and I^2, the percentage of the total variability due to between-studies variability (Higgins et al 2003). Publication bias was considered using Begg and Mazumdar rank correlations (Begg & Mazumdar 1994) and Egger's regression intercept test (Egger et al 1997). Finally, the influence of the depressed group's mean age, percentage of female participants, age at onset, current medication status, depression severity (HAM-D score), voxel volume, number of directions and number of excitations was analysed using fixed effect regression with Hedges' g.

Results

Titles and abstracts of one-hundred and fifty-nine identified citations were screened, of which seventeen met the inclusion criteria for the systematic review. A flow diagram of the identification and attrition of studies is provided in figure 3.2.

The participant details and data acquisition parameters of included studies are outlined in table 3.2. Results of ten ROI comparisons are detailed in table 3.3, and results of six VBA and three TBSS studies in table 3.4.

Figure 3.2: Identification and attrition of studies

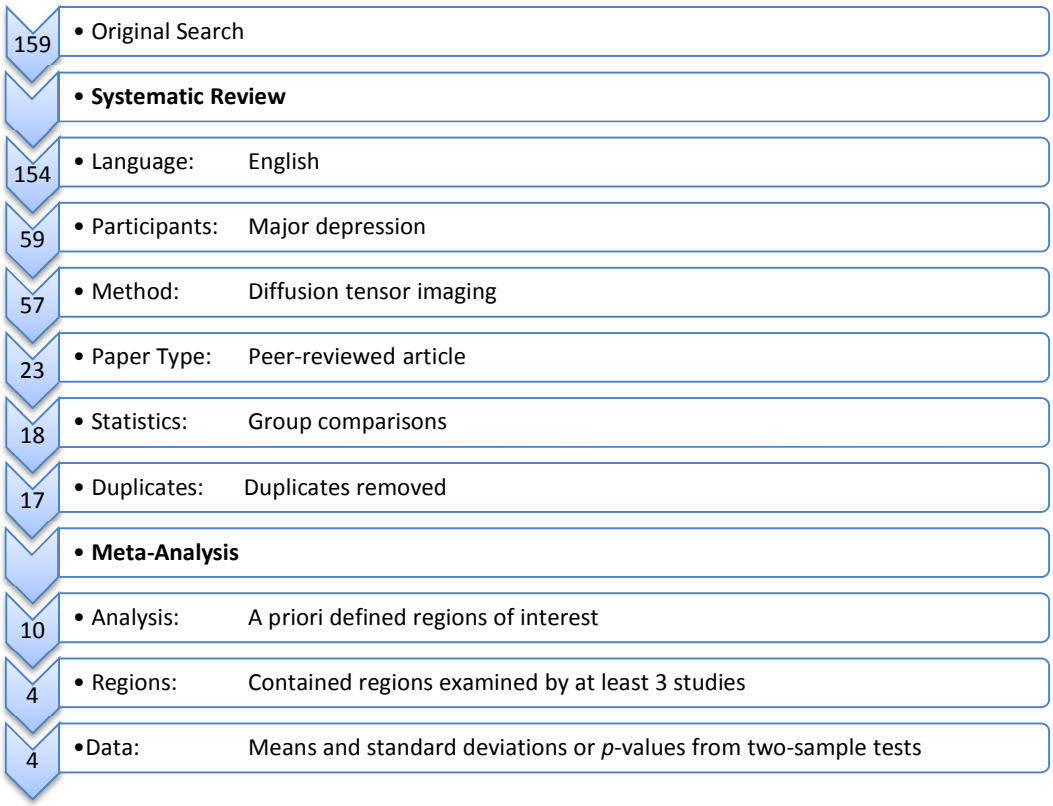


Table 3.2: Participant details and data analysis

Abbreviations – AD: antidepressants; AP: antipsychotics; AX: anxiolytics; C: control; D: depression; LS: lithium salts; MS: mood stabilisers.

Study	Group	Number of Participants	% of Females	Mean Age	Age at Onset	HAM-D	Current Medication	Field Strength (T)	Acquisition Voxel Size (mm)	No of Directions	No of Excitations
Abe et al (2010)	D	42	48	48.0 ± 13.2	42.1	9.2 ± 8.6	No (2); Yes (19) – AD	1.5	1.9 x 1.9 x 5.0	6	4
	C	21	48	48.1 ± 13.5							
Alexopoulos et al (2009)	D	27	Not stated	71.0 ± 6.3	53.0 8.7	15.4 ± 1.8	No - medication free 2 weeks	1.5	2.5 x 2.5 x 5.0	8	7
	C	27		71.1 ± 6.8							
Bae et al (2006)	D	106	69	70.4 ± 6.4	42.6 ± 20.8	9.9 ± 6.9	Yes - Duke STAGED Approach	1.5	1.9 x 1.9 x 7.5	6	1
	C	84	64	71.7 ± 6.0			(Steffens et al 2002)				
Cullen et al (2010)	D	14	71	16.8 ±1.3	14.0	N/A	No (3); Yes (11) - including	3.0	2.0 x 2.0 x 2.0	30	1
	C	14	57	16.8 ± 1.5			AD, AP (2), AX (1), MS (2), stimulants (2)				
Kieseppa et al (2010)	D	20	50	42.0 ± 11.6	27.9	N/A	Yes - AD (13), AP (1), AX (4)	1.5	1.8 x 1.8 x 5.0	12	1
	C	16	88	48.4 ± 10.3							
Li et al (2007)	D	19	79	28.1 ± 7.4	26.8 ± 7.5	28.0 ± 3.6	No – medication naïve	1.5	1.9 x 1.9 x 4.0	13	5
	C	20	80	26.7 ± 6.9							
Ma et al (2007)	D	14	86	28.9 ± 8.0	28.1 ± 7.8	N/A	No – medication naïve	1.5	1.9 x 1.9 x 4.0	13	5
	C	14	86	27.1 ± 6.7							
Nobuhara et al (2006)	D	13	69	62.8 ± 6.6	52.9 ± 7.3	33.4 ± 9.8	Yes – AD	1.5	1.9 x 1.9 x 8.0	6	4
	C	13	69	61.5 ± 4.8							
Shimony et al (2009)	D	76	23	70.0 ± 5.9	Not stated	21.6 ± 2.0	No - medication free > 3 weeks	1.5	2.0 x 2.0 x 6.0	6	4
	C	23	76	68.6 ± 7.7							
Steele et al (2005)	D	15	73	45.9	Not stated	27.3	Yes – including AC, AD,	1.5	1.9 x 1.9 x 4.0	6	1
	C	14	50	43.0			AP, AX, LS				
Taylor et al (2001)	D	14	57	69 ± 1.7	Not stated	N/A	Not stated	1.5	3.1 x 1.9 x 7.5	6	1
	C	19	53	69 ± 1.4							
Taylor et al (2004)	D	16	63	69.8 ± 6.4	41.7 ± 24	18.3 ± 2.2	Not stated	1.5	1.9 x 1.9 x 7.5	6	1
	C	17	67	67.5 ± 6.1							
Taylor et al (2007a)	D	18	67	70.8 ± 3.1	37.0 ± 21	N/A	Yes – AD	3.0	2.0 x 2.0 x 2.0	6	4
	C	19	63	72.2 ± 3.8							
Versace et al (2010)	D	16	33	32.3 ± 10.0	18.9 ± 7.2	17.1 ± 3.74	Yes – AD (14), AP (1), AX (5)	3.0	2.5 x 1.7 x 3.0	6	1
	C	24	60	29.5 ± 9.4							
Yang et al (2007)	D	31	65	64.6 ± 5.2	≥ 55	≥ 7	No (7); Yes (24) – AD < 6 weeks	1.5	1.0 x 0.8 x 3.0	25	1
	C	15	53	64.3 ± 4.2							
Yuan et al (2007)	D	16	56	66.9 ± 7.0	63.6 ± 5.6	3.4 ± 2.3	No - medication free > 3 months	1.5	1.9 x 1.9 x 4.0	25	2
	C	14	50	67.1 ± 4.8			previous medication AD				
Zou et al (2008)	D	45	67	32.2 ± 8.9	31.6 ± 8.9	23.8 ± 3.3	Yes – AD	3.0	1.9 x 1.9 x 3.0	15	2
	C	45	67	31.0 ± 10.3							

Table 3.3: Results of ROI studies

[1]frontal ROI excluded because of overlapping sample with (Bae et al 2006). Abbreviations – ACC: anterior cingulate cortex; ACD: apparent diffusion coefficient; CC: corpus callosum; FA: fractional anisotropy; IC: internal capsule; RA: relative anisotropy; ROI: region of interest; UF: uncinate fasciculus.

Study	Method	Anisotropy Measure	Diffusivity Measure	ROI / Tract	Significant Difference in Anisotropy	Significant Difference in Diffusivity
Bae et al (2006)	ROI	FA	ADC	Frontal, ACC, CC, IC	↓ Frontal (L, R), AC (R)	No significant differences
Cullen et al (2010)	Tractography			Subgenual ACC – Amygdala (UF), Subgenual ACC – Supragenual ACC	↓ AC – Amygdala (UF) (R)	N/A
Li et al (2007)	ROI	FA	N/A	Frontal	↓ Frontal (L, R)	N/A
Nobuhara et al (2006)	ROI	FA	N/A	Frontal, Temporal, Parietal, Occipital, CC	↓ Frontal, Temporal	N/A
Shimony et al (2009)	ROI	RA	MD	Frontal, Non-Prefrontal, CC, Deep WM	↓ Frontal	↑ Frontal, Non-Prefrontal, CC, Deep WM
Steele et al (2005)	ROI	FA	N/A	Brainstem	No significant differences	N/A
Taylor et al (2001)	ROI	FA	ADC	Frontal, Parietal, Caudate, Thalamus	No significant differences	No significant differences
Taylor et al (2004)	ROI	FA	N/A	Occipital [1]	No significant differences	N/A
Taylor et al (2007a)	Tractography	FA	N/A	UF	No significant differences	N/A
Yang et al (2007)	ROI	FA	N/A	Frontal, Temporal, CC	↓ Frontal (L, R), Temporal (R)	N/A

Table 3.4: Results of VBA and TBSS studies

Abbreviations – CC: corpus callosum; DA: axial diffusivity; DR: radial diffusivity; FA: fractional anisotropy; FA: fractional anisotropy; IC: internal capsule; ILF: interior longitudinal fasciculus; MD: mean diffusivity; SLF: superior longitudinal fasciculus; TBSS: tract-based spatial statistics; VBA: voxel-based morphometry.

Study	Method	Anisotropy Measure	Diffusivity Measure	Significant Difference in Anisotropy	MNI Co-Ordinates	Significant Difference in Diffusivity	MNI Co-Ordinates
Abe et al (2010)	VBA	FA	MD	No significant differences	N/A	↑ Frontal (L, R) ↑ Temporal (L, R) ↑ Insula (L) ↑ Pons (L, R) ↑ Cerebellum (L, R)	(-32, 22, 10), (-26, 8, -20), (44, 36, -6) (-40, 8, -14), (-38, -24, -8), (-36, -14, -18), (-20, 6, -26), (18, -16, -16), (36, -10, -22) (-42, -4, 2) (-4, -24, -38), (10, -20, -32) (-4, -58, -34), (8, -58, -32)
Alexopoulos et al (2009)	VBA	FA	N/A	↓ Frontal, Temporal, ↓ Parietal, Occipital ↓ CC, Thalamus, Midbrain ↓ ↑ Posterior Cingulate ↑ External Capsule ↑ Basal Ganglia	Not stated	N/A	N/A
Cullen et al (2010)	TBSS	FA	N/A	No significant differences	N/A	N/A	N/A
Kieseppa et al (2010)	TBSS	FA	N/A	No significant differences	N/A	N/A	N/A
Ma et al (2007)	VBA	FA	N/A	↓ Frontal (R) ↓ Occipital-Temporal (L) ↓ Parietal (R)	(32, 43, 18) (-40, -54, -2) (21, -49, 37), (37, -65, 23)	N/A	N/A
Steele et al (2005)	VBA	FA	N/A	↓ Temporal (R)	(64, -34, -26)	N/A	N/A
Versace et al (2010)	TBSS	FA	DA, DR	↓ ILF (L)	(-28, -67, 40)	No significant differences in ILF	N/A
Yuan et al (2007)	VBA	FA	N/A	↓ Frontal (L, R) ↓ Temporal (L) ↓ Parietal (R) ↓ Occipital (L, R) ↓ Putamen (R) ↓ Caudate (R)	(-54, 20, 22), (13, 9, 51) (-60, -5, -16) (46, -55, 43) (-26, -84, -12), (33, -77, 8) (31, -9, 5) (22, 30, 2)	N/A	N/A
Zou et al (2008)	VBA	FA	N/A	↓ IC (L) ↓ SLF (L)	(-13, 22, 5) (-34, -46, 33)	N/A	N/A

Overall, five ROI comparisons and seven VBA or TBSS comparisons detected decreases in anisotropy or increases in diffusivity in depression. Four ROI studies and two TBSS studies did not detect significant differences between groups. An increase in anisotropy in depression was detected by one VBM study, but not by any ROI study.

Frontal Lobe

Five of six ROI comparisons examining the frontal lobe detected a significant decrease in anisotropy in depression. A meta-analysis of four superior frontal ROI results resulted in a significant pooled effect size of 0.583 ($p < 0.001$; figure 3.3). Studies displayed a significant level of heterogeneity ($Q = 12.89$; $p = 0.005$, $I^2 = 77$). Greater effect size was associated with greater number of excitations (slope = 0.183, $p = 0.024$) and greater HAM-D scores (slope = 0.047, $p = 0.002$). Meta-regression was not significant for age, age at onset, percentage of females, current medication status, voxel size or number of directions. Begg and Mazumdar rank correlations were not significant ($\tau = 0.50$, two-tailed $p = 0.308$), while Egger's regression intercept was significant ($t = 5.68$, $p = 0.0296$), indicating a significant level of publication bias (figure 3.4).

Figure 3.3: Forest plot of effect sizes for superior frontal ROI

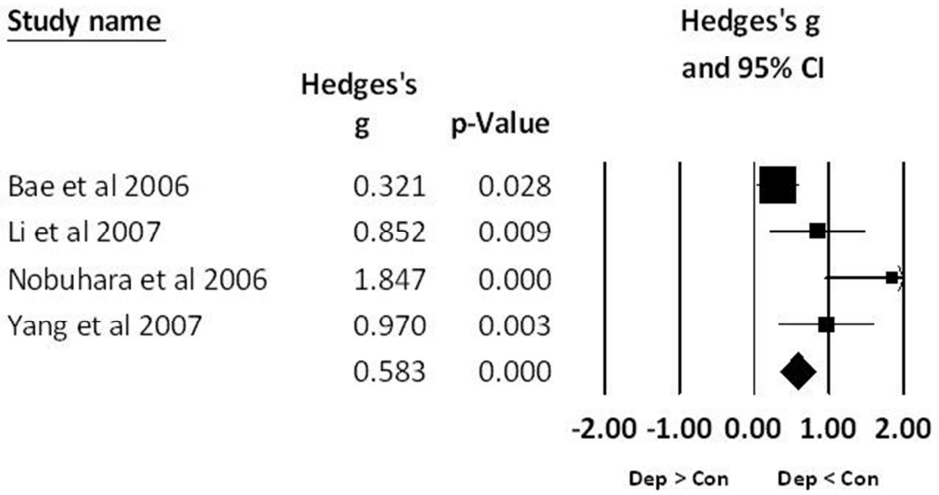
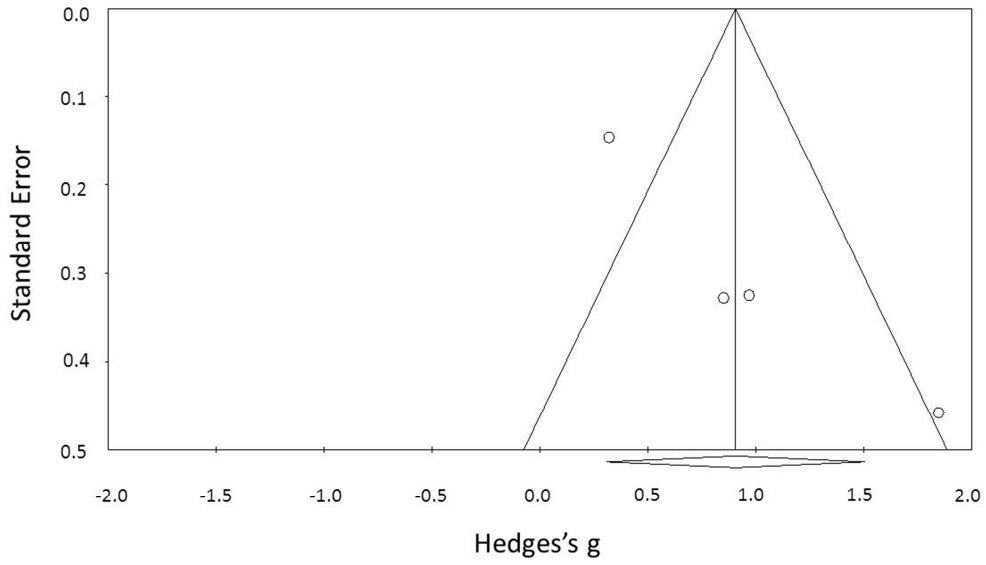


Figure 3.4: Funnel plot of standard errors plotted against effect sizes for superior frontal ROI



In line with ROI studies, three VBA studies detected a decrease in anisotropy in depression, including one in the superior frontal gyrus.

The three studies that detected a significant reduction in anisotropy in a frontal region in depression also compared diffusivity values. One study found a significant increase in diffusivity in depression, while two studies did not detect significant differences in diffusivity. One VBA study detected a significant increase in diffusivity in inferior frontal regions in depression, despite not finding any significant differences in anisotropy.

Temporal Lobe

Two studies examined regions in the temporal lobe and both detected a significant decrease in anisotropy in depression. Four VBA studies also detected a decrease in anisotropy in temporal or occipital-temporal regions in depression.

Of the two ROI studies that examined temporal anisotropy, neither studied diffusivity values. One VBA study detected a significant increase in diffusivity in temporal regions in depression, despite not finding significant differences in anisotropy.

Parietal Lobe

Two ROI studies examined the parietal lobe and neither detected a significant difference in anisotropy. In contrast, three VBA studies detected a significant decrease in parietal regions in depression.

The two ROI studies that examined parietal anisotropy did not study diffusivity. Parietal regions were not identified as significantly different between groups by the only VBA study to examine diffusivity.

Occipital Lobe

Of the two ROI studies that examined the occipital lobe, neither detected a significant difference in anisotropy. Anisotropy in occipital or occipital-temporal regions was, however, decreased in depression in three VBA studies.

Neither of the two ROI studies that examined occipital anisotropy studied diffusivity. Occipital regions were not identified as significantly different between groups by the only VBA study to examine diffusivity.

Corpus Callosum

The corpus callosum was not identified as significantly different between groups in any of the four ROI studies that examined the tract. Anisotropy was decreased in depression in one VBA study.

Three of the four ROI studies that failed to find significant differences in anisotropy also compared diffusivity values. One study detected a significant increase in diffusivity in depression, whereas two studies did not detect any significant difference. The corpus callosum was not identified by the only VBA study to examine diffusivity.

Discussion

In this section, WM abnormalities in depression were examined in a systematic review and meta-analysis of DTI studies. Overall, DTI studies consistently identified a reduction in anisotropy in participants with depression compared with control participants. Reductions in anisotropy were largely localised to the frontal and temporal lobes and detected in both hemispheres. A significant medium pooled effect size was detected in superior frontal WM, which contains fibres of the DLPFC and ACC circuits (Bonelli & Cummings 2007; Tekin &

Cummings 2002). Thus, findings support the hypothesis that WM abnormalities in frontal-subcortical and limbic networks play a key role in the pathophysiology of depression (Alexopoulos 2002).

The factors that underlie differences in anisotropy in participants with depression are as yet unknown and could involve a number of processes, including changes in the density of axons, axonal diameter, myelination, the coherence of the fibre tract, and localised water content. Examination of whether reductions in anisotropy are co-localised with differences in DA or DR, and consideration of GM abnormalities, may help in forming more specific hypotheses regarding the underlying causes of reductions in anisotropy (Burzynska et al 2010). For example, decreased myelination is associated with reductions in FA accompanied by increased DR but no change in DA (Burzynska et al 2010; Song et al 2003; Song et al 2002; Song et al 2005; Sun et al 2006). In contrast, Wallerian-like degeneration of WM resulting from GM pathology is characterised by reductions in FA accompanied by increases in DR and decreases in DA (Burzynska et al 2010; Pierpaoli et al 2001). Also, in the case of Wallerian-like degeneration, WM abnormalities would be expected to parallel the pattern of GM pathology. To date only one study has concurrently reported analysis of GM volumes and WM structure: Abe et al (2010) found some localised results, for example a decrease in GM volume in bilateral middle frontal gyri and an increase in MD in bilateral inferior frontal WM.

Methodological Considerations

This review included studies that varied greatly in terms of data acquisition, data analysis, and participant details, and were often limited in study size. Indeed, a significant degree of heterogeneity and, in one test, publication bias was detected in the meta-analysis. Results should therefore be interpreted with caution.

