Brain MRI correlates of depression and vascular risk: Whitehall Imaging sub-study

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Declaration of authorship

I, Dr Charlotte Louise Allan confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Date: 11th July 2014

Abstract

This thesis combines neuroimaging and epidemiological techniques to investigate the hypothesis that late-life depressive symptoms are partially caused by vascular risk factors. Magnetic resonance imaging (MRI) was used to study the structural brain changes associated with depressive symptoms, major depressive disorder and long-term exposure to vascular risk factors (hypertension, dyslipidaemia, diabetes, smoking and Framingham stroke risk). This was complemented by an epidemiological approach to investigate whether vascular risk factors are associated with depressive symptoms.

A sample of participants from the Whitehall II study were invited to take part in the Whitehall Imaging sub-study at the University of Oxford. Participants recruited between April 2012 and June 2013 (n=229, mean age 69, age range 60-82 years, 83% male) underwent detailed cognitive testing, a clinical interview and a multi-modal 3 Tesla MRI brain scan. Depressive symptoms were measured at previous Whitehall II phases, and again in 2012-2013 using a structured assessment for DSM-IV mood disorder and a self-report questionnaire. Long-term exposure to vascular risk factors was measured at five collection phases between 1985 and 2009.

Ten percent of participants (n=23) had current depressive symptoms and 13% (n=29) had late-onset depressive symptoms (depression onset after age 60). Current and late-onset depressive symptoms were associated with reduced white matter integrity in frontal-subcortical areas. Study of the MRI correlates of vascular risk factors also showed an association between long-term exposure to high fasting glucose (mean across five examinations between 1985 and 2009) and reduced white matter integrity in frontal-subcortical areas. However, long-term exposure to other vascular risk factors was not significantly associated with depressive symptoms.

In conclusion, while vascular risk factors were not consistently related to late-life depressive symptoms, long-term exposure to high glucose levels and depressive symptoms were both associated with reduced white matter integrity in frontal-subcortical areas.

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Abbreviations

AD	Axial Diffusivity
BNT	60-item Boston Naming Test
BNF	British National Formulary
BMI	Body Mass Index
CES-D	Centre for Epidemiological Studies Depression rating scale
CHD	Coronary Heart Disease
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DC	Digit Coding
DWM	Deep white matter hyperintensities
DSBW	Digit Span Backward
DSFW	Digit Span Forward
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition, text revision
DSS	Digit Span Substitution
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
FA	Fractional Anisotropy
FAST	FMRIB's Automated Segmentation Tool
FIRST	FMRIB's Integrated Registration and Segmentation Tool
FLAIR	Fluid Attenuated Inversion Recovery
FLIRT	FMRIB's Linear Image Registration Tool
FMRIB	Functional Magnetic Resonance Imaging Centre, University of Oxford
FNIRT	FMRIB's Non-Linear Image Registration Tool
FSL	FMRIB Software Library
FSRS	Framingham Stroke Risk Score
GHQ	General Health Questionnaire
HDL	High-Density Lipoprotein
HVLT	Hopkins Verbal Learning Test Revised
ICC	Intra-Class Correlation Coefficient
ICD-10	International Classification of Diseases and Related Health Problems, version 10

LDL	Low-Density Lipoprotein
MAP	Mean Arterial Pressure
MD	Mean Diffusivity
MEG	Magnetoencephalography
MI	Myocardial Infarction
MNI	Montreal Neurological Institute
MOCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
PVWM	Periventricular white matter hyperintensities
PET	Positron Emission Tomography
RCF	Rey-Osterrieth Complex Figure
RD	Radial Diffusivity
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM-IV diagnosis
SD	Standard Deviation
SPECT	Single Photon Emission Computed Tomography
TBSS	Tract Based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement
TIA	Transient Ischaemic Attack
TMTA	Trail Making Test A
TMTB	Trail Making Test B
TOPF	Test of Pre-morbid Functioning
VBM	Voxel Based Morphometry

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Chapter 1. Background

1.1 Introduction

This thesis examines the hypothesised vascular origins of depressive symptoms using a combination of neuroimaging and epidemiological methods. As such, it spans the disciplines of psychiatry, neuroscience and epidemiology. Chapter 1 provides an overview of each of these areas to set the research in context and to establish the value of this inter-disciplinary approach.