With regard to participant characteristics, increased severity was significantly associated with greater effect sizes in superior frontal ROI. This finding agrees with studies that have found a significant association between increased severity and increased FA (Nobuhara et al 2006; Zou et al 2008) in at least one region. However, several negative reports also exist (Abe et al 2010; Bae et al 2006; Li et al 2007; Versace et al 2010; Yang et al 2007). Effect size was not significantly associated with mean age, age at onset, percentage of female participants or current medication status of the LLD group. This may be due to the limited number of studies included in the meta-analysis, compounded by all measures not being available for all studies. Also, only a preliminary analysis of the effect of medication, simply based upon current medication status, was possible. A thorough investigation of medication by Versace et al (2010) that divided medication by class and also examined total medication load reported no association between DTI measures and current medication. Panic disorder (Han et al 2008), obsessive-compulsive disorder (Szeszko et al 2005), attention-deficit hyperactivity disorder (Ashtari et al 2005; Silk et al 2009) and substance use disorders (Arnone et al 2006; Ashtari et al 2009; De Bellis et al 2008; de Win et al 2007; Moeller et al 2007; Salo et al 2009) are all associated with changes in DTI measures. It was not possible to systematically investigate the effect of co-morbidity in the meta-analysis, as all authors used strict exclusion criteria. In the systematic review, Cullen et al (2010) included participants with co-morbidity that could have confounded their results.

With regard to data acquisition, the accuracy of the diffusion tensor and, in turn, the reliability of the data derived from it are influenced by the signal-to-noise ratio, image resolution, image distortion due to magnetic susceptibility effects, and motion artefacts. All four factors are interrelated and are influenced by acquisition parameters (including the field strength, number of excitations and number of directions), which differ from study to

study (table 3.1). Indeed, increased number of excitations was found to be associated with increased effect sizes.

With regard to data analyses, the anatomical specificity possible in this review is limited by the different data analysis methods utilised. With ROI analysis, there is a possibility of type II error; that is, important differences occurring outside of or overlapping the ROIs may go unobserved. Conversely, VBA can be significantly biased toward group differences that are highly localised in space and result in type I error (Davatzikos 2004). Differences in analysis methods may explain why positive findings in the parietal and occipital lobes were only detected by VBA studies and further studies examining WM integrity globally are needed to clarify the extent of WM abnormalities in depression.

Conclusion

In conclusion, DTI studies have consistently identified WM abnormalities in depression, with the most frequent positive findings occurring within frontal and temporal lobes and tracts. Although several limitations arise from grouping together heterogeneous studies, it is encouraging that WM abnormalities can be detected in participants who vary considerably in age, age at onset, severity and medication status. Clarification of the extent of WM abnormalities in depression and investigation of possible factors underlying reductions in anisotropy are key areas for future research.

3.3 Aims

In the following sections, WM integrity will be investigated in LLD and control groups globally using TBSS. In line with the results of the systematic review and meta-analysis, it is hypothesised that there will be reduced FA in the LLD group compared with the control

group in frontal-subcortical and frontal-temporal tracts. In particular, it is hypothesised that differences will be located within the anterior thalamic radiation, which connects the PFC and thalamus, and the uncinate fasciculus, which connects frontal and temporal lobes. In regions that display significant differences in FA, differences in DA and DR will be examined in order to gain a greater understanding of what may underlie WM abnormalities in LLD.

WM abnormalities will also be examined by rating periventricular and deep WMH. In line with previous studies (Herrmann et al 2008), it is hypothesised that that the LLD group will exhibit more severe WMH than the control group.

3.4 Methods

3.4.1 Participants

Participant recruitment and inclusion and exclusion criteria are outlined in section 2.4.1

3.4.2 Data Acquisition

All MRI scans were obtained at OCMR using a 3.0 Tesla Trio Siemens scanner with a 12-channel head-coil. Whole-brain DTI was acquired using an echoplanar imaging sequence (TR = 7900 / 7800 ms, TE = 98 / 82 ms, field of view = 240 mm, voxel size = 2.5 mm isotropic, b value = 1000, number of directions = 60, number of acquisitions = 2). T_2-weighted images were also acquired to characterise WMH (TR = 6000 ms, TE = 91 ms, field of view = 220 mm, voxel size = 0.7 x 0.7 x 4.0 mm).

3.4.3 Data Analysis

Image analysis was performed using FSL tools ((Smith et al 2004), www.fmrib.ox.ac.uk/fsl). DTI data were manually checked and artefacts removed before eddy current correction was run to correct for eddy current distortions and head motion.

Tract-Based Spatial Statistics

Analysis of the DTI data was carried out using TBSS (Smith et al 2006). FA images were created by fitting a tensor model to the raw diffusion data using FMRIB's diffusion toolbox, and then brain-extracted using BET (Smith 2002). All participants' FA data were then aligned into a common space using FMRIB's non-linear image registration tool (FNIRT) (Andersson et al 2007a; Andersson et al 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton that represents the centres of all tracts common to the group. Each participant's aligned FA data was then projected onto this skeleton. The non-linear warps and skeleton projection stages were then repeated using DA and DR values.

All voxelwise statistics were performed using 'randomise' (Nichols & Holmes 2002), with age and gender included as confound regressors. The significance threshold for between-group differences was set at $p < 0.05$, using the threshold-free cluster enhancement option in 'randomise' (Smith & Nichols 2009). Group differences in FA were investigated across the whole skeleton and group differences in DA and DR examined in regions where FA was significantly different.

In order to aid in the localisation of significant differences in FA, skeleton masks (tracts of interest, TOI) were created for the anterior thalamic radiation, genu, body, and splenium of the corpus callosum; cingulum; corticospinal tract; fornix; inferior longitudinal fasciculus;

superior longitudinal fasciculus; and uncinate fasciculus (table 3.5). TOI were based on the ICBM-DTI-81 white-matter labels atlas and the JHU white-matter tractography atlas within the FSL atlas tool, as well as the MRI Atlas of Human White Matter (Mori et al 2005). The percentage of mask voxels that were significantly different in FA was calculated for each TOI. To aid in the display of results, mean FA, DA and DR within voxels significantly different in FA within each TOI were converted to standardised z scores based on the mean and standard deviation of the control group. Signs were reversed for DA and DR so that reduced z scores represented increased DA and DR values in LLD.

Table 3.5: Tracts of interest

For each TOI a description of the tract and the size of the mask are provided. Association fibres connect cerebral areas within each hemisphere; commissural fibres connect the left and right hemispheres; and projection fibres connect cortical and subcortical GM.

Mask	Type	Regions Connected	Number of Voxels
Whole Skeleton	N/A	N/A	92043
Anterior Thalamic Radiation	Projection	Thalamus and prefrontal cortex	3229
Corticospinal Tract	Projection	Motor cortices and lower motor areas	5795
Cingulum	Association	Frontal, parietal and temporal lobes	1894
Corpus Callosum	Commissural		
- **Body**		Premotor, supplementary motor and motor cortex	3670
- **Genu**		Prefrontal cortex	1969
- **Splenium**		Parietal, occipital and temporal lobes	2221
Fornix	Commissural	Hippocampus, hypothalamus and thalamus	1299
Inferior Longitudinal Fasciculus	Association	Frontal, parietal and medial temporal lobes	3672
Superior Longitudinal Fasciculus	Association	Frontal, parietal, temporal and occipital lobes	2018
Uncinate Fasciculus	Association	Frontal and temporal lobes	2236

White Matter Hyperintensities

Periventricular and deep WMH were rated using the modified Fazekas scale (Fazekas et al 1987), which ranges from 0-3. For both periventricular and deep WMH, the number of scans rated 2 or 3 was below five for both control and LLD groups. As a result, scores between 1 and 3 were collapsed into a single group before χ^2 tests were performed. Unfortunately T_2-weighted images were not available for five LLD participants.

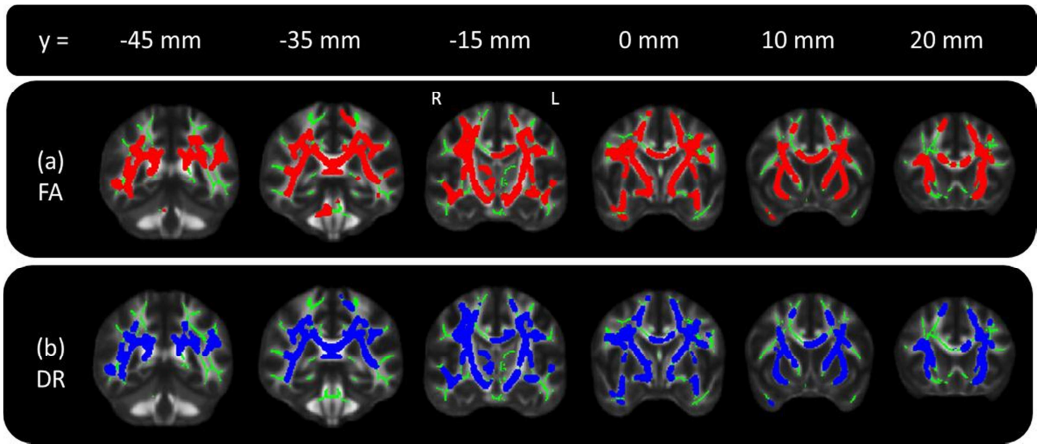
3.5 Results

There were widespread differences in FA, with 36% of skeleton voxels significantly lower in the LLD group at $p < 0.05$ and 16% at $p < 0.01$ (figure 3.5). There were no regions where FA was significantly higher in the LLD group.

DA and DR were then examined in regions of decreased FA. 83% of voxels that exhibited a decrease in FA in LLD exhibited a significant increase in DR at $p < 0.05$ (figure 3.5). In contrast, no voxels that exhibited a decrease in FA also exhibited a significant difference in DA.

Figure 3.5: Localisation of group differences in FA and DR

In panel (a), regions significantly reduced ($p < 0.05$) in FA in LLD are shown in red, overlaid on a green skeleton. In panel (b), regions significantly increased ($p < 0.05$) in DR, in addition to being significantly reduced in FA, are shown in blue, again overlaid on a green skeleton. Significant regions are dilated for illustrative purposes.



In order to aid in the localisation of significant differences in FA, TOI were created for a the anterior thalamic radiation, genu, body, and splenium of the corpus callosum; cingulum; corticospinal tract; fornix; inferior longitudinal fasciculus; superior longitudinal fasciculus; and uncinate fasciculus. The results of the TOI analysis are presented in table 3.6. At least 20% of voxels were significantly reduced in FA at $p < 0.05$ in all tracts. At least 50% of voxels were significantly reduced in FA at $p < 0.05$ in the anterior thalamic radiation, corticospinal tract, splenium of the corpus callosum, superior longitudinal fasciculus and uncinate fasciculus. Standardised z scores of mean FA, DR and DA in voxels significantly reduced in FA in LLD are shown in figure 3.6.

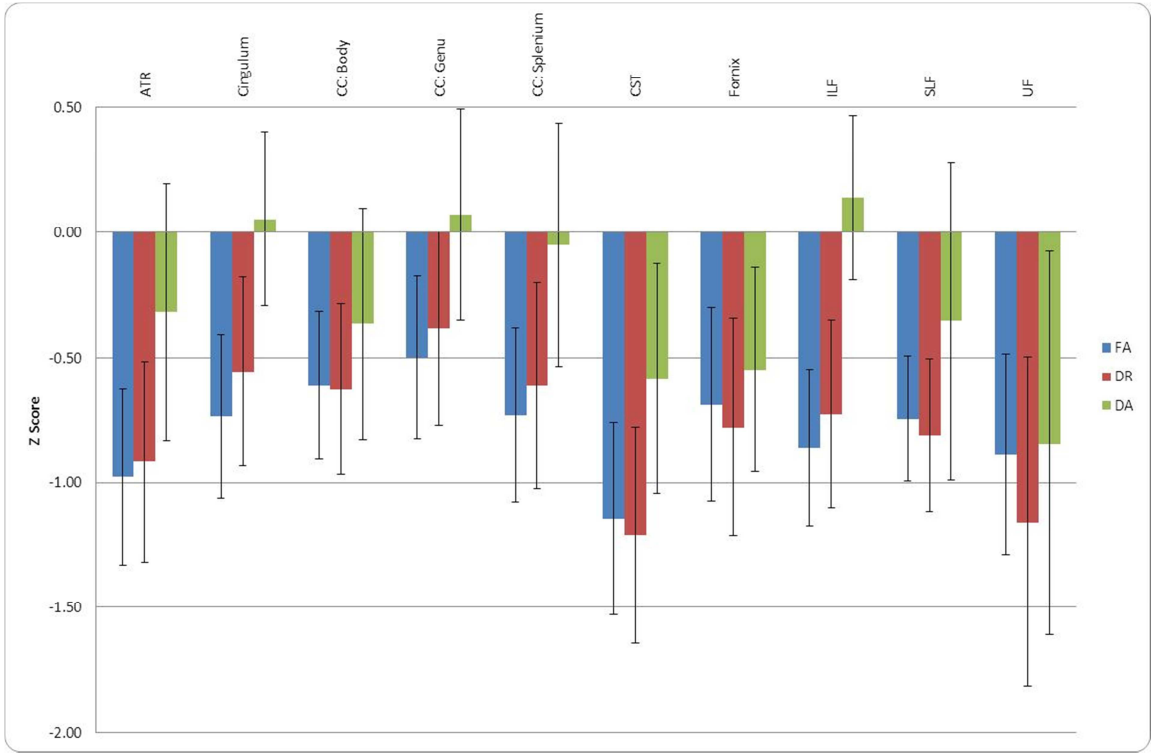
Table 3.6: Localisation of group differences in FA

Percentage of voxels significantly decreased ($p < 0.05$, $p < 0.01$) in FA in depression in each TOI.

Mask	% $p < 0.05$	% $p < 0.01$
Whole Skeleton	36	16
Anterior Thalamic Radiation	62	39
Cingulum	20	10
Corpus Callosum		
- **Body**	45	12
- **Genu**	48	0
- **Splenium**	66	34
Corticospinal Tract	59	37
Fornix	23	6
Inferior Longitudinal Fasciculus	38	14
Superior Longitudinal Fasciculus	60	24
Uncinate Fasciculus	64	40

Figure 3.6: Z scores of FA, DR and DA in voxels significantly reduced in FA in LLD

Mean z score ± two standard errors of the LLD group. Negative z scores represent reductions in FA and increases in DR and DA in LLD. By definition, z scores for the control group are zero. Abbreviations – ATR: anterior thalamic radiation; CC: corpus callosum; CST: corticospinal tract; ILF: inferior longitudinal fasciculus; SLF: superior longitudinal fasciculus; UF: uncinate fasciculus.



Fazekas scores for periventricular and deep WMH are presented in table 3.7. There were no significant differences between groups in periventricular WMH scores ($\chi^2 = 2.698$, $p = 0.100$) or deep WMH scores ($\chi^2 = 0.259$, $p = 0.611$).

Table 3.7: Fazekas scores

	Control	LLD
Periventricular WMH		
- 0	9 (36%)	18 (58%)
- 1	14 (56%)	12 (39%)
- 2	1 (4%)	1 (3%)
- 3	1 (4%)	0 (0%)
Deep WMH		
- 0	12 (48%)	17 (55%)
- 1	12 (48%)	11 (35%)
- 2	0 (0%)	3 (10%)
- 3	1 (4%)	0 (0%)

3.6 Discussion

In this chapter WM integrity in LLD and control participants was investigated using TBSS. As hypothesised, LLD was associated with reduced FA within frontal-subcortical and limbic tracts, with over 60% of voxels within the anterior thalamic radiation and uncinate fasciculus significant at $p < 0.05$. In addition, reductions in FA were detected in several other tracts, including within the corticospinal tract, superior longitudinal fasciculus and corpus callosum, thus supporting the existence of diffuse WM damage in depression, albeit with a frontal-subcortical emphasis (Shimony et al 2009).

Reductions in FA were largely accompanied by significant increases in DR but no change in DA, a pattern that has been interpreted as indicative of decreased myelination (Burzynska et al 2010; Song et al 2003; Song et al 2002; Song et al 2005; Sun et al 2006). While neurobiological interpretations of DTI findings should be made with caution, post-mortem

studies support the notion of decreased myelination and have identified decreased oligodendrocyte density (Hamidi et al 2004; Uranova et al 2004) and less intense myelin staining (Regenold et al 2007) in depression. In addition, microarray studies of post-mortem tissue have revealed decreased expression of myelination and myelination-related genes and transcription factors in depression (Aston et al 2005).

Given the absence of GM pathology in the Oxford LLD sample, detailed in chapter 2, the results do not support the hypothesis that reductions in FA result from Wallerian-like degeneration. Also, secondary Wallerian-degeneration is characterised by reductions in FA accompanied by increases in DR and decreases in DA (Burzynska et al 2010; Pierpaoli et al 2001) – a pattern not displayed in the current findings.

In contrast to the hypotheses, an increase in WMH in LLD was not detected. Although this finding differs from much of the literature (reviewed in (Herrmann et al 2008)), several studies in which groups were matched for vascular risk factors have failed to find increases in WMH scores or volume in LLD (O'Brien et al 2004; Rainer et al 2006; Sheline et al 2008; Shimony et al 2009), and there are a number of possible explanations. For example, it may be that it is the regional specificity of WMH, rather than the overall volume or severity rating, which is important in LLD. In support of this hypothesis, Sheline et al (2008) found that although the total volume of WMH was equal between LLD and control groups, the LLD group had greater WMH within tracts of the DLPFC circuit. Also, in a post-mortem study, Thomas et al (2002) found that ischemic DWMH were more frequently located in the DLPFC compared with the ACC and occipital cortex in LLD participants. However, in addition to failing to find overall differences in WMH volume, Shimony et al (2009) also failed to find differences between groups in WMH volume in any subregion, despite detecting widespread reductions in FA. As a result, the authors suggested that WMH represent a small portion of

the overall WM pathology in depression, with DTI metrics being far more sensitive measures of WM abnormalities compared with WMH.

3.6.1 Methodological Considerations

A key strength of this study was the data acquisition, which entailed two repeats of sixty-direction DTI. These parameters exceed the suggested minimum of thirty directions that are estimated to be necessary for robust estimation of both FA and MD (Jones 2004), and is in contrast to seventeen of the eighteen DTI studies reviewed in the systematic review, which acquired fewer than thirty directions.

The Oxford study also represented the first TBSS study of LLD. Employing TBSS in the analysis of DTI data allowed greater examination of the extent and spatial localisation of differences in FA compared with ROI approaches, and minimised registration errors compared with VBA. Unfortunately, assessment of WMH using the Fazekas scale did not allow detailed assessment of the anatomy of WMH.

3.6.2 Conclusion

Overall the systematic review, meta-analysis and TBSS study all strongly supported the hypothesis that WM abnormalities in frontal-subcortical and limbic networks play a key role in the pathophysiology of depression. The TBSS study also detected a pattern of FA reductions accompanied by increases in DR, but no change in DA, suggestive of decreased myelination.

Chapter 4: The Role of Functional Connectivity in Late-Life Depression

4.1 Abstract

Along with structural abnormalities, functional abnormalities within frontal-subcortical and limbic networks are hypothesised to play a key role in the pathophysiology of depression. In particular, abnormalities in functional connectivity within the default-mode network, the executive control network and the affective network have been proposed.

In this chapter, abnormalities in functional connectivity within resting-state networks are examined first in a systematic review of resting-state functional magnetic resonance imaging studies and, second, in an independent components analysis study comparing functional connectivity within the default mode network, the affective network and the executive control network between participants with late-life depression and control participants.

The systematic review identified ten studies that compared functional connectivity between participants with depression with control participants. Studies consistently identified increased connectivity within the default-mode network, but results within executive control and affective networks were more variable. Investigation of abnormalities in functional connectivity in late-life depression and examination of the pattern of differences in functional connectivity in multiple networks were identified as key areas for future research.

Next, independent components analysis followed by dual regression was employed to examine group differences in functional connectivity within the default mode network, the affective network and the executive control network in thirty-six participants with late-life

depression and twenty-five control participants. No differences in functional connectivity were detected in any network.

While the literature provided support for increases in connectivity within the default mode network in depression, this was not replicated by the Oxford independent components analysis study.

4.2 Background

Results of resting-state Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) studies have consistently identified decreased activation in dorsal neocortical and superior limbic structures and increased activation in ventral limbic, paralimbic and subcortical structures in depression (Fitzgerald et al 2008; Mayberg 1997; Seminowicz et al 2004). Such studies have been instrumental in the formation of network-based models of depression and subsequent development of novel treatment approaches, most notably deep-brain stimulation (Ressler & Mayberg 2007). However, PET and SPECT studies have significant limitations, including poor spatial resolution, and also require injection of radioactive isotopes. Also, while network-based models of depression propose failure of co-ordinated interactions of limbic-cortical networks in depression, PET and SPECT studies have typically examined differences in the amplitude of activity in brain regions rather than the coherence in activity within neural networks. Resting-state functional magnetic resonance imaging (fMRI) is an ideal tool to examine coherence in activity within neural networks, commonly referred to as functional connectivity.

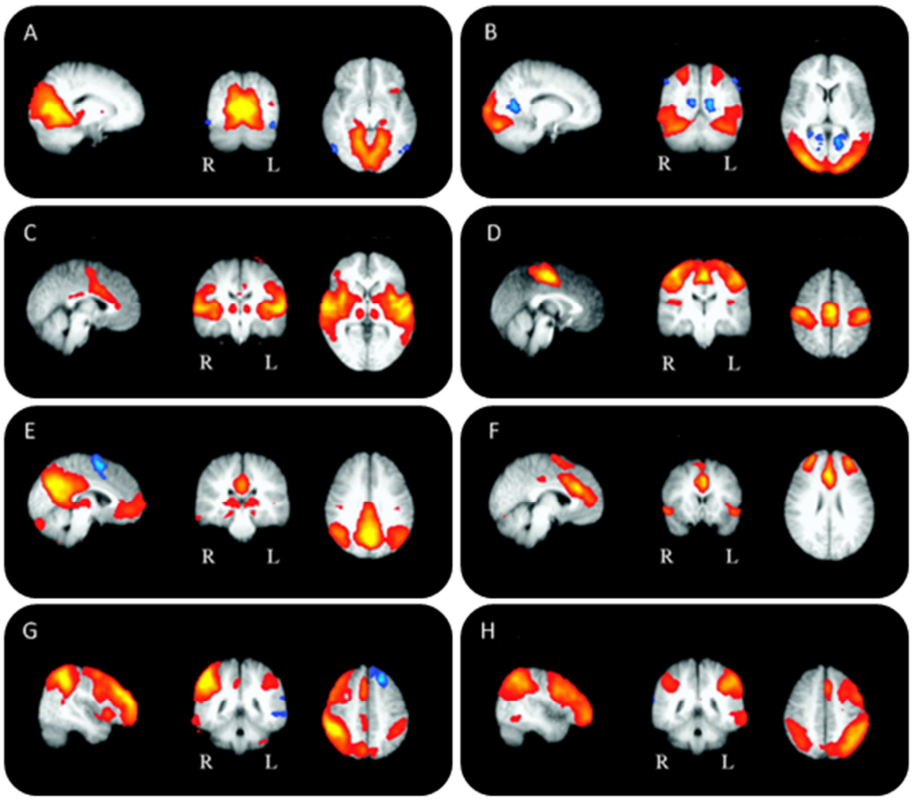
4.2.1 Resting-State Functional Magnetic Resonance Imaging

fMRI is a MRI technique that provides an indirect measure of neural activity by measuring the haemodynamic response to neuronal activity. Increased neuronal activity is associated with an increase in blood flow that exceeds the increase in oxygen consumption, resulting in an increase in the ratio of oxy- to deoxy-haemoglobin. As haemoglobin is diamagnetic when oxygenated, but paramagnetic when deoxygenated, neuronal activity leads to a decrease in magnetic susceptibility and an increase in the blood oxygen level dependent (BOLD) signal (Matthews & Jezzard 2004).

In the resting brain, the BOLD signal exhibits low-frequency spontaneous fluctuations (0.01-0.1 Hz) that are temporally correlated and correspond to resting-state networks (RSNs). Commonly identified networks include: visual, auditory, sensory-motor, default-mode, executive control and frontal-parietal RSNs (figure 4.1). The amplitude of the BOLD signal at rest is comparable with that displayed in task-related experiments (Damoiseaux et al 2006). Furthermore, there is close correspondence between the major brain networks identified at rest and those identified using brain maps derived from a database of task-related fMRI experiments involving nearly 30 000 participants (Smith et al 2009c).

Figure 4.1: Resting-state networks

Set of RSNs identified from a group of ten participants. All images were co-registered into the space of the MNI template. A: medial visual; B: lateral visual; C: auditory; D: sensory-motor; E: default mode; F: executive control; G: right frontal-parietal; H: left frontal-parietal. Adapted with permission from Philosophical Transactions of the Royal Society B: Biological Sciences, (Beckmann et al 2005) figure 6.



With regard to depression, the most frequently studied RSNs are the default mode network (DMN), the executive control network (ECN), and the affective network (AN). The DMN commonly incorporates the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and precuneus, and the lateral parietal cortex. However, there is evidence of disconnection between the anterior and posterior components in ageing (Andrews-Hanna et al 2007). The activity of the DMN increases during rest compared to during specific goal-directed behaviours (Raichle et al 2001; Smith et al 2009c), and as such is also referred to as the task-negative network. Increases are also noted during self-referential mental activity

and emotional processing (Andrews-Hanna et al 2010; Gusnard et al 2001). The core region associated with the ECN is the lateral PFC (LPFC), with MPFC, parietal and supplementary motor area activation also noted (Beckmann et al 2005; Seeley et al 2007; Sheline et al 2010). Activation of this network is associated with performance of cognitive tasks (Fox et al 2005; Smith et al 2009c) and is anti-correlated with the DMN (Fox et al 2005). As a result, the ECN is also referred to as the task-positive network or the cognitive control network. The AN includes the ventral division of the ACC that includes rostral, subcallosal and subgenual regions. The ventral ACC and its connections play a key role in mediating the affective aspects of depression (Alexopoulos et al 2008; Devinsky et al 1995; Johansen-Berg et al 2008; Mayberg 1997; 2003; Phillips et al 2003).

The two most popular methods for analysis of functional connectivity within RSNs are single seed region analysis and independent components analysis (ICA).

Single seed region analyses assess the temporal correlation between the BOLD time course of a predefined seed region and that of either a priori defined target regions or the whole brain on a voxel-wise basis. Single seed region analysis can only isolate a single network based upon the a priori defined seed region. For example, a PCC / precuneus seed is often used to investigate the DMN, a DLPFC seed to investigate the ECN, and a ventral ACC seed to investigate the AN. One limitation of seed region analysis is that the results may also be influenced by non-neuronal artefacts including respiration (Birn et al 2006).

ICA decomposes the dataset into a set of statistically independent spatial component maps and associated time courses without any model being specified. Voxel values reflect the correlation between the voxel's timeseries and the mean timeseries of that particular RSN (Beckmann et al 2005; Beckmann & Smith 2004). ICA can detect and separate several RSNs at once and automatically isolate sources of noise, including motion artefacts and

physiological confounds, such as the cardiac pulsation or the respiratory cycle (Birn et al 2008). However, ICA analysis can be insensitive to disconnection between regions in the same network. Also, the number and spatial pattern of RSNs produced using ICA varies according to the number of components generated. Thus, if ICA is performed in each participant separately, it can be difficult to consistently identify the same network across participants. An alternative approach is to perform ICA across all participants, and then, based upon the group-level components identified, generate individualised RSNs using dual regression (Filippini et al 2009; Zuo et al 2010).

4.2.2 Literature Review

Introduction

Although there have been broad reviews of resting-state fMRI studies of psychiatric disorders (Broyd et al 2009; Greicius 2008), no review has exclusively examined resting-state fMRI studies of depression. This section aims to provide an overview of resting-state fMRI studies of depression through conducting a systematic review of studies. As there has only been one resting-state fMRI study of LLD published to date, this review includes resting-state fMRI studies of depression across all ages.

Methods

Online searches of the databases EMBASE and MEDLINE were performed in September 2010, using the keywords ([“resting-state” or “default mode” or “DMN”] and [“functional magnetic resonance imaging” or “fMRI”] and [“depress*”]). Reference lists of included studies were then searched for additional studies.

Studies were screened for journal articles published in English that used resting-state fMRI (i.e. no task or emotional stimuli), to analyse group differences in the connectivity of RSNs between participants with major depression and healthy control participants. Studies that utilised regional homogeneity analysis to analyse functional connectivity were not considered. Such studies only provide a regional measure of functional connectivity, through measuring the correlation of the time series of a given voxel to those of its neighbouring voxels. Where studies examined participants at baseline and after antidepressant treatment, only baseline results are reported.

Key details regarding the participants, data acquisition, data analysis and results were recorded for all studies. If not stated, age at onset was calculated by subtracting duration of illness from mean age, or assumed to equal mean age if first-episode. If 17-item HAM-D was not available, HAM-D was converted from alternative HAM-D scores or from MADRS scores (Heo et al 2007). Voxel size was calculated from the field of view, matrix size, slice thickness and gap. As the method for labelling networks varied between studies, comparable networks were grouped together. Studies referring to the DMN, the task-negative network, or with a precuneus, precuneus / PCC, PCC or MPFC / PCC seed were labelled DMN. Studies referring to the ECN, the task-positive network, the cognitive control network, or with a DLPFC seed were labelled ECN. Studies referring to the AN, or with a ventral ACC seed, were labelled AN. As the method for labelling anatomy also differed considerably between studies, regions were grouped according to cerebral lobe (frontal, temporal, parietal, occipital and limbic) or structure (hippocampus, thalamus, etc.). To provide an overview of the anatomy of significant differences, the lobe or structure that was significantly different in functional connectivity ($p < 0.05$, unless a stricter limit was imposed by the authors) between participants with depression and control participants, after corrections and covarying, was recorded. For simplicity, the lateralisation of results was not presented.

Results

Titles and abstracts of fifty-six identified citations were screened, of which ten met the inclusion criteria for the systematic review. A flow diagram of the identification and attrition of studies is provided in figure 4.2.

The participant details and data acquisition parameters of included studies are outlined in table 4.1 and results in table 4.2.

Eight studies used seed-region analysis to examine functional connectivity; two studies used ICA analysis methods. Overall, six studies identified regions of increased connectivity in depression compared with controls. In contrast, four studies identified regions of decreased connectivity in depression compared with controls. One study did not identify any significant differences between groups.

Default Mode Network

The DMN, or constituents of the DMN, were examined by seven studies: five used seed region analysis; two studies used ICA analysis. Four of seven studies identified increases in connectivity within the DMN in depression, including increased connectivity with the MPFC and OFC, the ACC, and the PCC / precuneus. Increases in anti-correlation with elements of the ECN were detected by one study. A decrease in connectivity in depression was only detected by one study, in which a decrease was detected in the caudate. Two studies failed to find differences in connectivity between depressed and control groups.

Executive Control Network

Although the ECN was not examined by either of the ICA studies, three studies performed seed region analysis with seeds placed in the DLPFC. Two studies detected increases in connectivity in depression: one in the DMPFC, one in inferior / middle frontal gyri and inferior parietal cortex. Increases in anti-correlation with several regions of the DMN were also detected by one study. One study did not detect any significant group differences in DLPFC connectivity.

Affective Network

Five studies examined the connectivity of the ventral ACC using seed region analysis: four studies placed a seed region in the subgenual ACC, and two studies in the rostral ACC. Of the four studies to examine subgenual ACC connectivity, increases in connectivity in depression were detected by two studies. These included increases with the DMPFC, PCC / precuneus, lateral parietal lobe and anterior temporal lobe. In contrast, one study reported decreases in connectivity between the subgenual ACC and the frontal cortex, temporal cortex, supragenual ACC and insula cortex. One study failed to detect any significant group differences.

With regard to the two studies that placed a seed in the rostral ACC, one study detected decreases in connectivity with the thalamus and pallidostriatum. In contrast, the other study failed to find any significant group differences.

Figure 4.2: Identification and attrition of studies

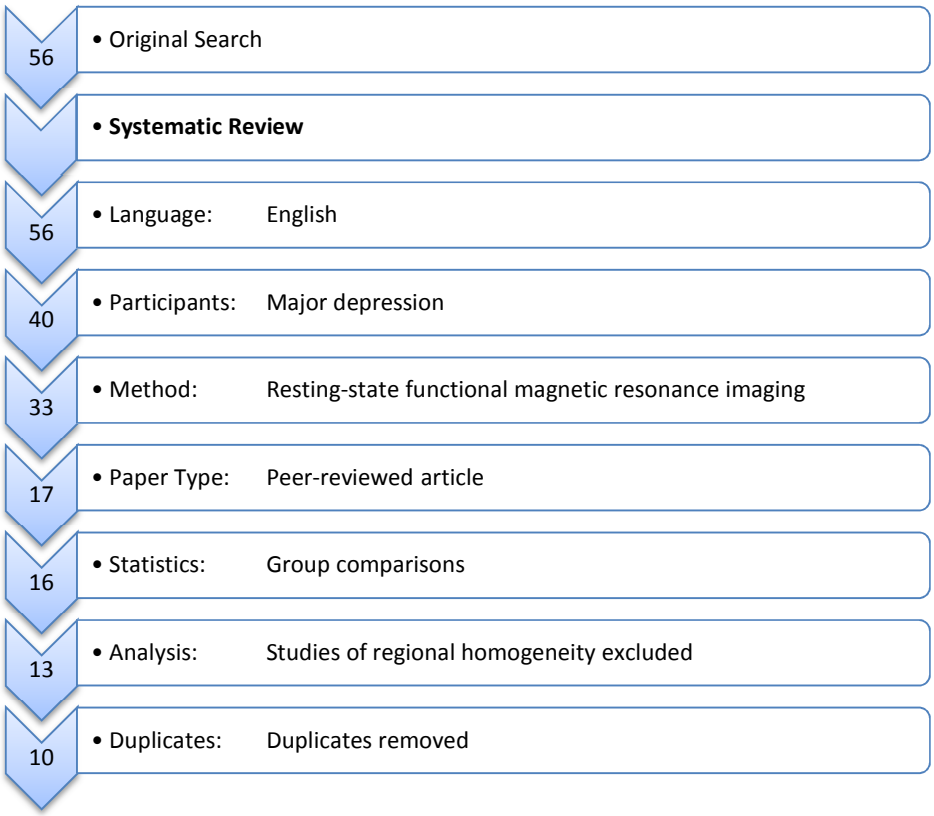


Table 4.1: Participant details and data acquisition

Abbreviations – AC: anticonvulsants; AD: antidepressants; AP: antipsychotics; AX: anxiolytics; C: control; D: depression; MS: mood stabilisers; NERI: norepinephrine reuptake inhibitors.

Study	Group	Number of Participants	% of Females	Mean Age	Age at Onset	HAM-D	Medication	Field Strength (T)	Acquisition Voxel Size (mm)	Repetition Time (s)
Anand et al (2005a)	D	15	73	28 ± 7	22	21.1 ± 5.4	No (15)	1.5	3.8 x 3.8 x 7.0	0.4
	C	15	73	28 ± 9						
Bluhm et al (2009)	D	14	64	21.9 ± 5.1	21.9 ± 5.1	N/A	No (13); Yes (1) – AD (1)	4	4.0 x 4.0 x 4.0	3.0
	C	15	73	23.5 ± 5.4						
Craddock et al (2009)	D	20	60	43.2 ± 10.8	Not stated	23.7 ± 1.6	Not stated	3	3.4 x 3.4 x 4.0	2.0
	C	20	60	28.9 ± 7.2						
Cullen et al (2009)	D	12	75	16.5 ± 0.95	14.2	N/A	No (2); Yes (10) - AD (10); MS (2); AP (2); stimulants (2); NERI (1)	3	3.4 x 3.4 x 4.0	2.0
	C	14	57	16.8 ± 1.5						
Greicius et al (2007)	D	28	57	38.5	Not stated	20.6 ± 3.2	No (8); Yes (20) - AD (19); AP (9); AX (5); MS (2)	3	3.1 x 3.1 x 4.5	2.0
	C	20	55	35.4						
Hamilton et al (2010)	D	16	62	34.6 ± 1.6	Not stated	N/A	Not stated	3	3.4 x 3.4 x 5.0	1.2
	C	14	43	30 ± 2.35						
Kenny et al (2010)	D	16	50	76.4 ± 7.2	47.4 ± 18.5	4.5 ± 2.5	Yes (16) - AC (2); AD (12); AP (2); AX (2)	3	2.0 x 2.0 x 6.0	3.0
	C	17	35	75.7 ± 7.6						
Sheline et al (2010)	D	18	39	35.9 ± 9.3	Not stated	20.2 ± 2.9	No (18)	3	4.0 x 4.0 x 4.0	2.5
	C	17	71	30.9 ± 6.5						
Veer et al (2010)	D	19	58	36.2 ± 9.7	36.2 ± 9.7	10.6 ± 6.7	No	3	2.3 x 2.3 x 3.0 3.5 x 3.5 x 3.0	2.3
	C	19	58	36.1 ± 10.6						
Zhou et al (2010)	D	18	78	38.9 ± 9.9	38.9 ± 9.9	16.7 ± 3.7	No (18)	3	3.4 x 3.4 x 4.0	2.0
	C	20	70	40.6 ± 10.7						

Table 4.2: Data analysis and results

Abbreviations - ACC: anterior cingulate cortex; AN: affective network; D: dorsal; DMN: default-mode network; ECN: executive control network; ICA: independent components analysis; L: lateral; M: medial; OFC: orbital frontal cortex; PFC: prefrontal cortex; PCC: posterior cingulate cortex; V: ventral

Study	Method and Seed Regions / ICA Networks	Connectivity of Seed Region / ICA Network Calculated In	Significant Differences in Connectivity Compared With Controls
Anand et al (2005a)	Seed region analysis of the AN using: - Rostral ACC	Medial thalamus Amygdala Pallido-Striatum	↓ Connectivity between rostral ACC and - Thalamus - Pallido-Striatum
Bluhm et al (2009)	Seed region analysis of the DMN using: - PCC / Precuneus	Frontal: PFC, OFC Temporal: parahippocampal Limbic: ACC (dorsal, subgenual) Cuneus / Precuneus, Caudate, Thalamus	↓ Connectivity between PCC / Precuneus and - Caudate
Craddock et al (2009)	Seed region analysis of the DMN using: - ventral PCC Seed region analysis of the ECN using: - DLPFC Seed region analysis of the AN using: - ACC (subcallosal, subgenual, rostral) Seed region analysis using: - Frontal: DMPFC, VMPFC, OFC - Limbic: mid-cingulate - Amygdala, Hippocampus, Hypothalamus, Insula, Thalamus, Nucleus accumbens	Seed regions	No significant differences
Cullen et al (2009)	Seed-region analysis of the AN using: - Subgenual ACC Seed-region analysis using: - Limbic: Supragenual ACC - Amygdala	Whole brain: voxel-wise	↓ Connectivity between subgenual ACC and - Frontal: medial; superior; inferior - Temporal: superior temporal cortex - Limbic: supragenual ACC - Insula
Greicius et al (2007)	ICA analysis performed in each participant individually to isolate the - DMN	Whole brain: voxel-wise	↑ Connectivity between DMN and - Frontal: MPFC / OFC - Parietal-Occipital: cuneus / precuneus - Limbic: subgenual ACC - Thalamus
Hamilton et al (2010)	Seed-region analysis of the DMN using: - MPFC and PCC	Whole brain: voxel wise; statistics only performed in ventral ACC	↑ Connectivity between MPFC and PCC and - Limbic: ventral ACC
Kenny et al (2010)	Seed region analysis using: - Caudate	Whole brain: voxel-wise	↑ Connectivity between the Caudate and - Frontal: precentral; paracentral; middle frontal; subgyral - Temporal: superior temporal gyrus - Parietal: postcentral; precuneus; inferior; supramarginal gyrus - Limbic: cingulate - Thalamus, Insula

Sheline et al (2010)	Seed-region analysis of the DMN using: - Precuneus Seed-region analysis of the ECN using: - DLPFC Seed-region analysis of the AN using: - Subgenual ACC Seed-region analysis using: - DMPFC	Whole brain: voxel-wise	↑ Connectivity between DLPFC, precuneus and subgenual ACC and - Frontal: DMPFC - Additional significant regions not stated ↑ Connectivity between DMPFC and - Frontal: DM, DL - Temporal: parahippocampus - Occipital: visual - Parietal: superior precuneus - Limbic: pregenual ACC, subgenual ACC, PCC - Hippocampus
Veer et al (2010)	ICA performed in all participants, followed by dual regression, to isolate: - Attention - Auditory - DMN - Hippocampus-Amygdala - Lateral: left, right - Precuneus - Salience - Sensory-Motor - Ventral Stream - Visual: primary, lateral, medial	Network: voxel-wise	↓ Connectivity between Auditory and - Amydala - Insula ↑ Connectivity between Auditory and - Frontal: inferior frontal gyrus ↓ Anti-Correlation between Attention and - Frontal: pole ↓ Connectivity between Medial Visual and - Occipital: lingual gyrus
Zhou et al (2010)	Seed-region analysis of the DMN using: - Frontal: MPFC / MOFC, MSF - Temporal: anterior, parahippocampal - Parietal: lateral - Limbic: subgenual ACC, PCC / Precuneus - Cerebellum: uvula, tonsil Seed-region analysis of the ECN using: - Frontal: DLPFC, IF, OF, dorsal premotor - Temporal: middle - Parietal: inferior - Limbic: mid-PCC - SMA - Insula - Cerebellum: inferior	DMN, ECN: voxel-wise	↑ Connectivity between elements of the DMN and - Frontal: medial PFC / OFC, middle frontal gyrus - Temporal: anterior - Parietal: lateral - Limbic: PCC / precuneus ↑ Anti-correlation between elements of the DMN and - Frontal: middle / inferior frontal gyrus - Temporal: middle - Parietal: inferior - Insula ↑ Connectivity between elements of the ECN and - Frontal: inferior / middle gyrus - Parietal: inferior, superior ↑ Anti-correlation between elements of the ECN and - Frontal: mPFC / OFC - Temporal: anterior - Parietal: lateral - Limbic: PCC / precuneus

Discussion

In this section, abnormalities in functional connectivity in depression were examined in a systematic review of resting-state fMRI studies to date. Overall, the most frequent positive finding was increased connectivity within the DMN in depression. It has been hypothesised that increased connectivity within the DMN reflects increased self-referential focus in depressed participants (Greicius et al 2007). Indeed, in a task-based study, Sheline et al (2009) detected DMN over-activity during both implicit and explicit emotional regulation. Compared with studies of the DMN, fewer studies examined the ECN or AN, and results are less consistent. Further studies are needed to clarify differences in functional connectivity in these networks.