1.2 Depression

Depression is the leading cause of disability worldwide and is a major contributor to the global burden of disease (1). Depressive symptoms span a broad spectrum, ranging from normal sadness in response to a difficult life event, through mild symptoms that have limited effect on daily activities, to severe symptoms that cause a profound change in an individual's ability to function. The gold standard method for diagnosing depression is through clinical interview, informed by standard classification criteria based on the World Health Organisation's International Classification of Diseases or the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (Table 1) (2, 3). Regardless of age at onset, the core features of depression are similar and include low mood and anhedonia (loss of pleasure); the number of additional symptoms allows the severity of depression to be classified (Table 1).

Depression is a common condition seen in people of all ages and cultures. Population-based epidemiological studies have shown that the prevalence of major depression is 10 - 15% (4, 5). The prevalence of depression tends to decrease with age, from 20% in mid-life (30 to 44 years) to 10% in those over 60 years (5, 6). While the percentage of older patients suffering depression is smaller, the absolute numbers are increasing because of demographic changes. It is thus an important condition to understand, prevent and treat. Certain groups have an increased risk of depression. For example, depressive symptoms have been shown to increase after the age of 75 years (7), and the prevalence of depression in older adults living in institutions is approximately 25% (8). Late-life depression is particularly important given its association with increased morbidity, reduced quality of life, delayed recovery from physical illness, cognitive impairment and increased mortality (9-14). People developing depression in later life frequently have somatic symptoms, increased anxiety, psychomotor retardation,

reduced interest in activities and executive dysfunction compared with younger age groups (10, 15).

Table 1. Diagnostic criteria for depression

	ICD-10 (2)	**DSM-IV** (3)
Core criteria	Symptoms present most of the time for at least two weeks; not secondary to drug or alcohol misuse, medication, medical disorder or bereavement*	
Symptoms	Depressed mood, anhedonia, weight change, reduced appetite, disturbed sleep, psychomotor agitation or retardation, loss of energy, reduced libido, feelings of worthlessness and guilt, poor concentration, indecisiveness, thoughts of death or suicide, delusions, hallucinations	
Severity	**Mild** 2-3 symptoms; able to continue with daily activities **Moderate** ≥ 4 symptoms; difficult to continue daily activities **Severe** Several symptoms which are marked and distressing; ordinary activities impossible, psychotic symptoms may be present	**Minor** ≥ 2 symptoms, with minimal effect on function **Major** ≥ 5 symptoms, with clinically significant distress or impairment in functioning

*Bereavement exclusion clause removed in DSV-5

In studies the age cut-off for late-life depression has varied from 50 to 65 years, but is generally thought of as occurring over the age of 60, either for the first time or as part of a recurring pattern of mood disorder (16). The precise value is less important than the principle that late-life depression may have a different aetiology to depression occurring earlier in life. Depression can be precipitated by increasing age and age-related chronic conditions, altered social circumstances (including retirement, bereavement and reduced independence), and psychological adaptations related to role transition and lack of resilience to stress (17-20). However, some studies have found that those developing late-life depression are less likely to have had recent adverse life events, including bereavement (21) or pre-disposing psychological

factors (e.g. low self-esteem, perfectionism and poor resilience to stress), or a family history of depression (22, 23). Indeed, for many people later life is associated with fewer risk factors for depression than middle age – that is, it represents a period of financial and social stability, with increased freedom to explore new interests without the constraints imposed during working life. For these reasons, psychological and social factors are not sufficient to explain the aetiology of late-life depression, and biological factors are thought to make a significant contribution to aetiology (10).

Vascular pathology has been proposed as particularly relevant to the aetiology of late-life depression. Existing studies suggest that vascular disease may affect brain structure and function, increasing individual susceptibility to depression (24). Clinical observations were the starting point for the development of this concept, which followed the recognition that stroke and cardiovascular disease could lead to depression, and that people with depression had higher rates of cardiovascular illness (25, 26). Vascular damage may affect the brain, disrupting structures or neural circuits, thereby precipitating depression. However, some studies suggest that depression itself could cause pathological changes that increase the risk of vascular disease (27). Therefore, the association between depression and cardiovascular disease might be bi-directional, perhaps mediated by common physiological and behavioural mechanisms (28). Furthermore, the later the onset of depression, the greater the contribution from co-morbid organic brain disease (29).

In addition to cardiovascular disease, other biological factors such as inflammatory markers may be involved in the neurobiological changes found in late-life depression (24, 30-33). The effects of genetics and family history may become less important in older people, compared to younger adults (22, 23). Late-life depression is associated with a high prevalence of cognitive impairment (24, 34), specifically with reductions in processing speed and executive function (35). Changes in cognitive function have prompted scientists to explore structural brain changes in depression using MRI.