The relationship between the DMN, ECN and AN in depression also remains unclear. Zhou et al (2010) detected increases in anti-correlation between the DMN and the ECN in depression. In contrast, Sheline et al (2010) detected increases in connectivity between the DMN, ECN and AN, and the DMPFC, and consequently suggest that the DMPFC may play a key role in 'hot wiring' networks together. Clarification of the pattern of differences in functional connectivity in multiple networks is a key area for future research.

Methodological Considerations

As with all systematic reviews, results should be interpreted with caution because of the heterogeneity of studies in terms of participant details, data acquisition and data analysis, and the limited study sizes.

With regard to participant details, the majority of depressed participants were currently medication free in five studies, compared with receiving a range of medications in three studies. The effect of medication on functional connectivity is not yet understood, although

Anand et al (2005b) have examined connectivity at rest before and after antidepressant treatment. At baseline, depressed participants had decreased rostral ACC connectivity compared with control participants. After six weeks of sertraline treatment, rostral ACC connectivity increased in the depressed group. However, as the baseline finding of decreased rostral ACC connectivity has not yet been replicated, the generalisability of such medication effects is unclear. Age and depression severity were less heterogeneous than medication status: in nine of ten studies the depressed group had an average age of younger than forty-five and depression scores indicative of moderate to severe depression. Further studies are thus needed to examine whether findings of increased DMN connectivity in depression can be replicated in participants with LLD and / or participants in remission.

With regard to data acquisition, in addition to differences in acquisition parameters (field strength, voxel size, repetition time); studies also differed in the 'at rest' condition. For example, Cullen et al (2009) allowed participants to listen to music of their choice in order to increase tolerability to scanning. Also, although no study took the 'at rest' condition from interleaved resting blocks from task-based designs, it was preceded or followed by cognitive tasks or exposure to emotional stimuli in some studies (Anand et al 2005a; Veer et al 2010).

With regard to data analysis, eight of ten studies included used seed-region analysis. Seed regions consistently included the PCC / precuneus for the DMN, the DLPFC for the ECN, and the ventral ACC for AN. Encouragingly, Zhou et al (2010) found comparable results when using other elements of the DMN and the ECN as seed regions. However, even when using comparable seed regions, variability in the anatomy of isolated networks can remain. For example, Sheline et al (2010) and Zhou et al (2010) used comparable seed regions for the analysis of the DMN and ECN, but differences in the anatomy of the networks isolated means their results are difficult to compare. Sheline et al (2010) detected increases in

connectivity between the ECN and the DMPFC in depression, with the DMPFC an element of both the DMN and ECN in the depressed group. In contrast, Zhou et al (2010) detected increases in anti-correlation between the ECN and the MPFC in depression, but the MPFC had been defined as an element of the DMN, but not the ECN. Finally, few studies considered the influence of GM or resting blood flow on their results. In the only study to repeat analyses with the inclusion of GM maps as an additional covariate, Veer et al (2010) did not find any differences in their results.

Conclusion

In conclusion, the majority of resting-state fMRI studies have identified increased connectivity within the DMN in depression. Future studies are needed to examine whether such results can be replicated in participants with LLD and / or participants in remission. Clarification of differences in functional connectivity within the ECN and AN in depression and examination of the pattern of differences in connectivity in multiple networks are also key areas for future research.

4.3 Aims

In the following sections functional connectivity will be examined in the DMN, ECN and AN using ICA followed by dual regression. As there is evidence to support disconnection between anterior and posterior elements of the DMN in ageing (Andrews-Hanna et al 2007), functional connectivity within anterior and posterior DMN components will also be examined. In line with the results of the systematic review, it is hypothesised that there will be increased functional connectivity within the DMN.

4.4 Methods

4.4.1 Participants

Participant recruitment and inclusion and exclusion criteria are outlined in section 2.4.1

4.4.2 Data Acquisition

All MRI scans were obtained at OCMR using a 3.0 Tesla Trio Siemens scanner with a 12-channel head-coil. Whole-brain resting-state fMRI was performed using a gradient echoplanar imaging sequence (TR = 2500 ms, TE = 30 ms, flip angle = 89°, field of view = 192 mm, voxel dimension 3.0 mm isotropic). Participants were instructed to lie still in the scanner, keep their eyes open, and refrain from falling asleep.

4.4.3 Data Analysis

Image analysis was performed using FSL tools ((Smith et al 2004), www.fmrib.ox.ac.uk/fsl).

fMRI data were manually checked and volumes with major artefacts replaced by the mean of the preceding volume and the following volume.

Group averaged resting-state networks were defined using probabilistic independent component analysis (Beckmann & Smith 2004) as implemented in multivariate exploratory linear decomposition into independent components (MELODIC) Version 3.09, part of FSL. The following data pre-processing was applied to the input data: masking of non-brain voxels; voxel-wise de-meaning of the data; and normalisation of the voxel-wise variance. Pre-processed data of twenty-five LLD participants and twenty-five control participants were whitened and projected into a 25- or 70-dimensional subspace using principal component

analysis. 25- and 70-dimensional subspaces were chosen to identify the major networks and sub-networks, respectively, in line with previous studies (Damoiseaux et al 2006; Filippini et al 2009; Smith et al 2009c). The whitened observations were decomposed into sets of vectors which describe signal variation across the temporal domain (time-courses), the participant domain and across the spatial domain (spatial maps) by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique (Hyvarinen 1999). Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values (Beckmann & Smith 2004). RSNs of interest were identified based upon a set of previously defined maps (Beckmann et al 2005).

Dual regression was then used to identify individual temporal dynamics and associated spatial maps of RSNs of interest in all participants (Filippini et al 2009). First, spatial regression was performed using ICA spatial maps in a linear model fit against each participant's fMRI data set, resulting in matrices describing temporal dynamics for each component in each participant. Second, temporal regression was performed using each participant's time course matrices in a linear model fit against their fMRI data set, resulting in participant-specific spatial maps.

Voxelwise statistics were performed using 'randomise' (Nichols & Holmes 2002), with age and gender included as confound regressors. The significance threshold for between-group differences was set at $p < 0.05$ using the threshold-free cluster enhancement option in 'randomise' (Smith & Nichols 2009). Group differences were subsequently spatially masked with a binary image of group activation maps of the network under investigation.

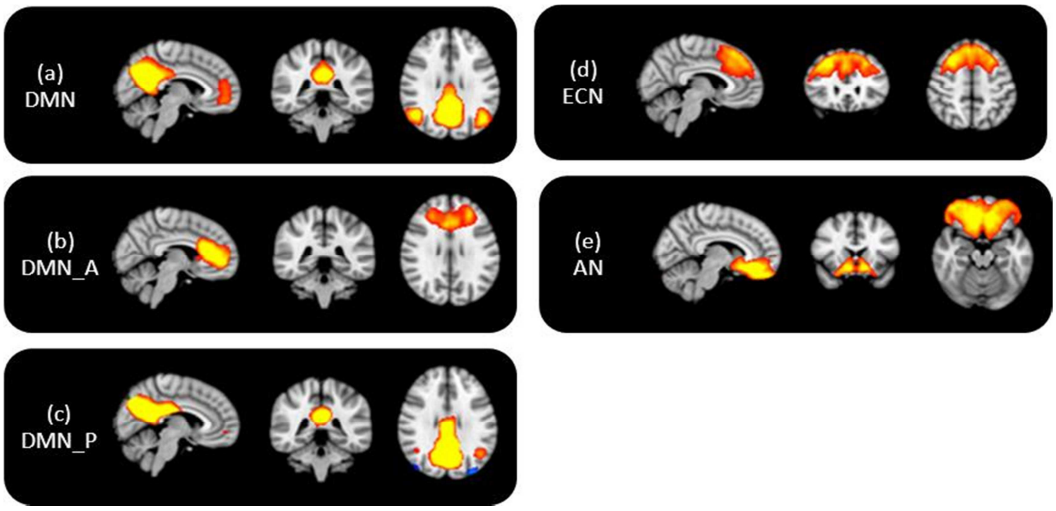
4.5 Results

DMN, ECN and AN components were identified from 25-component ICA (figure 4.3). The DMN component included MPFC, PCC and precuneus, and lateral parietal activation. The ECN component included superior and middle frontal gyri and paracingulate activation. The AN network included MPFC, subgenual and subcallosal ACC and caudate activation.

Posterior and anterior DMN components were identified from 70-component ICA (figure 4.3). The posterior DMN component included PCC, precuneus and lateral partietal activation. The anterior DMN component included MPFC and ACC activation.

Figure 4.3: ICA-defined networks

ICA-defined networks: (a) DMN, (b) anterior DMN, (c) posterior DMN, (d) ECN, (e) AN



No significant differences in functional connectivity were detected between LLD and control groups within the DMN, anterior DMN, posterior DMN, ECN or AN.

4.6 Discussion

In this section, differences in functional connectivity within the DMN, ECN and AN between LLD and control groups were investigated using ICA. No significant differences in functional connectivity were detected between LLD and control groups within the DMN. Although this finding is in contrast to the hypothesis and several previous studies (Greicius et al 2007; Hamilton et al 2010; Sheline et al 2010; Zhou et al 2010), two other studies have also failed to find differences in connectivity between depressed and control groups in the DMN (Craddock et al 2009; Veer et al 2010). Differences in functional connectivity were also not detected within the anterior DMN, posterior DMN, ECN or AN.

4.6.1 Methodological Considerations

There are several factors that could have contributed to the lack of significant differences in functional connectivity in this study. For example, negative findings may be related to characteristics of the LLD group, including the relatively low HAM-D score of the depressed group compared with previous studies. Increases in DMN activity in depression have been attributed to increases in self-referential focus (Andrews-Hanna et al 2010; Sheline et al 2009), which may be evident only in participants who are currently depressed. While two studies have detected a significant correlation between functional connectivity and HAM-D score in depression (Sheline et al 2010; Zhou et al 2010), three studies did not find any significant correlations between functional connectivity and symptom severity (Bluhm et al 2009; Cullen et al 2009; Veer et al 2010). The influence of current severity on functional connectivity within the DMN, ECN and AN in the Oxford LLD group will be examined in chapter 6.

The age of the participants may also impact upon functional connectivity. In all four studies that detected increased connectivity within the DMN the average age of the depressed group was younger than forty (Greicius et al 2007; Hamilton et al 2010; Sheline et al 2010; Zhou et al 2010). As there is evidence of disconnection between the anterior and posterior DMN components in ageing (Andrews-Hanna et al 2007), anterior and posterior DMN were examined separately, but this also did not identify any regions significantly different in functional connectivity.

Alternatively, it may be that differences in functional connectivity at rest are subtle compared with differences in functional connectivity during exposure to emotional stimuli or participation in cognitive tasks. Or it may be that there are differences in the amplitude, but not the coherence, of activity within networks. For example, reduced activity in the DLPFC and reduced functional connectivity between the DLPFC and dorsal ACC has been detected in LLD during an executive control task (Aizenstein et al 2009).

4.6.2 Conclusions

While the literature provided support for increases in functional connectivity within the DMN in depression, this was not replicated by the Oxford ICA study.

Chapter 5: The Neuropsychology of Late-Life Depression

5.1 Abstract

Neuropsychological impairment is a key feature of late-life depression, with deficits observed across multiple domains. However, it is unclear whether deficits in multiple domains represent relatively independent processes with specific neural correlates, or whether they can be explained by core cognitive deficits, for example in executive function or processing speed.

In this chapter, group differences between depressed and control participants were examined across five domains: episodic memory, executive function, language skills, processing speed and visuospatial skills. The influence of executive function and processing speed deficits on other neuropsychological domains was also investigated. Magnetic resonance imaging correlates of executive function, processing speed and episodic memory were explored in the late-life depression group.

Relative to the control group, the late-life depression group performed significantly worse in the domains of executive function, processing speed, episodic memory and language skills. Impairments in executive function or processing speed were sufficient to explain differences in episodic memory and language skills. Executive function was correlated with anisotropy of the anterior thalamic radiation and uncinate fasciculus; processing speed was correlated with anisotropy of genu of the corpus callosum. Episodic memory was correlated with anisotropy of the anterior thalamic radiation, the genu and body of the corpus callosum and the fornix.

In conclusion, both executive function and processing speed appear to represent core cognitive deficits in late-life depression that contribute to deficits in other domains, and are related to reductions in anisotropy in frontal tracts.

5.2 Background

Neuropsychological impairment is a key feature of LLD and remains after clinical recovery (Bhalla et al 2006; Butters et al 2000; Kohler et al 2010; Murphy & Alexopoulos 2004; Nebes et al 2003). Case-control studies using a variety of manual and computerised tasks have revealed reduced performance in LLD across multiple domains, including executive function, processing speed, episodic memory, language skills and visuospatial skills (Butters et al 2004; Dillon et al 2009; Elderkin-Thompson et al 2007; Herrmann et al 2007; Kohler et al 2010; Sheline et al 2006). However, it is unclear whether deficits in multiple domains represent relatively independent processes with specific neural correlates, or whether they can be explained by core cognitive deficits, for example in executive function or processing speed (Butters et al 2004; Elderkin-Thompson et al 2007; Kohler et al 2010; Sheline et al 2006).

5.2.1 Executive Function

Executive function refers to the ability to plan complex cognitive processes, and monitor and adapt actions appropriately. Measures of planning, working memory, attention and cognitive flexibility are all used to assess impairment in this domain. Executive function has been proposed as a primary cognitive deficit in LLD, as deficits cannot be fully explained by impairments in processing speed, but can contribute to deficits in other domains (Alexopoulos 2003; Elderkin-Thompson et al 2007; Sheline et al 2006). For example, deficits in executive function can impact upon strategic controlled encoding and retrieval in tasks

assessing episodic memory (Buckner 2004; Elderkin-Thompson et al 2007). However, other studies have argued that impaired executive function is mediated by slowed processing speed (Butters et al 2004).

It is hypothesised that impaired executive function in LLD results from the disruption of frontal-striatal-limbic networks (Alexander et al 1986; Alexopoulos 2003; Mayberg 1997). In support of this hypothesis, several studies have detected significant associations between executive function and FA in frontal-striatal-limbic regions in LLD (Alexopoulos 2002; Murphy et al 2007; Schermuly et al 2010; Yuan et al 2007).

5.2.2 Processing Speed

Processing speed refers to the speed at which cognitive tasks can be executed and is examined using simple tasks in which processing speed is likely to be the primary influence on performance. It is hypothesised that reductions in processing speed can impact upon other neuropsychological domains due to either 'limited time' or 'simultaneity' mechanisms (Salthouse 1996). Timed tasks are particularly susceptible to the limited time mechanism, which describes decreased processing speed increasing the amount of time needed to successfully complete each component of a task. In contrast, complex, multi-stage tasks can be affected by the simultaneity mechanism. The simultaneity mechanism involves decreased processing speed reducing the amount of simultaneously available information, as products of early processing are no longer available when later processing is complete. Several studies examining the relationship between neuropsychological deficits in LLD have suggested that neuropsychological impairment in multiple domains may be partially or fully mediated by deficits in processing speed (Butters et al 2004; Kohler et al 2010; Sheline et al 2006).

In the only DTI study of depression to date to examine DTI correlates of processing speed, correlations were observed between processing speed and anisotropy of a prefrontal ROI, and mean diffusivity of prefrontal, deep WM and corpus callosum ROIs (Shimony et al 2009).

5.2.3 Episodic Memory

Episodic memory refers to the ability to encode and retrieve personal experiences and assessment includes measures of immediate and delayed recall and recognition. Episodic memory is typically supported by the circuitry of the medial temporal lobe, including the hippocampus (reviewed in (Dickerson & Eichenbaum 2010)). In support of this model, impairments in episodic memory in LLD have been associated with reduced volumes of the hippocampus (Avila et al 2009; Ballmaier et al 2008) and cingulate gyrus (Yuan et al 2008). Reductions in executive function and processing speed have also been found to contribute to deficits in episodic memory (Butters et al 2004; Elderkin-Thompson et al 2007; Kohler et al 2010; Sheline et al 2006).

5.2.4 Language and Visuospatial Skills

Both language and visuospatial skills have been found to be impaired in LLD (Butters et al 2004; Dillon et al 2009; Herrmann et al 2007; Sheline et al 2006). However, deficits have been attributed to impairments in processing speed (Butters et al 2004; Sheline et al 2006), and have not been related to specific neural correlates in LLD.

5.3 Aims

In this chapter, the pattern of neuropsychological impairment in LLD will be investigated in thirty-six participants with LLD and twenty-five control participants, as well as the

relationships between neuropsychological impairment and MRI measures in LLD participants.

First, group differences will be examined across five domains: executive function, processing speed, episodic memory, language skills and visuospatial skills. In line with previous studies, it is hypothesised that deficits will be observed across all domains, with executive function, processing speed and episodic memory most severely impaired (Butters et al 2004; Herrmann et al 2007).

Second, the influence of deficits in executive function and processing speed on other neuropsychological domains will be investigated. It is hypothesised that deficits in executive function and processing speed will contribute to deficits in other domains.

Third, the relationship between MRI measures and executive function, processing speed and episodic memory will be explored in LLD. As analysis of group differences in GM, WM and functional connectivity only revealed significant differences in WM measures (chapters 2, 3, and 4 respectively), the relationship between reduced FA and neuropsychological impairment will be the focus of this analysis. The relationship between hippocampal volume and neuropsychological impairment will also be explored: although hippocampal volume was not found to be reduced in LLD, several previous studies of LLD have reported a significant relationship between reduced hippocampal volume and impaired episodic memory. It is hypothesised that FA of tracts with frontal projections will be associated with deficits in executive function and processing speed. As episodic memory is hypothesised to be dependent upon executive function and processing speed it is hypothesised that episodic memory will also be associated with FA of frontal tracts, in addition to FA of hippocampal tracts and hippocampal volume.

5.4 Methods

5.4.1 Participants

Participant recruitment and inclusion and exclusion criteria are outlined in section 2.4.1

5.4.2 Data Acquisition

Neuropsychological Tests

All participants completed a comprehensive battery of neuropsychological tests valid for use within an elderly population with depression, including:

CANTAB Reaction Time

The CANTAB reaction time task is a computerised task in which the participant is asked to react as soon as a yellow dot appears on the screen. There are five stages in this task, the first three of which are training exercises. At the first stage, a yellow dot appears within a circle in the centre of the screen and the participant is asked to respond by touching the circle on the screen. At the second stage, the yellow dot may appear in one of five circles and the participant is asked to respond by touching the circle in which the dot appeared. At the third stage, a yellow dot appears within a single circle in the centre of the screen and the participant is asked to hold down a press-pad and release the button after the dot has appeared. At the fourth stage, termed the simple task, the yellow dot again appears within a single circle in the centre of the screen but the participant is required to hold down the press-pad and then release the button and touch the circle on the screen after the dot has appeared. At the fifth stage, termed the 5-choice task, the yellow dot may appear in one of five circles and the participant is required to hold down the press-pad until the dot appears

and then release the button and touch the circle in which the dot appeared. The outcome measures are the reaction time and movement time for the simple and 5-choice tasks (Sahakian et al 1993).

CANTAB Stockings of Cambridge

The CANTAB stockings of Cambridge task is a computerised task in which the participant is shown two displays containing three coloured balls, which can be perceived as stacks of balls held in stockings. The participant is asked to move the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved. The mean number of moves for n-move problems and the number of problems solved with the minimum number of moves are recorded (Owen et al 1990).

Copied Drawings

The copied drawings task is contained within the ACE-R (Mioshi et al 2006) and entails copying a diagram of overlapping pentagons and a wire cube.

Clock Drawing

The clock drawing task is contained within the ACE-R (Mioshi et al 2006) and involves drawing a clock face marking the hours, with the hands indicating a particular time.

Digit Span

The digit span task involves repeating digit sequences of increasing length either forwards (Digit Span: Forward) or backwards (Digit Span: Backward) (Wechsler 1997). One point is scored for each correct trial.

Digit Symbol

In the digit symbol task a key pairing the numbers 1 to 9 with symbols is provided and the participant is asked to draw as many symbols under their corresponding numbers in two minutes (Wechsler 1997). One point is scored per correct symbol.

Fluency

In the category fluency task the participant is asked to name as many animals as possible in one minute, with one point scored per animal.

In the letter fluency task the participant is asked to name as many words, not including names of people or places, beginning with the letter p as possible in one minute. One point is scored per word.

Both the category fluency and letter fluency tasks are contained within the ACE-R (Mioshi et al 2006).

Graded Naming Test

In the graded naming test the participant is asked to identify thirty different line drawings of objects, with one point scored per correct answer (McKenna & Warrington 1980).

Hopkins Verbal Learning Task Revised (HVLT-R)

The Hopkins verbal learning task revised (HVLT-R) includes three learning trials of twelve words from four semantic categories and, after 20-25 minutes, a delayed recall trial and recognition trial (Brandt 1991). The recognition trial consists of a randomised list that includes the twelve target words and twelve non-target words, six of which are drawn from

the same four semantic categories as the targets. Scores are derived for Total Recall, Delayed Recall, and Recognition (number of true positive responses minus number of false positive responses).

Rey-Osterrieth Complex Figure (RCF)

In the Rey-Osterrieth complex figure (RCF): copy condition the participant is asked to copy a complex figure that is not easily verbally encoded. The RCF: immediate and delay tasks involve reproducing the RCF after a 3 and 30 minute delay after the initial RCF: copy task, respectively (Osterrieth 1944).

Trail Making Test

In the trail making test (TMT): A the participant is asked to connect randomly arranged numbers sequentially (1, 2, 3, 4 …) (Reitan 1958). Reitan scoring is used, with errors pointed out for correction as they occur and the score being the time taken to completion.

The TMT: B task involves connecting randomly arranged numbers and letters alternatively (1, A, 2, B …). As with the TMT: A task, errors are pointed out for correction as they occur and the score is the time taken to completion.

MRI Acquisition

T_1-weighted MRI acquisition is outlined in 2.4.2 and DTI acquisition in section 3.4.2.

5.4.3 Data Analysis

Neuropsychological Impairment

First, raw neuropsychological data were converted to standardised z scores based on the mean and standard deviation of the control group. Where necessary, signs were reversed to ensure that higher z scores represented a better performance for all variables (e.g. TMT: A and B, CANTAB: reaction time). Second, composite scores were calculated by summing the z scores within the following neuropsychological domains and Cronbach's alpha computed. Cronbach's alpha at or above 0.70 was classified as indicative of a high level of internal consistency.

Executive Function

The executive function domain included digit span: forward, digit span: backward, letter fluency and TMT: B. Cronbach's alpha for this domain was 0.70. This domain was also planned to contain results from CANTAB stockings of Cambridge task. However, as four LLD participants were unable to complete CANTAB stockings of Cambridge task, results from this test were excluded.

Processing Speed

The processing speed domain included digit symbol, TMT A, CANTAB: simple reaction time, CANTAB: simple movement time, CANTAB: 5-choice reaction time and CANTAB: 5-choice movement time. Cronbach's alpha for this domain was 0.80.

Episodic Memory

The episodic memory domain included measures of visual episodic memory (RCF: immediate, RCF: delay) and verbal episodic memory (HVLT-R: total, HVLT-R: recall, HVLT-R: recognition). Cronbach's alpha for this domain was 0.84.

Language Skills

The language skills domain included the graded naming test and category fluency. Cronbach's alpha for this domain was 0.73.

Visuospatial Skills

The visuospatial skills domain included clock drawings, copied drawings and RCF: copy. Cronbach's alpha for this domain was 0.73.

Group differences were investigated using a multi-variate GLM, with age and gender as covariates. The percentage of LLD and control participants whose performance fell below the 10th percentile of the control group for each domain was also calculated, as in previous studies (Butters et al 2004).

In order to examine whether multiple deficits are mediated by core deficits in executive function or processing speed, analyses were repeated but with the z scores of the executive function or processing speed included as an additional covariate.

MRI Correlates of Neuropsychological Impairment

Processing of the DTI data was carried out using TBSS as detailed in section 3.4.3. Partial correlation analysis, with age and gender as covariates, was performed between mean

values of DTI measures in voxels showing significant differences between groups in each TOI (detailed in section 3.5) and composite z scores for executive function, episodic memory and processing speed in LLD participants.

Segmentation of the hippocampus was performed using FIRST, as detailed in section 2.4.3. Partial correlation analysis was performed between executive function, processing speed and episodic memory and WB volume, with age and gender as covariates, and between executive function, processing speed and episodic memory and hippocampal volume, with age, gender and WB volume as covariates.

5.5 Results

5.5.1 Neuropsychological Impairment

Raw scores and z scores of neuropsychological tests are presented in table 5.1 and figure 5.1, respectively. Composite z scores of neuropsychological domains are presented in table 5.2 and figure 5.2.

After covarying for age and gender, the LLD group performed significantly worse than the control group in executive function, processing speed, episodic memory and language skills, but not visuospatial skills (table 5.2, figure 5.2). Significant differences in episodic memory and language skills did not survive the addition of executive function or processing speed as a covariate. Differences in executive function remained significant after covarying for processing speed, but differences in processing speed were reduced to a trend after covarying for executive function.

Table 5.1: Raw scores of neuropsychological tests

Values presented are: mean ± standard deviation. Where applicable, maximum scores are presented in brackets. Abbreviations –HVLT-R: Hopkin's verbal learning test revised; RCF: Rey-Osterrieth complex figure; TMT: trail making test.

	Control	LLD
Executive Function		
Digit Span Forward (14)	10.08 ± 1.73	8.11 ± 2.07
Digit Span Backward (14)	8.32 ± 2.46	6.42 ± 2.05
Letter Fluency	16.36 ± 4.91	15.19 ± 5.43
TMT B	83.60 ± 35.69	103.34 ± 35.55
Processing Speed		
Digit Symbol	59.04 ± 17.52	51.11 ± 14.29
TMT A	39.08 ± 8.83	51.08 ± 16.28
CANTAB: Simple Reaction Time	337.85 ± 50.33	369.32 ± 83.20
CANTAB: 5-Choice Reaction Time	388.52 ± 70.45	420.98 ± 91.14
CANTAB: Simple Movement Time	468.49 ± 137.10	559.81 ± 178.91
CANTAB: 5-Choice Movement Time	415.87 ± 102.39	507.06 ± 139.21
Episodic Memory		
RCF: Immediate (36)	21.70 ± 7.22	15.83 ± 8.16
RCF: Delay (36)	20.66 ± 7.34	15.83 ± 7.66
HVLT-R: Total Recall (36)	23.92 ± 6.12	21.97 ± 5.20
HVLT-R: Delayed Recall (12)	8.60 ± 3.15	7.97 ± 2.31
HVLT-R: Recognition (12)	10.36 ± 1.73	10.36 ± 1.46
Language Skills		
Category Fluency	20.96 ± 5.63	18.36 ± 5.63
Graded Naming Test (30)	15.12 ± 5.99	10.14 ± 5.84
Visuospatial Skills		
Copied Drawings (3)	2.80 ± 0.50	2.61 ± 0.73
Clock Drawing (5)	4.72 ± 0.46	4.67 ± 0.59
RCF: Copy (36)	34.88 ± 1.67	32.51 ± 5.12

Figure 5.1: Z scores of neuropsychological tests

Mean z score ± two standard errors of the LLD group. By definition, z scores for control group are zero. Abbreviations – GNT: graded naming test; HVLT-R: Hopkin's verbal learning test revised; MT: movement time; RCF: Rey-Osterrieth complex figure; RT: reaction time; TMT: trail-making test.

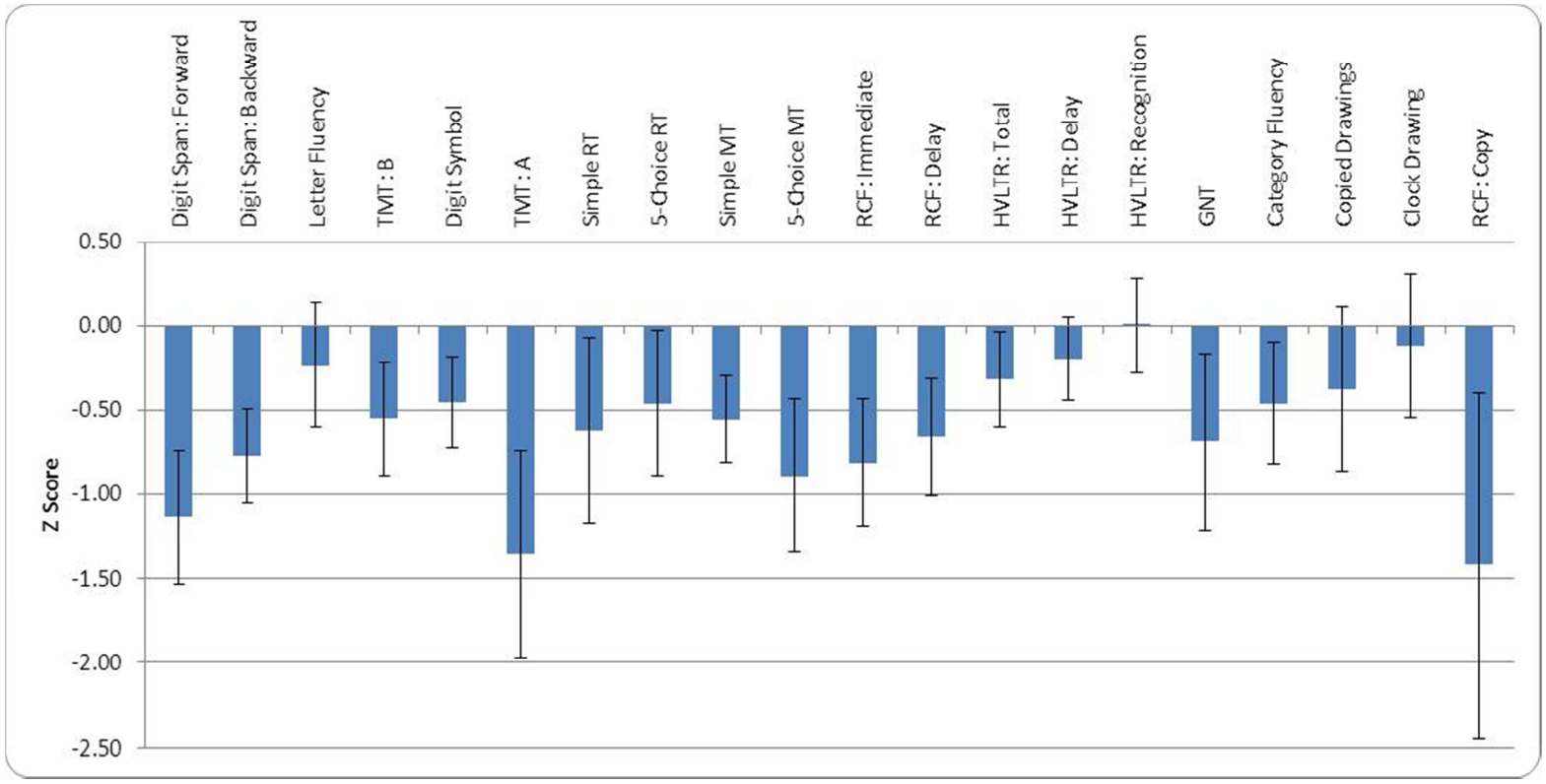


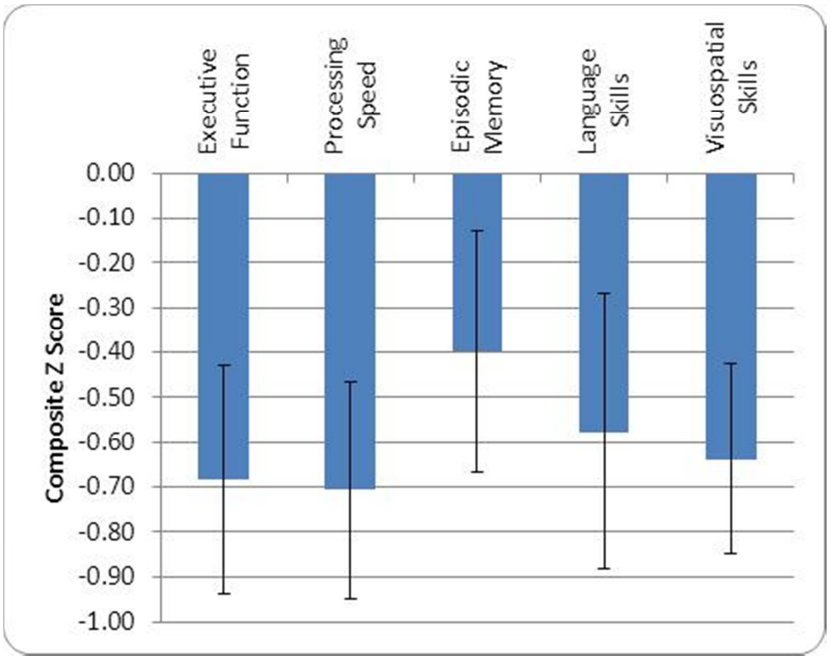
Table 5.2: Z scores of neuropsychological domains

Values presented are: mean z score ± standard deviation. *p*-values are presented for analyses with (a) age and gender as covariates, (b) age, gender and executive function (EF) as covariates, and (c) age, gender and processing speed (PS) as covariates. Significant values are presented in red.

	Depression	*p*-value (a)	*p*-value (b) EF	*p*-value (c) PS
Executive Function	-0.68 ± 0.76	<0.001	N/A	0.011
Processing Speed	-0.71 ± 0.72	0.001	0.082	N/A
Episodic Memory	-0.40 ± 0.80	0.030	0.417	0.307
Language Skills	-0.58 ± 0.92	0.026	0.548	0.305
Visuospatial Skills	-0.64 ± 0.63	0.077	0.480	0.261

Figure 5.2: Z scores of neuropsychological domains

Mean z score ± two standard errors of the LLD group. By definition, z scores for control group are zero.



The percentage of participants performing below the 10th percentile for each neuropsychological domain is presented in table 5.3. 72% of LLD participants performed below the 10th percentile in at least one domain, compared with 32% of control participants. Executive function was the most frequently impaired domain in LLD, with 44% of participants performing below the 10th percentile.

Table 5.3: Percentage of participants performing below 10th percentile

Percentage of participants performing below the 10th percentile in each neuropsychological domain, and in the total number of neuropsychological domains, is presented.

Domain	% Control	% Depression
Executive Function	12	44
Processing Speed	12	33
Episodic Memory	12	22
Language Skills	12	31
Visuospatial Skills	12	31
0 Domains	68	28
1 Domain	16	31
2 Domains	8	17
3 Domains	4	8
4 Domains	4	11
5 Domains	0	6

5.5.2 MRI Correlates of Neuropsychological Impairment

Correlations between FA and executive function, processing speed and episodic memory within the LLD group are presented in table 5.4 and figure 5.3. Executive function was associated with FA of the anterior thalamic radiation (r = 0.428, *p* = 0.012) and uncinate fasciculus (r = 0.425, *p* = 0.012). Processing speed was associated with FA of the genu of the corpus callosum (r = 0.422, *p* = 0.013). Episodic memory was associated with FA of the anterior thalamic radiation (r = 0.435, *p* = 0.010), body and genu of the corpus callosum (body: r = 0.382, *p* = 0.026; genu: r = 0.430, *p* = 0.011) and fornix (r = 0.424, *p* = 0.013).

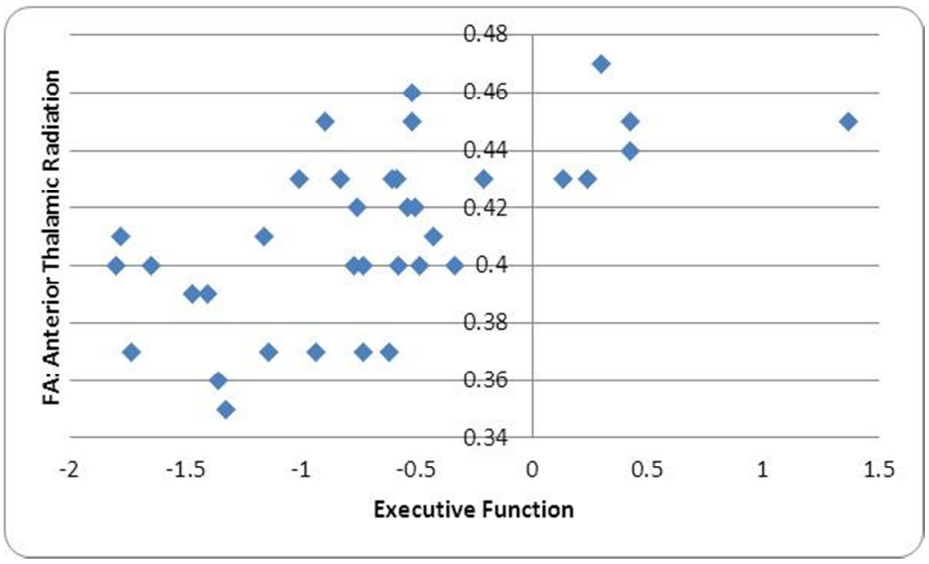
Table 5.4: Correlations between FA and neuropsychological impairment within the LLD group

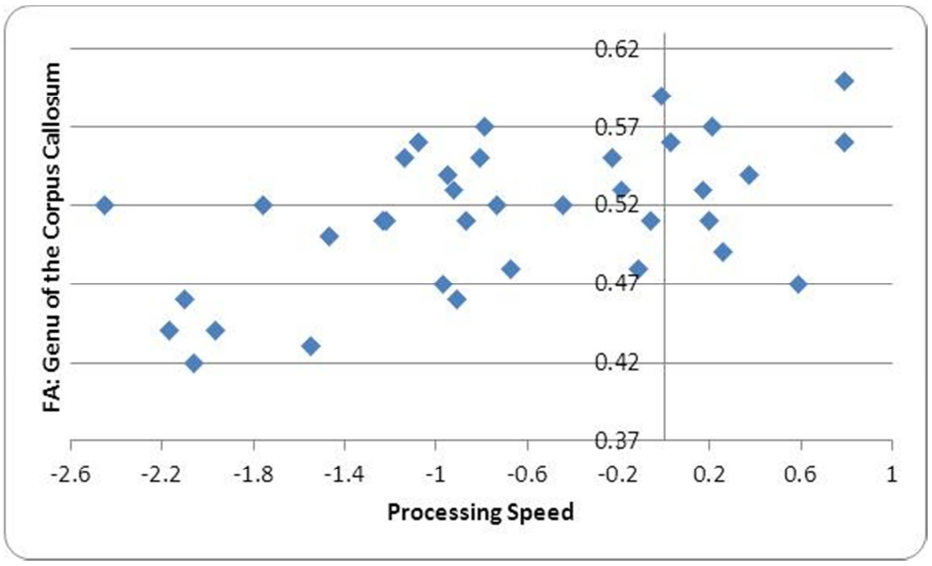
Correlation values (r) and *p*-values are presented for correlations between FA and executive function, processing speed, and episodic memory. Significant values are presented in red.

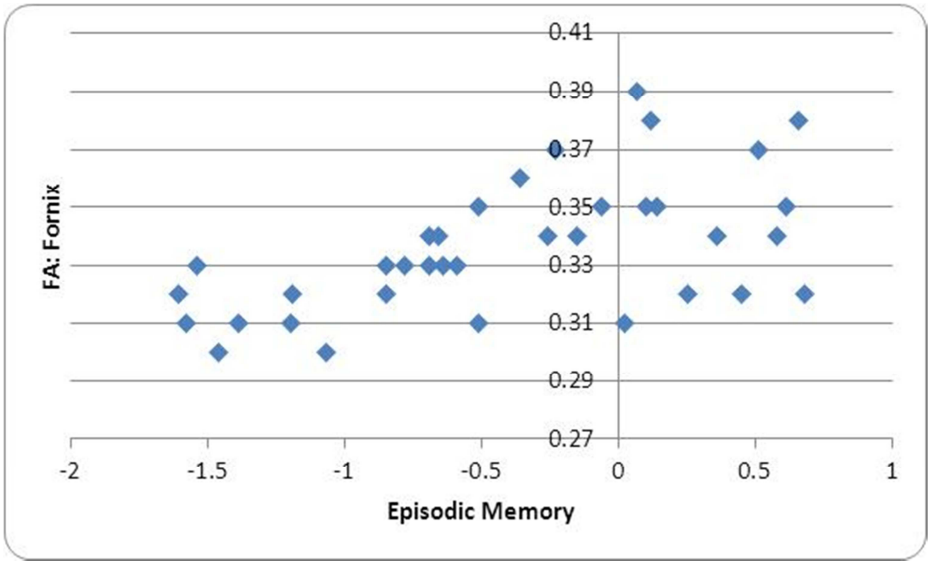
	Executive Function		Processing Speed		Episodic Memory	
	r	*p*	r	*p*	r	*p*
Anterior Thalamic Radiation	0.428	0.012	0.270	0.122	0.435	0.010
Corpus Callosum						
- **Body**	0.157	0.375	0.104	0.558	0.382	0.026
- **Genu**	0.270	0.123	0.422	0.013	0.430	0.011
- **Splenium**	0.084	0.637	-0.055	0.757	0.288	0.099
Cingulum	0.213	0.226	-0.122	0.492	0.330	0.057
Corticospinal Tract	-0.019	0.916	0.276	0.114	0.281	0.107
Fornix	0.345	0.045	0.297	0.088	0.424	0.013
Inferior Longitudinal Fasciculus	0.200	0.256	0.143	0.420	0.187	0.291
Superior Longitudinal Fasciculus	0.197	0.265	-0.011	0.951	0.187	0.291
Uncinate Fasciculus	0.425	0.012	.0194	0.271	0.187	0.289

Figure 5.3: Correlations between FA and neuropsychological impairment within the LLD group

Graphs illustrating correlations within the LLD group between FA of the anterior thalamic radiation and executive function; FA of the genu of the corpus callosum and processing speed; and FA of the fornix and episodic memory.