A large body of research supports the notion that late-life depression is accompanied by changes in brain structure and function. Grey matter structural changes include ventricular enlargement (36) and regional atrophy in frontal, temporal, hippocampal (36, 37) and caudate regions (38). White matter changes are particularly prominent in late-life depression (34, 39). These changes are thought to be of vascular aetiology (40, 41) consistent with the vascular

hypothesis of depression (24). However, doubt has recently been cast on the association between vascular risk factors and white matter hyperintensities, given evidence that vascular risk factors and large-artery atheroma have only a small effect on white matter hyperintensities (42). Depression is also associated with changes in brain function. Frontal hypoperfusion is common and may explain reductions in executive function noted in cognitive testing (43).

One limitation is that these studies have tended to focus largely on comparisons between participants with clinical late-life depression and healthy controls; they frequently fail to consider those who have depressive symptoms, but who do not qualify for a diagnosis of clinical depression. Sub-syndromal depressive symptoms are common in the general population, and may be associated with functional disability and medical comorbidity to a degree similar to major or minor depression (44, 45). Those with high scores on a depression rating scale only, also show brain atrophy and white matter lesions (46). This suggests that depressive *symptoms*, as well as depressive *disorder*, may be associated with structural changes, but this aspect requires further detailed investigation. The use of participants drawn from the Whitehall II study, who exhibit a wide-range of depressive symptoms, provides a further opportunity to investigate this. Additionally, this provides the opportunity to draw on long-term data on depressive symptoms to facilitate investigation of whether the associations between depression and brain structure are causal or explained by some other factors.

1.3 Standard vascular risk factors

Vascular risk factors, such as hypertension and smoking, increase the risk of vascular disease, affecting the heart, brain and other major organs such as the kidneys. Vascular disease (e.g. myocardial infarction or stroke) is the leading cause of mortality worldwide (47). The impact of vascular risk factors and disease on the brain, in terms of depression and dementia, is now increasingly recognised as important for increasing morbidity and mortality (48). According to the American Heart Association (http://www.heart.org/HEARTORG/) and the World Health Organisation (47), the most important modifiable risk factors for cardiovascular diseases are: hypertension, dyslipidaemia, diabetes mellitus, smoking, physical inactivity and obesity. Other risk factors, such as increasing age, male sex and family history are also important, but cannot be modified. Individual vascular risk factors contribute to vascular disease, but in order to evaluate their combined effect, a composite algorithm based on validated risk predication

tools such as QRISK (well calibrated to the UK population), ASSIGN or the Framingham score (49-51) can be used.

The pathology most commonly linking vascular risk factors to vascular disease is atherosclerosis (52). In atherosclerosis, lipid deposits in the endothelium of vessels lead to structural and functional changes, such as an irregular, narrowed vessel lumen, and altered blood flow. Lipid deposits within the endothelium are prone to rupture, leading to a thrombotic event and end organ ischemia. This is particularly significant if it occurs in the coronary arteries (leading to myocardial infarction) or the brain (leading to a stroke). Of interest is whether the effects of vascular damage to small vessels in the brain can precipitate depression in those without a previous history of depressive symptoms, or perpetuate depression in those who are already vulnerable.

Blood pressure

Hypertension is the leading cardiovascular risk factor (47). It is defined as blood pressure ≥140/90 mm Hg, with further classifications of severity that can be made in accordance with National Guidelines (Table 2) (53). The prevalence of hypertension rises with age, and in the UK, over half of adults over the age of 65 have hypertension, making this a significant and important risk factor (Table 3) (54). Hypertension has a significant association with mortality: at age 40 to 69 years, each increment of 20 mm Hg in systolic blood pressure (approximately equivalent to 10 mm Hg diastolic blood pressure) is associated with a two-fold increase in mortality from stroke, ischaemic heart disease and other vascular causes (55).

The effects of hypertension are mediated by local changes in blood vessels, and the increased strain placed on the heart (47). Persistently raised blood pressure damages the endothelium of blood vessels contributing to the development of atherosclerosis; weakened vessel walls are more prone to the development of aneurysms. Higher blood pressures can damage small vessels by causing them to rupture, particularly if vessels are already weakened through atherosclerosis. This can lead to end organ damage in the brain, the heart or kidneys. Higher blood pressures require greater force from the heart and the increased force required can lead to the development of hypertrophy in the left ventricle, ultimately contributing to heart failure.