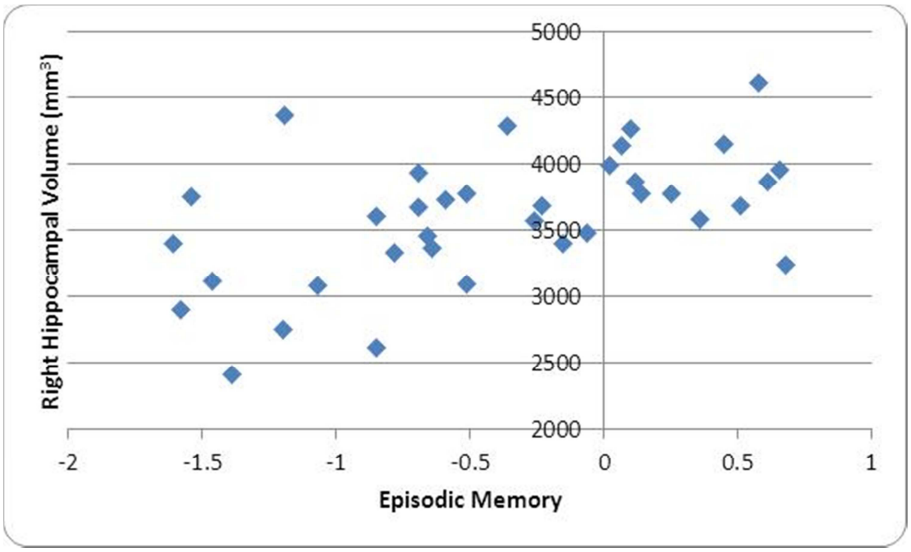


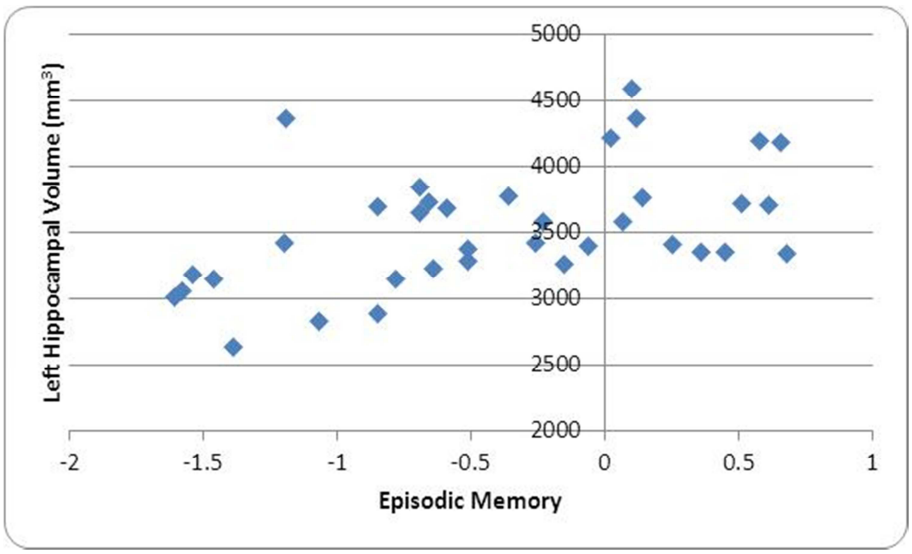

FA: Genu of the Corpus Callosum
0.62
0.57
0.52
0.47
0.42
0.37
-2.6
-2.2
-1.8
-1.4
-1
-0.6
-0.2
0.2
0.6
1
Processing Speed


FA: Fornix
0.41
0.39
0.37
0.35
0.33
0.31
0.29
0.27
-2
-1.5
-1
-0.5
0
0.5
1
Episodic Memory

After covarying for age and gender, WB volume was not associated with executive function, processing speed or episodic memory. After covarying for age, gender and WB volume, hippocampal volume was associated with episodic memory bilaterally (left: r = 0.281, *p* = 0.113; right: r = 0.381, *p* = 0.029; figure 5.4). Hippocampal volume was not associated with executive function or processing speed.

Figure 5.4: Correlations between hippocampal volume and episodic memory within the LLD group





5.6 Discussion

In this chapter, the pattern of neuropsychological impairment in LLD and the relationships between neuropsychological impairment and MRI measures were investigated. In line with the hypotheses and previous studies, the LLD group performed worse across multiple neuropsychological domains (Butters et al 2000; Dillon et al 2009; Elderkin-Thompson et al 2007; Herrmann et al 2007; Kohler et al 2010; Sheline et al 2006). The percentage of LLD participants performing below the 10th percentile was also comparable with previous studies, with over 60% of LLD participants substantially impaired in at least one domain (table 5.3) (Butters et al 2000).

In agreement with the hypotheses and previous studies, executive function appeared to be a core deficit in LLD (Alexopoulos 2003; Kohler et al 2010; Sheline et al 2006). Executive function was the most frequently impaired neuropsychological domain, with 44% of participants performing below the 10^{th} percentile of the control group. Furthermore, inclusion of executive function as an additional covariate was sufficient to reduce deficits in all other neuropsychological domains to non-significant levels, while deficits in executive function could not be fully accounted for by slowed processing speed. In the LLD group, executive function was correlated with FA of the anterior thalamic radiation, which connects the PFC and thalamus, and uncinate fasciculus, which connects frontal and temporal lobes. Thus, findings support the importance of frontal-striatal-limbic connections in executive function in LLD (Alexopoulos 2002; Murphy et al 2007; Schermuly et al 2010; Yuan et al 2007).

Processing speed was also found to contribute to deficits in episodic memory, language skills and visuospatial skills, in line with previous studies (Butters et al 2000; Kohler et al 2010; Sheline et al 2006). Processing speed was associated with FA of the genu of the corpus

callosum. This localisation is in line with the findings of Shimony et al (2009), who reported that processing speed was associated with relative anisotropy in the prefrontal cortex and MD in the corpus callosum, PFC, and deep WM in LLD. Also, reduced FA within the genu of the corpus callosum has also been related to slow processing speed in studies of healthy adults (Kennedy & Raz 2009; Kochunov et al 2010).

Deficits in episodic memory did not survive additional covarying for executive function or processing speed. In line with these findings, impaired episodic memory was associated with reduced FA in the anterior thalamic radiation and genu of the corpus callosum, tracts also associated with executive function or processing speed. Episodic memory was also associated with FA of the fornix, a key tract in hippocampal circuitry, and hippocampal volume.

5.6.1 Methodological Considerations

A key strength of this study was that it included assessment of multiple neuropsychological tests, which were then categorised into five key neuropsychological domains. Cronbach's alpha was at or above 0.70 in all domains; indicating a high level of internal consistency and supporting the categorisation of neuropsychological tests. However, few tests can be easily attributed to a single domain and categorisation always remains somewhat arbitrary (Veiel 1997).

Assessment of processing speed using the computerised CANTAB reaction time tests allowed accurate assessment of processing speed and automatic data collection. However, assessment of executive function using the CANTAB stockings of Cambridge task was excluded from the analyses as four LLD participants were unable to complete the task. It may be that the use of computerised tests for the assessment of executive function may be

unsuitable in LLD, with the complexity of the task compounded for participants unfamiliar with using a touch-screen computer.

Analysis of MRI correlates of neuropsychological impairment did not include correction for multiple comparisons, and results should therefore be considered as exploratory. Multiple tracts were included as widespread regions were significantly different in FA between groups. Although analysis could have been limited to the a priori hypotheses of executive function and processing speed being associated with FA of tracts with frontal projections, and episodic memory being associated with FA of tracts with frontal and hippocampal projections, it was thought that displaying the full pattern of correlations would be most informative and transparent.

5.6.2 Conclusion

In conclusion, both executive function and processing speed appear to represent core cognitive deficits in LLD, contribute to deficits in other domains, and are related to reductions in FA in frontal tracts. In contrast, deficits in episodic memory may be influenced by executive dysfunction and slowed processing speed. In support of this model, impairments in episodic memory were associated with reductions in FA within frontal tracts, in addition to reductions in FA in hippocampal tracts.

Chapter 6: Relationships between MRI Measures, Age at Onset and Severity

6.1 Abstract

Clinical variables including age at onset and current symptom severity may contribute to the heterogeneity observed in magnetic resonance imaging measures within studies of late-life depression. Understanding the relationships between these clinical variables and magnetic resonance imaging measures may aid in the interpretation of the group differences reported in chapters 2 to 4 and may also support particular hypotheses regarding the nature and aetiology of network disruption in late-life depression. For example, a negative correlation between age at onset and white matter deficits would be compatible with the vascular depression hypothesis. A positive association between age at onset and hippocampal volume would provide support for the glucocorticoid cascade hypothesis. Variation in functional connectivity may be state dependent and associated with current severity, in line with the limbic-cortical network hypothesis.

In order to explore the aetiology of late-life depression, the relationships between age at onset, symptom severity, and magnetic resonance imaging measures of grey matter, white matter and functional connectivity were examined in thirty-six participants with late-life depression.

Significant negative correlations were observed between age at onset and anisotropy of widespread tracts, in particular the anterior thalamic radiation and superior longitudinal fasciculus. Age at onset was also negatively correlated with left hippocampal volume.

However, there were no significant correlations between age at onset and right hippocampal volume or hippocampal shape. Symptom severity was not associated with any measure of grey matter, white matter or functional connectivity.

Overall, results were strongly compatible with the vascular hypothesis, and provided some support for the glucocorticoid cascade hypothesis.

6.2 Background

Clinical variables including age at onset and current symptom severity may contribute to the range of MRI measures observed within studies of LLD. Examination of the relationships between age at onset, current severity and MRI measures may aid in the interpretation of the group differences reported in chapters 2 to 4 and may also support particular hypotheses regarding the nature and aetiology of network disruption in LLD. For example, a negative relationship between age at onset and WM deficits would be in line with the vascular hypothesis. A positive association between age at onset and hippocampal volume would provide support for the glucocorticoid cascade hypothesis. A positive correlation between symptom severity and functional deficits would concur with the limbic-cortical network hypothesis.

6.2.1 Age at Onset

Age at onset is most frequently defined as the age at which an individual experienced their first episode of major depression, and is often subdivided into early-onset depression (EOD, typically age at onset younger than sixty years) and late-onset depression (LOD, typically age at onset older than sixty years). The vascular depression hypothesis (Alexopoulos et al 1997) proposes that cardiovascular factors may 'predispose, precipitate, or perpetuate' LOD.

Specifically, vascular factors are hypothesised to cause WM damage within frontal-subcortical circuits (Alexopoulos 2002; Alexopoulos et al 1997). In support of this hypothesis, compared with EOD, LOD is associated with more frequent and severe WMH (Herrmann et al 2008), and there is increasing evidence supporting a vascular basis for WMH in depression (Chen et al 2006; Smith et al 2009b; Thomas et al 2002; Thomas et al 2003). However, to date, only one study has examined the correlation between age at onset and WM integrity in LLD using DTI, and failed to detect a significant relationship (Bae et al 2006).

Relationships between age at onset and MRI measures will also be influenced by those with earlier age at onset typically having a greater duration of illness. The glucocorticoid cascade hypothesis was developed from animal models, in which stress-induced increases in glucocorticoid levels lead to regression of dendritic processes, inhibition of neurogenesis and neurotoxic effects in the hippocampus (Sapolsky 2000). Furthermore, as the hippocampus is a major site in the glucocorticoid negative feedback circuit on the HPA axis such effects, in turn, result in further increases in glucocorticoid levels (Sapolsky et al 1986). In line with this theory, it follows that greater duration of illness will result in greater hippocampal damage due to repeated exposure to elevated glucocorticoid levels. Indeed, two studies have found negative associations between the duration of illness and hippocampal volume (Bell-McGinty et al 2002; Sheline et al 1996). However, several studies have failed to replicate this finding (Andreescu et al 2008; Janssen et al 2007a; Lloyd et al 2004; Weber et al 2010). Also, age at onset has not been significantly associated with hippocampal volume in several studies of LLD (Andreescu et al 2008; Ashtari et al 1999; Steffens et al 2000), and has even been found to be negatively associated with age at onset in one study (Lloyd et al 2004).

6.2.2 Severity

The limbic-cortical network hypothesis proposes that depressive episodes are associated with abnormal patterns of functional activation within limbic-cortical networks (Mayberg 1997). PET and SPECT studies have shown that depression is associated with decreases in activation in dorsal areas and relative increases in ventral areas, and that following pharmacological or psychological treatment there is a reversal of these findings (Brody et al 2001; Fitzgerald et al 2008; Goldapple et al 2004). As detailed in chapter 4, case-control resting-state fMRI studies have detected differences in functional connectivity in depression, in particular increases in functional connectivity within the DMN. It follows that such abnormalities in functional connectivity may also be state-dependent. Indeed, Sheline et al (2010) detected a significant relationship between HAM-D scores and connectivity values of the DMPFC, a region that displayed increased functional connectivity with the DMN, ECN and AN.

Relationships between severity and structural MRI measures have also been studied, with variable results. For example, increased severity has been associated with reduced volume in the hippocampus (Ashtari et al 1999; Zhao et al 2008) and OFC (Egger et al 2008), although several negative reports exist (Avila et al 2009; Bell-McGinty et al 2002; Janssen et al 2004; Koolschijn et al 2010; Lai et al 2000). Also, two DTI studies have found a significant association between increased severity and increased FA (Nobuhara et al 2006; Zou et al 2008) in at least one region. However, again, several negative reports also exist (Abe et al 2010; Bae et al 2006; Li et al 2007; Versace et al 2010; Yang et al 2007).

6.3 Aims

In the following sections, the relationships between age at onset, current severity and MRI measures of GM, WM and functional connectivity will be examined in thirty-six participants with LLD.

There are three main hypotheses. First, that WM integrity will be negatively associated with age at onset, in line with the vascular hypothesis. Second, that hippocampal volume and shape will be positively associated with age at onset, in line with the glucocorticoid cascade hypothesis. Third, that functional connectivity will increase with current symptom severity, in line with the limbic-cortical network hypothesis.

6.4 Methods

6.4.1 Participants

Participant recruitment and inclusion and exclusion criteria are outlined in section 2.4.1

6.4.2 Data Acquisition

Clinical assessment and T_1-weighted MRI acquisition is outlined in section 2.4.2, DTI acquisition in section 3.4.2, resting-state fMRI in section 4.4.2 and neuropsychological assessment in section 5.4.2.

6.4.3 Data Analysis

Demographic Data

Statistical analysis was performed using PASW Statistics version 18.

Pearson's correlation was performed between age at onset and current symptom severity (HAM-D) and age, gender, education, duration of illness, cognitive impairment (ACE-R, MMSE), Framingham Stroke Risk and number of medications.

Neuropsychological Data

Composite z scores were obtained for executive function, processing speed, episodic memory, language skills and visuospatial skills, as detailed in section 5.4.3. Partial correlation analysis, with age and gender as covariates, was performed between age at onset and current severity and composite z scores for all five neuropsychological domains. To control for multiple comparisons, a statistical threshold of $p < 0.01$ (0.05 divided by 5) was employed.

Hippocampal Volume and Shape

Segmentation and vertex analysis of the hippocampus was performed using FIRST, as detailed in section 2.4.3. Partial correlation analyses were performed between age at onset and severity and WB volume, with age and gender as covariates, and between age at onset and severity and hippocampal volume, with age, gender and WB volume as covariates.

Vertex-wise statistics examining hippocampal shape were performed using 'first_utils', with age, gender and WB volume included as confound regressors. False Discovery Rate correction for multiple comparisons was then applied to obtain thresholded F statistics.

Voxel-Based Morphometry

VBM analysis was performed using FSL-VBM as detailed in section 2.4.3. The significance threshold with age at onset or symptom severity was set at $p < 0.05$, using the threshold-free cluster enhancement option in 'randomise', with age and gender included as confound regressors.

White Matter Integrity

Analysis of the DTI data was carried out using TBSS as detailed in section 3.4.3. Voxel-wise statistics were performed using 'randomise' with age and gender included as confound regressors. The significance-threshold for correlations with age at onset or symptom severity was set at $p < 0.05$, using the threshold-free cluster enhancement option.

Resting-State Networks

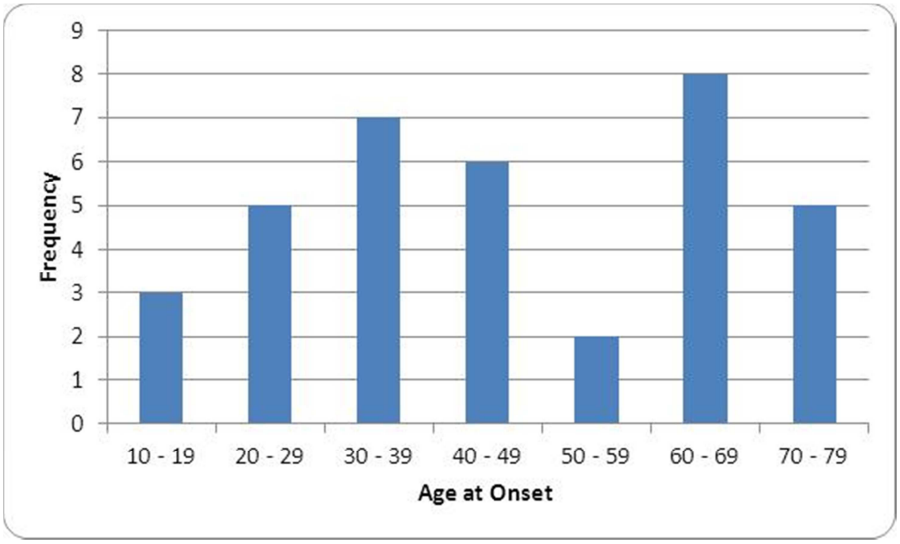
Group averaged resting-state networks were defined using probabilistic ICA (Beckmann & Smith 2004) and dual regression of the DMN, anterior and posterior DMN, ECN and AN was performed, as detailed in section 4.4.3. Voxel-wise statistics were performed using 'randomise' with age and gender included as confound regressors. The significance-threshold for correlations with age at onset or depression severity was set at $p < 0.05$, using the threshold-free cluster enhancement option. Group differences were subsequently spatially masked with a binary image of group activation maps of the network under investigation.

6.5 Results

6.5.1 Age at Onset

The distribution of age at onset in the LLD group is illustrated in figure 6.1. Age at onset was not correlated with age, gender, education, Framingham Stroke Risk, or number of medications. Age at onset was negatively associated with duration of illness (r = -0.916, p < 0.001), ACE-R (r = -0.369, p = 0.027) and MMSE (r = -0.348, p = 0.038). Age at onset was not significantly associated with the composite z score of any neuropsychological domain.

Figure 6.1: Distribution of age at onset



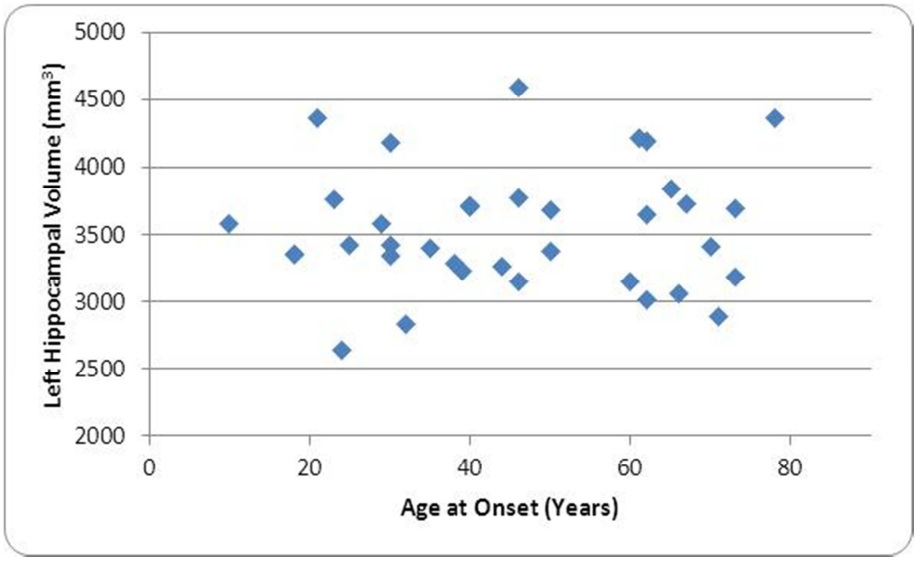
Grey Matter

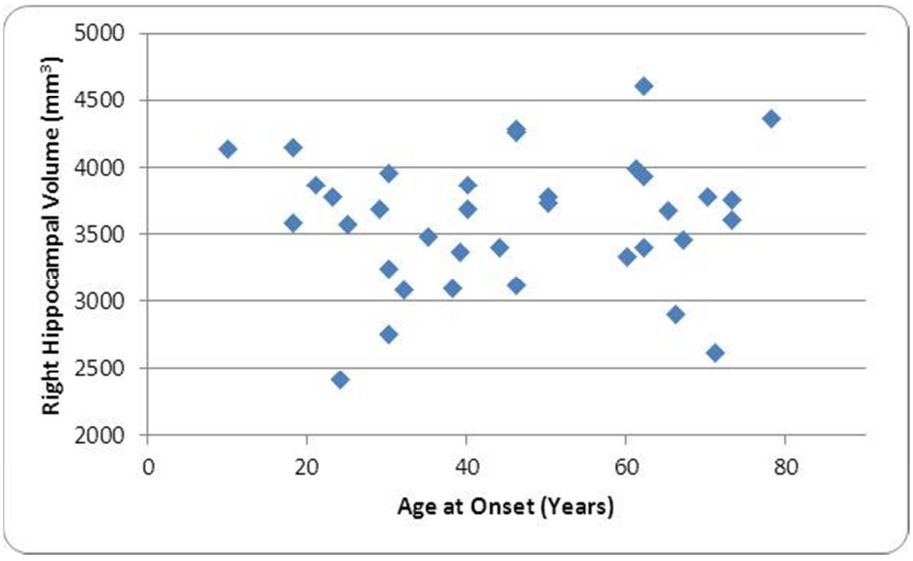
Age at onset was significantly negatively correlated with WB volume (r = -0.372, p = 0.030, figure 6.2) and positively with left hippocampal volume (r = 0.365, p = 0.037, figure 6.3). Age at onset was not correlated with right hippocampal volume (r = 0.280, p = 0.114, figure 6.3).

There were no significant correlations between age at onset and hippocampal shape. Also, no significant correlations between age at onset and GM were detected using FSL-VBM.

Figure 6.2: Correlation between whole brain volume and age at onset

Figure 6.3: Correlations between hippocampal volume and age at onset





White Matter

There were widespread negative correlations between age at onset and FA, with 20% of skeleton voxels significant at $p < 0.05$. The spatial distribution of significant negative correlations is summarised in figure 6.4 and table 6.1. The anterior thalamic radiation and superior longitudinal fasciculus were particularly affected with 63% and 54% of voxels significant, respectively (table 6.1, figure 6.5). There were no regions where age at onset was positively correlated with FA.

Figure 6.4: Localisation of correlations between FA and age at onset

Regions showing significantly correlated ($p < 0.05$) between age at onset and FA in LLD is shown in red, overlaid on a green skeleton. Significant regions are dilated for illustrative purposes.

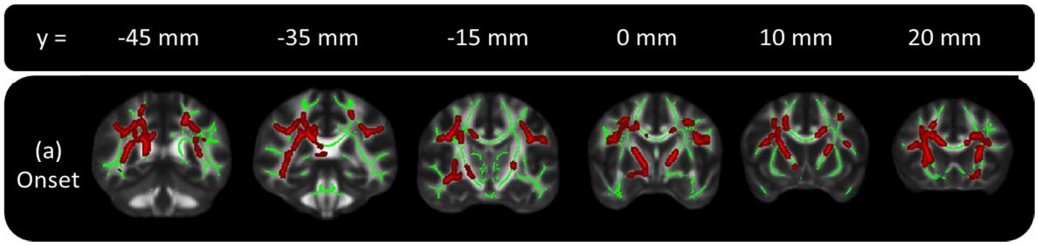


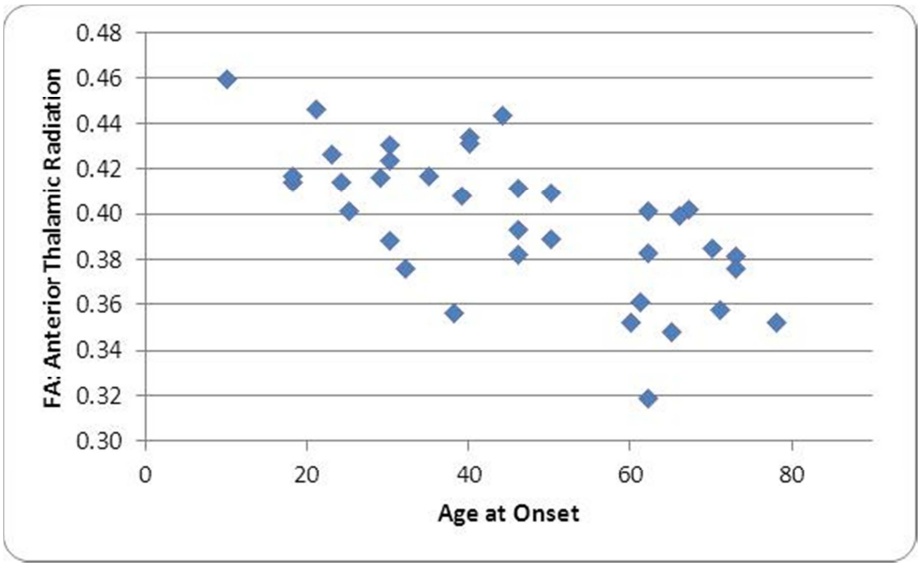
Table 6.1: Localisation of correlations between FA and age at onset

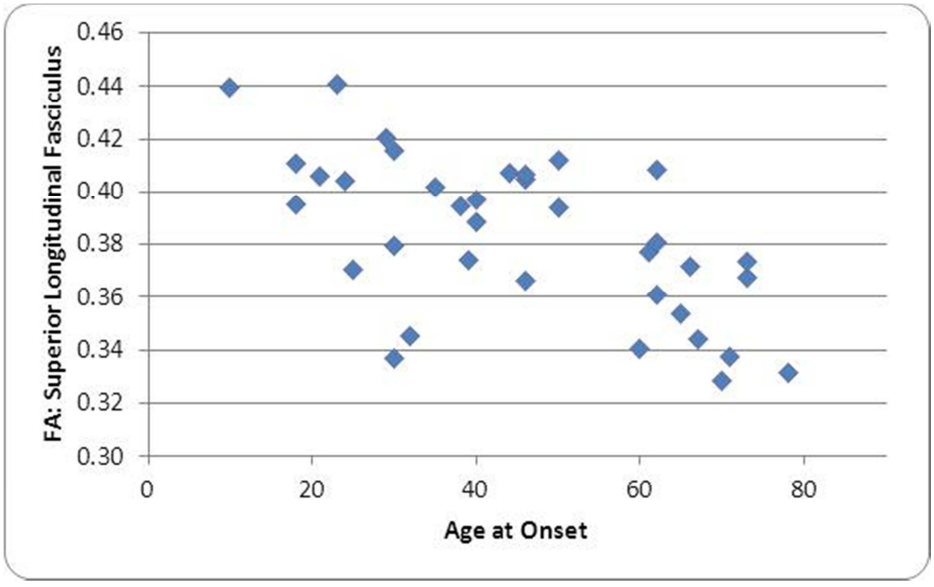
Percentage of voxels significantly decreased ($p < 0.05$) in FA in depression in each TOI

Mask	%
Whole Skeleton	20
Anterior Thalamic Radiation	63
Corticospinal Tract	8
Cingulum	6
Corpus Callosum	
- **Body**	17
- **Genu**	25
- **Splenium**	21
Fornix	12
Inferior Longitudinal Fasciculus	10
Superior Longitudinal Fasciculus	54
Uncinate Fasciculus	6

Figure 6.5: Correlations between FA and age at onset

Mean FA in anterior thalamic radiation and superior longitudinal fasciculus voxels significantly correlated with age at onset, plotted against age at onset.





Resting-State Networks

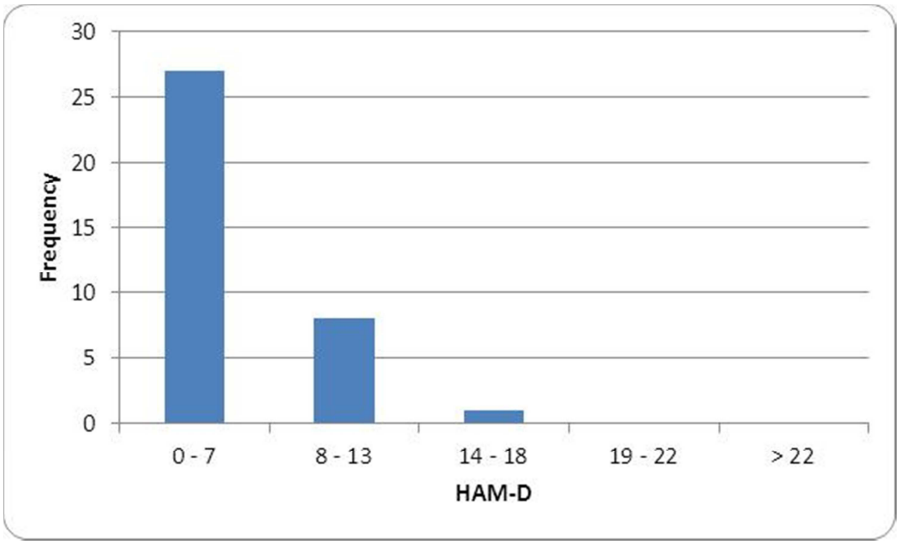
No significant correlations were detected between age at onset and functional connectivity within the DMN, anterior DMN, posterior DMN, ECN or ACN.

6.5.2 Severity

The distribution of symptom severity in the LLD group is illustrated in figure 6.6. Symptom severity was not correlated with age, gender, education, MMSE, Framingham Stroke Risk, age at onset, duration of illness, or number of medications. Severity was significantly associated with ACE-R (r = -0.332, *p* = 0.048), but not with the composite z score of any neuropsychological domain.

Figure 6.6: Distribution of HAM-D scores

HAM-D scores between 0 and 7 are within the normal range; scores between 8 and 13 indicate mild depression, 14 and 18 moderate depression, 19 and 22 severe depression, and scores of 23 and over indicate very severe depression.



Grey Matter

Severity was not significantly correlated with WB volume (r = -0.320, *p* = 0.065), hippocampal volume (left: r = -0.233, *p* = 0.193; right: r = -0.060, *p* = 0.741) or hippocampal shape. No significant correlations between severity and GM were detected using FSL-VBM.

White Matter

No significant correlations were detected between symptom severity and FA using TBSS.

Resting-State Networks

No significant correlations were detected between symptom severity and functional connectivity within the DMN, ECN or ACN.

6.6 Discussion

In this chapter, the relationships between age at onset, symptom severity and MRI measures of GM, WM and functional connectivity were investigated.

Age at onset was negatively correlated with FA in widespread regions. In particular, later age at onset was associated with reduced FA within the anterior thalamic radiation and superior longitudinal fasciculus, both of which project to the frontal lobe. This result is in line with a greater prevalence and severity of WMH in LOD compared with EOD (Herrmann et al 2008), and is compatible with the vascular depression hypothesis, which proposes that a later age at onset is associated with a greater degree of WM abnormalities in frontal-subcortical and limbic tracts (Alexopoulos et al 1997). A positive correlation between age at onset and Framingham Stroke Risk score would have added further support to the vascular depression hypothesis, but was not detected. However, it has been proposed that stroke risk factors may not be sensitive to more subtle cerebrovascular disease (Thomas et al 2004).

Age at onset was positively correlated with left hippocampal volume. As age at onset was strongly negatively correlated with duration of illness, this finding is in line with studies that found that greater duration of illness was associated with reduced hippocampal volume

(Bell-McGinty et al 2002; Sheline et al 1996). Furthermore, this result is compatible with the glucocorticoid cascade hypothesis, which proposes that hippocampal damage results from repeated exposure to elevated cortisol levels (Sapolsky 2000). However, a study directly examining the relationship between hippocampal volume and cortisol levels in LLD found that hippocampal volume reduction was not associated with increased cortisol levels (O'Brien et al 2004). Also, as age at onset was not associated with right hippocampal volume or hippocampal shape, positive results should be treated with caution.

Symptom severity was not associated with any MRI measure of GM, WM or functional connectivity. However, as the LLD group did not include any participants with HAM-D scores above 18, representing severe or very severe depression, the analyses may have been insufficiently powered. Thus, it remains a possibility that the relatively low HAM-D scores of the LLD group contributed to the absence of significant differences between LLD and control groups in GM and functional connectivity measures.

6.6.1 Methodological Considerations

A key strength of this study was the wide range of age at onset within the LLD group, which spanned from ten to seventy-eight years of age. However, while patient testimony was combined with referral to hospital notes, estimation of age at onset may have been susceptible to recall bias where hospital notes were limited (Prusoff et al 1988; Wiener et al 1997). The definition of age at onset as the age at which an individual experiences their first episode of major depression did not take into account prior episodes of subsyndromal depression, which may have resulted from the same pathophysiology as later episodes of major depression. However, consistent and accurate identification of the onset of

subsyndromal depression is arguably more difficult to obtain compared with the onset of major depression (Lyness et al 1994).

Significant relationships between age at onset and left hippocampal volume were discussed with consideration of the negative correlation between age at onset and duration of illnesses in the LLD group. Illness duration was calculated by subtracting age at onset from current age. Calculation of the total number of days depressed using the total number of episodes and the length of each episode may represent a more accurate marker of illness duration, but is strongly susceptible to recall bias in LLD participants.

As the majority of LLD participants were receiving antidepressant medication, severity of symptoms will have been confounded to a point by treatment resistance; that is, LLD participants with greater HAM-D scores may have been more treatment resistant. Thus, any ostensible relationships between symptom severity and MRI measures would have been difficult to interpret.

6.6.2 Conclusion

Overall, older age at onset was associated with reduced FA in frontal tracts, supportive of the vascular hypothesis. Younger age at onset was associated with greater duration of illness and reduced left hippocampal volume, compatible with the glucocorticoid cascade hypothesis. Symptom severity was not associated with any MRI measure of GM, WM or functional connectivity. However, this absence of positive findings may be due to the limited range of HAM-D scores in the LLD group.

Chapter 7: Conclusions and Future Directions

The overall aim of this thesis was to examine network disruption in LLD using MRI techniques. In the following sections, each of the three major aims of the thesis is revisited, the main results summarised, and future directions suggested.

To clarify the roles of grey matter, white matter and functional connectivity in the pathophysiology of late-life depression

To clarify the roles of GM, WM and functional connectivity in the pathophysiology of LLD, systematic reviews and meta-analyses of T_1-weighted MRI studies of LLD, DTI studies of depression, and resting-state fMRI studies of depression were performed. Overall, the literature provided support for GM and WM abnormalities within frontal-subcortical and limbic networks, and increased functional connectivity within the DMN.

While the systematic reviews summarised studies that examined GM, WM or functional connectivity individually, no study to date had concurrently examined GM, WM and functional connectivity. In order to directly examine whether results gained from different techniques are complementary, multi-modal MRI was used to compare GM, WM and functional connectivity between thirty-six participants with LLD and twenty-five control participants in the Oxford study. WM integrity was widely reduced in LLD, without significant differences between groups in GM or functional connectivity.

Overall, the results of the systematic review, meta-analysis and the Oxford study all strongly support the hypothesis that WM abnormalities in frontal-subcortical and limbic networks play a key role in the pathophysiology of LLD. Furthermore, the Oxford study detected a

pattern of FA reductions accompanied by increases in DR, but no change in DA, suggestive of myelin pathology. In order to more directly examine the nature of WM pathology in LLD, further post-mortem studies examining WM in LLD are warranted.

While the literature supported volume reductions in several GM regions, and increased functional connectivity within the DMN in depression, such results were not replicated in the Oxford study. It may be that abnormalities in GM and functional connectivity are subtle or of less importance than WM abnormalities in LLD. Alternatively, negative results in the Oxford study may be related to the characteristics of the LLD group, in particular, the relatively low HAM-D score of the LLD group compared with previous studies. Although correlations between current severity and measures of GM and functional connectivity were not significant, the Oxford study did not include any participants with HAM-D scores corresponding to severe or very severe depression. A longitudinal study that scanned participants when severely depressed, and again when in remission, would allow greater examination of the role of structural and functional abnormalities in the pathophysiology of LLD, and would also allow assessment of whether structural and functional abnormalities in LLD represent state or trait characteristics.

To examine the pattern of neuropsychological impairment in late-life depression and the relationships between neuropsychological impairment and MRI measures

In order to examine whether deficits in multiple neuropsychological domains in LLD represent relatively independent processes with specific neural correlates, or whether they can be explained by a core cognitive deficit, the pattern of neuropsychological impairment in LLD and the relationships between neuropsychological and MRI measures were examined. Relative to the control group, the LLD group performed significantly worse in the domains of

executive function, processing speed, episodic memory and language skills. Examination of the pattern of neuropsychological impairment in LLD indicated that both executive function and processing speed represent core cognitive deficits in LLD that contribute to deficits in other domains, and are related to reductions in FA in frontal tracts. In contrast, deficits in episodic memory appeared to be influenced by impairments in executive function and processing speed. In support of this model, impairments in episodic memory were associated with reductions in FA within frontal tracts, in addition to reductions in FA in hippocampal tracts.

One avenue for future studies is to examine interventions that could help improve neuropsychological impairment in LLD. For example, the beneficial effects of exercise on multiple cognitive domains, and in particular on executive function, are well documented in healthy older adults (Colcombe & Kramer 2003). However, precisely how the brain mediates such effects is poorly understood. To address this, a longitudinal study examining the effect of physical activity on MRI measures is planned in collaboration with Dr Heidi Johansen-Berg (Head of Plasticity in Disease group, FMRIB) and Dr Helen Dawes (Senior Lecturer in Exercise Physiology, Oxford Brookes University). Ninety relatively sedentary adults aged between sixty-five and seventy-five will be randomly assigned to one of three groups (no exercise; one exercise session per week; three exercise sessions per week) for twelve weeks. The effects of exercise on brain structure and function will then be examined using MRI techniques, and the relationship with cognition will also be evaluated using a battery of neuropsychological tests. If this study yields positive results, interventions could be extended to patient populations.

To explore the aetiology of depression by examining the relationship between age at onset, symptom severity and MRI measures of grey matter, white matter, and functional connectivity

To explore the aetiology of LLD, the relationships between age at onset, symptom severity and MRI measures of GM, WM and functional connectivity were investigated. Earlier age at onset was associated with greater duration of illness and reduced left hippocampal volume, in line with the glucocorticoid cascade hypothesis. However, further studies that also utilise measures of cortisol levels are needed (O'Brien et al 2004). Later age at onset was associated with reduced WM integrity, in line with the vascular depression hypothesis. In order to more directly assess the vascular hypothesis, future studies should include markers of vascular disease, for example measures of caratoid intima-media thickness, pulse wave velocity, pulse wave analysis, orthostatic hypotension, heart rate variability or baroreflex sensitivity (Chen et al 2006; Paranthaman et al 2010; Richardson et al 2009; Smith et al 2009b; Vasudev et al 2010).

Also, the direction of the relationships between vascular factors, depression and MRI measures have not been determined and it remains unclear whether vascular factors 'predispose, precipitate or perpetuate' LOD. The Whitehall II study has been accumulating rich longitudinal data on physical health and lifestyle, including genetic, biological and social information, for twenty-five years in a cohort of UK civil servants, and currently includes over six-thousand participants. The follow-up of this cohort into Phase 11 (2012-14) has now been funded, and the cohort will have an age profile optimal for a study of aging: almost 90% will be over sixty-five and over 30% will be aged between seventy-five and eighty-five. Examination of a subset of this cohort using MRI techniques is proposed and would allow a unique insight into the cumulative effect of vascular factors on depressive

symptoms and MRI measures. While such an epidemiological approach means that the severity of depression is likely to be lower than in a clinically collected sample, a subclinical sample has the advantage of not being medicated. Thus one possible confounder to neuropsychological and MRI measures is absent.

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Appendices

A. T_1-weighted MRI Data

Volumes of CSF, WM, GM, WB and subcortical structures are provided for all participants. Abbreviations – CON: control; CSF: cerebrospinal fluid; GM: grey matter; L: left; LLD: late-life depression; R: right; WB: whole brain; WM: white matter.