Table 2: Classification of hypertension
Based on NICE guidelines, 2011 (53)

Classification	Definition
Stage 1 hypertension	Systolic/diastolic blood pressure ≥140/90 mm Hg in clinic and Subsequent ambulatory or home monitoring is ≥135/85 mm Hg
Stage 2 hypertension	Blood pressure ≥160/100 mmHg in clinic and Subsequent ambulatory or home monitoring is ≥150/95 mm Hg
Severe hypertension	Systolic blood pressure ≥180 mm Hg in clinic or Diastolic blood pressure ≥110 mm Hg in clinic

Table 3: Prevalence of vascular risk factors in England
Based on Coronary Heart Disease Statistics published by the British Heart Foundation, 2012 (54).

	Prevalence of vascular risk factors by age		
Age range, *years*	55 – 64	65 – 74	75 +
High blood pressure, *%* [a]			
Men	51	65	79
Women	47	63	79
Dyslipidaemia, *%** [b]			
Men	70	53	39
Women	83	75	66
Diabetes, *%* [a]			
Men	11	15	16
Women	8	12	13
Coronary Heart Disease, *%* [d]			
Men	11	21	29
Women	4	10	19
Smoking, *%* [c]			
Men		14	
Women		15	

[a] 2010 data, [b] 2008 data, [c] 2004 data, [d] 2006 data

*Dyslipidaemia is the presence of abnormal levels of blood lipids; different lipid components may be either too high, or too low

Cholesterol

Cholesterol is an important component of cell structures and is needed for the synthesis of hormones and vitamins (56). It is transported in the body by lipoproteins. High serum levels make a significant contribution to the development of atherosclerosis and therefore of cardiovascular disease (47). There is a log-linear relationship between raised total cholesterol and risk of coronary heart disease (51). High cholesterol is usually defined as ≥5.0 mmol/L for total cholesterol (51). However, it is also important to consider the components of total cholesterol. Low-density lipoprotein (LDL) transports cholesterol from the liver to other parts of the body and LDL cholesterol levels ≥3.0 mmol/L are considered high. High-density lipoprotein (HDL) transports cholesterol from the body back to the liver, enabling it to be

broken down and excreted. HDL cholesterol is therefore protective and levels should be ≥1.0 mmol/L. The ratio of total cholesterol to HDL cholesterol can be used to estimate cardiovascular risk. Triglyceride levels are also important; triglycerides are the main form of fat in the body and are transported by lipoproteins. Triglyceride levels are defined as high if they are ≥2.0 mmol/L.

Dyslipidaemia is common. It is found in over 50% of adults in high income countries (47), which is consistent with prevalence rates in England. Interestingly, the prevalence reduces in men and women over the age of 75 (Table 3) (54). This may be due to a reduction in LDL synthesis due to decreased liver function with increasing age (56), as well as a healthy survivor effect (i.e. those with severe dyslipidaemia are more likely to have fatal cardiovascular disease and drop out from studies compared to those with normal lipid levels). Dyslipidaemia is important to recognise because it is a modifiable risk factor, and its effects and health implications can be minimised through attention to diet, increased exercise and use of lipid-regulating medication (51). Decisions regarding treatment (e.g. use of statins) are not based solely on blood cholesterol levels, but should take into account the overall risk of developing cardiovascular disease (51). This has been highlighted by recent American Heart Association guidelines which confirm that statin treatment should be offered to those with elevated cardiovascular risk, and not only based on cholesterol levels (57, 58).

Diabetes

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia and insufficient insulin production, or lack of response to insulin. In type 1 diabetes, which usually starts in childhood, insulin is not produced. In type 2 diabetes, commonly developing later in life, there is reduced insulin secretion, or reduced insulin sensitivity. The diagnosis is made based on clinical history and plasma glucose concentration: random plasma glucose ≥11.1 mmol/L, or two-hour post load glucose ≥11.1 mmol/L, or fasting plasma glucose ≥7.0 mmol/L on two occasions (59, 60) or Haemoglobin A1c (HbA1c) concentration ≥6.5% (61). In pre-diabetes, glycaemic indices are higher than normal, but do not meet criteria for a diagnosis of diabetes. It is defined using the same tests as follows: random plasma glucose 7.8-11.0 mmol/L, or two-hour post load glucose 7.8-11.0 mmol/L, or fasting plasma glucose 5.5-6.9 mmol/L (59, 60) or HbA1c 5.7-6.4% (61).

The prevalence of diabetes increases with age and is found in approximately 10-15% of older adults in the UK (Table 3) (54). The risk of cardiovascular events, particularly stroke, is two to three times higher in those with type 1 or type 2 diabetes (47). Adverse cardiovascular effects are mediated by chronic hyperglycaemia, recurrent hypoglycaemia and metabolic changes which can cause endothelial dysfunction, inflammation, dyslipidaemia and changes in blood-brain barrier permeability (62). These microvascular and macrovascular changes cause end organ damage in multiple systems, including the brain (62). This means not only that macrovascular problems such as stroke are common, but also that cognitive impairment and depression may be more likely in those with diabetes. Lastly, there is increasing evidence of the harm caused to end organs by the presence of pre-diabetes (63).