ID	CSF	WM	GM	WB	Amgydala		Caudate		Hippocampus		Pallidum		Putamen		Thalamus	
					L	R	L	R	L	R	L	R	L	R	L	R
	cm^3	cm^3	cm^3	cm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3	mm^3
CON01	473	481	511	1465	995	1067	3022	3761	2921	2923	2029	1975	3784	3556	6526	6012
CON02	374	493	530	1397	1345	1367	3567	3684	3132	3674	2065	2076	4726	4070	6614	6309
CON03	419	609	613	1641	1550	1611	3308	3451	3674	4334	1767	1720	4837	4996	8335	8190
CON04	416	538	598	1552	1081	1144	3456	3669	3467	3648	2002	1974	4684	4652	7463	7125
CON05	389	521	492	1402	1058	962	3403	3503	3652	3605	1729	1772	5103	4820	6905	6429
CON06	355	546	571	1472	996	913	3386	3621	3952	4068	1451	1642	4117	4435	7206	7174
CON07	314	517	557	1388	1100	874	2986	3386	3765	3961	2254	1985	4226	4452	7890	7373
CON08	518	568	644	1730	1659	1575	3607	3735	3861	3399	1727	1725	4188	4542	6804	7625
CON09	324	487	503	1314	996	691	2986	2792	3751	3045	1694	1607	4050	4562	6623	6185
CON10	483	607	622	1712	1497	1424	3447	3445	4376	3962	1680	1438	4785	4950	6449	6628
CON11	329	520	515	1364	969	871	3695	3885	3613	3727	2182	2429	4554	4652	6682	6538

CON12	427	521	538	1487	1214	1231	3496	3781	3695	4290	1835	1739	4693	4602	7395	7074
CON13	502	661	692	1856	1648	1628	3534	3607	3549	4271	1904	1796	4425	5004	8454	8148
CON14	423	635	633	1690	1591	1846	4179	4385	3829	4119	2134	2042	5438	5285	8437	7972
CON15	355	506	585	1446	1179	1256	3111	3368	4231	4244	1330	1528	4164	4124	7204	6723
CON16	546	567	595	1708	1371	1522	3431	3466	3372	3589	1600	1630	4134	4423	7566	7387
CON17	450	560	596	1606	1383	1131	3458	3524	4000	4344	1642	1665	4183	4559	8080	7536
CON18	407	593	632	1632	998	855	3653	3857	4385	4460	1735	1726	4728	4585	8513	8437
CON19	369	516	523	1408	790	557	2977	3330	3618	3021	2217	1714	3969	4218	7174	6789
CON20	415	547	562	1524	1306	1437	3761	3945	4051	4070	1713	1649	4682	4426	6510	6302
CON21	398	510	531	1439	1376	549	3413	3552	3238	3466	1397	1471	3856	3627	6778	6678
CON22	431	516	497	1444	1330	1072	3078	3574	3774	2361	1628	1447	4936	4447	6715	5882
CON23	332	560	597	1490	1046	1121	3182	2874	3737	4171	1646	1650	5023	4899	7424	7026
CON24	360	508	497	1364	1111	1045	3348	3445	2013	2923	1856	1780	4210	4153	6592	6776
CON25	416	586	516	1519	1495	1171	2882	3174	3355	3695	2702	2354	4244	4147	7812	7533
LLD01	397	483	547	1427	990	942	3147	3214	3230	3371	1686	1323	3174	3438	6354	6263
LLD02	335	488	534	1357	940	947	3199	3319	3268	3404	1603	1516	3572	3754	6584	6402
LLD03	459	475	499	1433	1337	1132	3371	3773	3422	2753	1666	1812	3857	3926	6543	5672
LLD04	374	592	598	1563	1095	1215	3392	3881	3709	3863	1751	1436	3950	4043	7803	7393
LLD05	437	542	543	1522	1116	1167	2989	3639	3355	4152	1872	2088	4404	4350	6789	6453
LLD06	409	579	613	1600	1157	1453	2964	3143	4184	3952	1722	1594	5295	4883	8716	8095
LLD07	526	540	450	1516	834	848	2652	2879	2643	2412	1113	1017	3006	2980	5591	5251
LLD08	369	594	610	1573	1445	974	3475	3832	3581	3680	2019	2188	5288	5501	8072	7869
LLD09	417	446	481	1344	1086	777	3376	3044	3154	3112	1533	1430	4324	4708	6082	5856
LLD10	376	534	526	1435	1052	980	3449	3814	3420	3567	1815	2102	4956	4817	7071	6858
LLD11	351	510	525	1385	1248	896	3242	3711	3395	3475	1941	2140	4280	4296	6412	6479

LLD12	441	622	636	1699	1279	1232	3736	4141	3760	3774	1826	1553	5118	4002	7917	7692
LLD13	456	580	636	1672	1248	1310	2674	2787	3770	4290	1695	1835	4977	4992	8137	7847
LLD14	421	444	471	1336	1026	1575	3161	3192	3283	3091	1648	1712	4772	3876	6364	5984
LLD15	431	470	492	1394	1073	1022	2578	2859	3338	3244	1525	1737	3388	3278	5559	5455
LLD16	423	503	488	1414	1047	607	2170	2476	2836	3081	1324	1223	3689	3524	5841	5891
LLD17	392	528	571	1491	1227	1194	3073	3348	3354	3587	1476	1604	4065	4186	6922	6884
LLD18	322	577	565	1463	1487	1058	3962	3990	4364	3871	2145	2133	4990	4991	8041	7732
LLD19	401	632	630	1663	1209	1517	3645	3707	3579	4138	3732	3763	4442	4457	8227	7623
LLD20	366	588	606	1561	1350	840	3118	3232	4587	4268	1791	1909	5053	4610	7315	7489
LLD21	314	503	510	1328	1060	1190	3364	3561	3379	3779	1853	1723	3802	4229	7300	7305
LLD22	434	596	624	1654	1555	1323	3916	4207	3679	3724	2518	2572	4902	5184	7321	6978
LLD23	321	491	494	1306	1247	1402	2785	2993	3722	3685	1680	1992	3815	3771	6827	6739
LLD24	370	396	482	1247	856	993	2694	2649	2894	2614	1201	1251	3004	3364	5538	5442
LLD25	320	486	514	1321	1208	1260	3669	3468	3647	3933	1592	1643	4845	4398	6516	6149
LLD26	307	458	482	1247	888	1051	2905	2856	3190	3756	1488	1428	3671	3781	6418	6377
LLD27	322	470	491	1283	1012	1048	2919	3084	3840	3673	1542	1276	3734	3722	7091	6554
LLD28	399	543	583	1526	1129	1312	3388	3271	4198	4609	1662	1672	5014	4829	7314	7184
LLD29	361	442	486	1289	875	918	2488	2625	3150	3329	1405	1373	3576	3781	6140	5896
LLD30	347	493	560	1400	992	464	3466	3462	3690	3605	1551	1545	3711	3884	7128	6726
LLD31	476	629	628	1733	1264	475	3450	4127	4361	4364	2089	2225	4389	5722	7977	8083
LLD32	303	510	504	1317	1024	1123	3114	3220	3729	3459	1588	1684	4348	4332	6935	6603
LLD33	384	445	426	1256	986	1000	2682	2814	3063	2899	1455	1563	3088	3072	6154	5740
LLD34	484	520	594	1598	1407	1337	3158	3665	3414	3774	1546	1504	4695	4774	7439	7210
LLD35	375	616	603	1595	1116	1575	3934	4449	4217	3992	1588	1653	6649	5806	7854	7437
LLD36	444	492	520	1456	882	1025	2850	3198	3013	3402	1417	1437	4195	4563	6570	6339

B. DTI Data

Mean FA values in voxels significantly different between control and LLD groups are provided for all participants. Abbreviations – ATR: anterior thalamic radiation; CC: corpus callosum; CST: corticospinal tract; ILF: inferior longitudinal fasciculus; SLF: superior longitudinal fasciculus; UF: uncinate fasciculus.

ID	Whole Skeleton	ATR	Cingulum	CC: Body	CC: Genu	CC: Splenium	CST	Fornix	ILF	SLF	UF
CON01	0.37	0.38	0.35	0.48	0.42	0.57	0.48	0.34	0.36	0.36	0.30
CON02	0.41	0.42	0.38	0.60	0.57	0.63	0.48	0.36	0.37	0.40	0.34
CON03	0.41	0.47	0.40	0.58	0.57	0.64	0.49	0.37	0.41	0.39	0.35
CON04	0.42	0.44	0.41	0.59	0.58	0.65	0.50	0.35	0.42	0.40	0.34
CON05	0.36	0.41	0.34	0.52	0.47	0.56	0.44	0.32	0.35	0.34	0.28
CON06	0.43	0.45	0.44	0.61	0.57	0.65	0.52	0.36	0.41	0.42	0.33
CON07	0.43	0.45	0.44	0.62	0.60	0.66	0.49	0.36	0.41	0.42	0.36
CON08	0.39	0.41	0.41	0.57	0.51	0.63	0.48	0.32	0.37	0.41	0.30
CON09	0.43	0.46	0.40	0.58	0.55	0.66	0.50	0.39	0.42	0.45	0.29
CON10	0.44	0.45	0.38	0.63	0.57	0.68	0.52	0.34	0.42	0.44	0.35
CON11	0.43	0.41	0.40	0.62	0.58	0.67	0.52	0.37	0.42	0.44	0.37
CON12	0.43	0.45	0.40	0.59	0.58	0.66	0.51	0.35	0.41	0.43	0.36
CON13	0.43	0.47	0.43	0.61	0.57	0.67	0.51	0.37	0.42	0.42	0.36
CON14	0.43	0.49	0.43	0.64	0.58	0.68	0.51	0.37	0.42	0.39	0.33
CON15	0.39	0.42	0.39	0.56	0.53	0.63	0.47	0.33	0.36	0.40	0.33
CON16	0.40	0.45	0.42	0.54	0.47	0.57	0.50	0.31	0.37	0.42	0.34
CON17	0.42	0.46	0.42	0.60	0.54	0.68	0.51	0.37	0.39	0.42	0.34

CON18	0.40	0.45	0.40	0.57	0.56	0.65	0.47	0.36	0.39	0.37	0.29
CON19	0.39	0.42	0.39	0.58	0.57	0.64	0.47	0.35	0.38	0.37	0.33
CON20	0.39	0.42	0.44	0.57	0.53	0.64	0.46	0.34	0.40	0.39	0.34
CON21	0.35	0.40	0.37	0.47	0.44	0.55	0.45	0.32	0.35	0.32	0.29
CON22	0.42	0.46	0.43	0.59	0.52	0.63	0.50	0.34	0.42	0.42	0.33
CON23	0.39	0.40	0.42	0.60	0.56	0.63	0.46	0.35	0.39	0.38	0.33
CON24	0.39	0.43	0.38	0.51	0.50	0.62	0.48	0.33	0.36	0.35	0.32
CON25	0.43	0.46	0.42	0.59	0.52	0.64	0.51	0.38	0.41	0.45	0.35
LLD01	0.36	0.41	0.38	0.55	0.51	0.56	0.43	0.33	0.35	0.35	0.27
LLD02	0.41	0.46	0.38	0.57	0.56	0.64	0.50	0.34	0.40	0.39	0.32
LLD03	0.37	0.40	0.35	0.46	0.43	0.53	0.48	0.31	0.35	0.35	0.31
LLD04	0.40	0.45	0.38	0.60	0.57	0.64	0.48	0.35	0.35	0.37	0.36
LLD05	0.38	0.43	0.38	0.54	0.48	0.63	0.46	0.32	0.35	0.38	0.29
LLD06	0.40	0.45	0.44	0.59	0.57	0.65	0.47	0.38	0.41	0.38	0.35
LLD07	0.37	0.41	0.35	0.58	0.44	0.61	0.44	0.31	0.37	0.40	0.24
LLD08	0.42	0.44	0.40	0.58	0.54	0.64	0.50	0.37	0.42	0.41	0.34
LLD09	0.36	0.40	0.33	0.50	0.49	0.56	0.42	0.30	0.34	0.39	0.30
LLD10	0.39	0.41	0.40	0.56	0.52	0.62	0.48	0.34	0.41	0.36	0.28
LLD11	0.39	0.43	0.38	0.54	0.48	0.61	0.48	0.35	0.37	0.38	0.31
LLD12	0.40	0.43	0.41	0.54	0.55	0.66	0.47	0.35	0.40	0.43	0.31
LLD13	0.39	0.40	0.39	0.58	0.53	0.63	0.46	0.36	0.37	0.40	0.32
LLD14	0.36	0.37	0.39	0.50	0.44	0.56	0.44	0.31	0.34	0.39	0.29
LLD15	0.39	0.43	0.38	0.58	0.53	0.63	0.46	0.32	0.37	0.38	0.31
LLD16	0.35	0.39	0.34	0.49	0.46	0.56	0.43	0.30	0.36	0.35	0.29
LLD17	0.40	0.43	0.43	0.55	0.54	0.63	0.48	0.34	0.39	0.39	0.34

LLD18	0.42	0.45	0.42	0.61	0.60	0.65	0.53	0.38	0.41	0.40	0.31
LLD19	0.42	0.47	0.40	0.61	0.59	0.65	0.48	0.39	0.40	0.42	0.37
LLD20	0.39	0.43	0.38	0.57	0.56	0.61	0.46	0.35	0.39	0.35	0.32
LLD21	0.40	0.42	0.42	0.60	0.55	0.65	0.49	0.35	0.38	0.39	0.33
LLD22	0.38	0.40	0.40	0.55	0.52	0.62	0.46	0.33	0.36	0.40	0.29
LLD23	0.41	0.45	0.40	0.58	0.56	0.65	0.48	0.37	0.40	0.38	0.38
LLD24	0.35	0.37	0.34	0.52	0.42	0.59	0.41	0.33	0.36	0.33	0.24
LLD25	0.38	0.35	0.37	0.53	0.53	0.61	0.46	0.33	0.37	0.36	0.31
LLD26	0.38	0.40	0.40	0.51	0.52	0.58	0.47	0.33	0.35	0.36	0.31
LLD27	0.37	0.37	0.36	0.51	0.51	0.58	0.47	0.34	0.36	0.35	0.32
LLD28	0.40	0.42	0.42	0.58	0.55	0.63	0.49	0.34	0.37	0.40	0.30
LLD29	0.37	0.37	0.36	0.56	0.50	0.60	0.45	0.33	0.36	0.34	0.28
LLD30	0.37	0.39	0.39	0.57	0.51	0.59	0.44	0.32	0.35	0.37	0.28
LLD31	0.33	0.36	0.33	0.50	0.46	0.54	0.40	0.32	0.32	0.32	0.29
LLD32	0.38	0.42	0.38	0.56	0.51	0.62	0.46	0.34	0.35	0.34	0.32
LLD33	0.39	0.43	0.38	0.55	0.52	0.61	0.47	0.31	0.36	0.37	0.30
LLD34	0.37	0.40	0.37	0.46	0.47	0.49	0.48	0.32	0.36	0.35	0.27
LLD35	0.37	0.37	0.37	0.55	0.51	0.60	0.45	0.31	0.35	0.38	0.29
LLD36	0.39	0.40	0.41	0.52	0.47	0.62	0.47	0.32	0.40	0.38	0.29

C. Neuropsychological Data

Raw neuropsychological data are provided for all participants. Abbreviations – CON: control; GNT: graded naming test; HVLT-R: Hopkin's verbal learning test revised; LLD: late-life depression; MT: movement time; RCF: Rey-Osterrieth complex figure; RT: reaction time; TMT: trail-making test.

ID	RCF: Immediate	RCF: Delay	RCF: Total	HVLT-R: Delay	HVLT-R: Recognition	Digit Span: Forward	Digit Span: Backward	Letter Fluency	TMT B	GNT	Category Fluency	Digit Symbol	TMT A	Simple RT	Simple MT	5-Choice RT	5-Choice MT	Copied Drawings	Clock Drawing	RCF: Copy
CON01	14.0	13.0	27	9	10	10	7	14	143	23	15	54	29	376	393	367	387	3	5	36.0
CON02	14.5	10.5	13	8	12	9	10	10	71	24	14	71	34	301	514	364	461	3	4	35.0
CON03	32.0	33.0	32	12	12	10	9	16	49	28	22	48	37	394	346	404	346	3	4	36.0
CON04	29.0	28.0	26	12	9	11	10	25	34	28	24	73	29	281	448	303	457	3	5	36.0
CON05	27.0	27.0	22	7	10	9	12	16	58	30	23	56	48	306	402	373	413	3	5	34.0
CON06	26.0	25.0	29	11	12	12	11	26	44	30	30	81	27	235	261	293	278	3	5	36.0
CON07	30.0	30.0	29	11	12	10	7	20	177	28	26	80	39	277	456	332	418	3	5	36.0
CON08	8.5	8.0	14	4	8	8	4	8	130	24	15	44	53	410	552	447	550	3	5	33.0
CON09	15.5	14.5	33	11	12	9	6	17	145	23	17	34	50	416	402	607	322	2	5	36.0
CON10	21.5	23.5	25	1	8	13	12	17	75	23	20	50	44	335	452	452	390	3	5	36.0
CON11	19.0	20.5	17	8	9	8	5	13	65	25	11	53	52	320	689	350	672	3	4	33.0
CON12	22.5	23.5	20	7	10	9	6	12	88	28	23	56	42	371	357	451	372	3	4	36.0
CON13	24.0	24.0	29	12	12	10	9	11	66	30	22	63	41	342	379	414	384	3	5	36.0
CON14	30.0	28.0	22	11	12	10	9	18	66	25	16	81	30	311	460	313	328	3	5	36.0
CON15	25.0	25.0	28	12	12	14	12	27	41	28	30	88	27	310	283	328	254	3	5	33.0
CON16	16.5	11.5	14	6	8	11	10	15	75	21	21	39	46	418	605	446	439	2	4	36.0
CON17	15.0	16.0	28	8	10	12	12	12	88	28	29	71	29	317	533	380	454	3	5	30.0

CON18	30.0	29.0	23	4	11	13	6	18	115	28	25	79	40	370	363	368	341	3	5	36.0
CON19	30.5	27.5	32	12	12	10	8	19	55	27	30	18	26	254	339	290	312	3	5	35.0
CON20	23.5	22.0	28	11	11	9	8	13	89	21	17	51	36	316	455	343	427	3	5	36.0
CON21	24.0	22.0	17	7	9	7	8	15	107	26	16	48	54	407	876	479	570	3	5	33.0
CON22	7.0	11.0	27	10	9	9	9	19	73	27	22	70	36	339	484	366	444	3	4	36.0
CON23	27.0	20.5	25	10	12	10	6	13	57	28	25	76	41	359	664	429	631	3	5	36.0
CON24	13.5	11.0	14	3	6	8	4	13	97	20	13	40	38	368	438	427	388	1	4	34.0
CON25	17.0	12.5	24	8	11	11	8	22	82	26	18	52	49	311	563	387	360	2	5	32.0
LLD01	13.5	15.5	20	7	10	6	6	27	105	23	12	38	33	322	396	412	412	2	4	32.0
LLD02	10.5	6.5	34	9	12	8	6	16	78	23	32	38	37	276	480	330	487	1	4	34.0
LLD03	12.0	8.0	14	7	9	7	8	5	169	22	13	39	49	433	610	549	628	3	5	34.0
LLD04	22.5	23.5	29	11	12	5	5	17	64	27	21	58	41	279	490	331	437	3	5	36.0
LLD05	27.0	27.0	23	10	11	6	7	14	82	29	25	45	58	342	512	374	501	3	5	26.0
LLD06	24.5	24.5	28	11	12	9	11	24	96	29	32	53	63	399	440	411	430	3	5	36.0
LLD07	1.0	0.5	20	7	10	6	4	7	123	21	5	44	53	566	767	475	639	2	3	21.5
LLD08	20.0	18.0	23	8	10	11	11	18	94	23	25	70	36	320	429	336	400	3	5	34.0
LLD09	10.5	15.5	12	5	7	7	7	18	83	23	17	52	31					2	5	36.0
LLD10	8.5	12.5	27	11	11	8	4	11	105	28	17	53	43	373	714	350	643	2	4	29.0
LLD11	19.0	17.5	22	10	11	8	8	19	140	27	21	50	54	341	310	366	339	3	5	33.0
LLD12	17.5	17.5	24	11	12	9	6	10	68	29	17	63	45	378	473	377	430	3	5	36.0
LLD13	13.5	11.0	23	10	11	9	5	11	57	28	22	75	29	388	533	446	512	3	5	36.0
LLD14	16.0	22.0	20	7	9	7	6	11	81	26	19	41	83	430	804	456	681	3	5	36.0
LLD15	23.0	23.5	29	12	12	6	6	17	115	28	19	50	56	394	668	387	514	3	5	34.0
LLD16	10.0	8.0	18	6	10	9	5	14	198	24	14	28	89	404	589	527	540	3	5	33.0
LLD17	23.5	23.5	28	9	11	13	6	15	66	28	24	51	49	463	423	436	517	3	5	36.0
LLD18	17.5	16.5	26	10	12	6	5	21	-59	28	22	60	-34	-261	286	349	271	3	5	36.0
LLD19	19.0	17.5	26	10	11	12	6	23	95	23	15	53	44	325	450	362	385	3	5	34.0

LLD20	19.0	18.0	25	9	12	9	6	18	70	27	16	80	32	314	318	341	306	3	5	34.0
LLD21	15.5	16.0	20	8	10	7	7	18	90	28	27	63	51	356	990	372	541	3	5	36.0
LLD22	19.0	19.0	12	8	10	10	5	13	113	24	16	49	67	653	516	432	377	3	5	34.0
LLD23	28.0	24.5	26	10	11	12	11	26	37	26	26	89	36	358	895	601	736	2	5	36.0
LLD24	9.5	10.5	21	7	10	7	6	12	118	15	15	38	61	319	979	500	935	3	4	30.0
LLD25	9.5	11.0	20	8	11	7	8	6	130	24	11	46	60	262	295	303	329	3	4	32.5
LLD26	2.0	2.0	21	5	9	6	5	10	162	10	12	20	97	418	802	397	683	0	3	19.0
LLD27	3.5	6.0	24	9	12	8	9	14	138	25	26	65	41	292	546	325	441	1	4	14.0
LLD28	33.0	33.0	21	6	12	9	5	14	105	23	16	47	59	432	555	419	525	3	4	36.0
LLD29	3.0	6.5	23	8	12	6	4	11		16	14	34	52	339	513	715	511	2	4	29.5
LLD30	16.0	16.5	18	5	9	4	4	17	110	24	21	54	42	426	626	494	692	3	5	33.0
LLD31	14.5	14.0	16	6	7	8	5	15	177	23	11	30	57	346	554	362	568	2	5	29.0
LLD32	16.0	16.0	24	7	8	11	4	14	95	20	15	45	56	335	549	444	547	3	5	36.0
LLD33	5.0	5.0	17	2	10	10	8	22	100	28	17	53	38		416	578	349	3	5	33.0
LLD34	30.5	24.5	27	8	9	9	9	14	103	23	20	61	32	245	502	331	390	3	5	36.0
LLD35	27.0	27.0	19	7	10	9	9	6	84	25	17	57	66	412	540	470	521	3	5	34.0
LLD36	10.0	12.0	11	3	8	8	4	19	107	12	9	48	65	360	628	377	531	3	5	36.0