Smoking

Smoking is associated with a substantial increase in mortality rates from cardiovascular disease (64-67). Its mechanism of action is through increased atherosclerosis, caused by heightened response to vascular injury and raised inflammatory markers (65). With greater awareness of its adverse effects, the prevalence of smoking in Great Britain has steadily decreased from nearly half the adult population in 1972 to approximately 20% in 2010 (54). Smoking prevalence is lower in older adults (currently about 15% in men and women, Table 3) and in those of higher socio-economic status (54). Despite these trends it remains an important modifiable vascular risk factor for which a number of secondary prevention therapies are available (68).

1.4 Cardiovascular diseases

The most common presentations of cardiovascular diseases are coronary heart disease and stroke; both are discussed here.

Coronary heart disease

Coronary Heart Disease (CHD) leads to clinical conditions such as angina and myocardial infarction (MI). It is usually caused by atherosclerosis in the coronary arteries that supply the myocardium. As atherosclerotic plaques develop, coronary arteries become narrowed, leading to reduced perfusion and clinical symptoms of angina, or become blocked, causing MI. Diagnosis of angina and MI is based on clinical history, electrocardiogram (ECG), and sometimes other investigations, such as coronary angiography. Coronary heart disease is

common, particularly in men, and exhibits increasing prevalence with age (Table 3). It is a leading cause of death and disability in the UK as well as globally (47). In view of the many modifiable risk factors for CHD, primary and secondary prevention is a major public health focus nationally and internationally (47, 69). Encouragingly, there is emerging evidence that age-standardised mortality rates have been decreasing since the 1980s, which may be partly due to significant efforts towards prevention (70).

Stroke

Stroke is diagnosed when there is evidence of cerebral haemorrhage or ischemia, associated with a change in neurological functioning. After ischaemic heart disease it is the second most common cause of death worldwide (47). A Transient Ischemic Attack (TIA) is similar, however, in a TIA there is *temporary* cerebral ischemia associated with a *brief* change in neurological function that resolves within 24 hours (and usually resolves in less than two hours) (71). Atherosclerosis makes a major contribution to the aetiology of stroke and TIA, particularly for ischaemic stroke. Risk factors for stroke are similar to those for coronary heart disease, and include: increasing age, hypertension (particularly for haemorrhagic stroke), dyslipidaemia, atrial fibrillation, smoking and diabetes (47). Improved management of modifiable risk factors can lead to substantial reductions in the incidence of stroke (72). Stroke is associated with significant mortality (approximately 50% mortality within one year of a stroke), as well as increased morbidity resulting from physical, cognitive and neuropsychiatric changes (72, 73). Early treatment can lead to improved outcomes (72).

There is already a well-established literature describing the association between stroke and increased risk of depression (74-77). At least one third of patients will develop post-stroke depression, and these people have increased morbidity and mortality, including cognitive impairment (77, 78). The pathology and mechanisms associated with these conditions are linked to lesion location, cognitive changes and psychosocial adjustment related to disability and loss of role (74). A previous history of depression and anxiety, as well as disability, cognitive impairment, stroke severity and vascular risk factor burden, are predictors of post-stroke depression (78-83).

MRI is used clinically and in research to identify the extent, location and type of stroke (71, 84). As well as major lesions, it can detect small lesions which may not have caused noticeable clinical symptoms, but nevertheless indicate cerebrovascular disease or a previous TIA. The

effect of stroke in terms of macroscopic damage to grey and white matter provides an obvious mediating anatomical pathway leading to depression through damage to cortical circuits involved in monoamine production and mood regulation (85). Frontal lobe atrophy subsequent to ischemic stroke may have a role in the development of depressive symptoms (86). Periventricular white matter hyperintensities predict poorer functional outcomes after stroke (87). While gross anatomical changes in regions that regulate mood can lead to depression, these macroscopic changes are accompanied by important microscopic sub-cortical changes, including lacunas and deep white matter hyperintensities, which play an important role in post-stroke depression (85, 88).

The strength of evidence linking stroke and depressive symptoms means that the investigation of stroke and depression using MRI in this thesis would not constitute a novel approach: the association with depression is not controversial, unlike the association with other vascular risk factors. Furthermore a previous stroke or TIA may reduce the effectiveness of MRI processing and analysis. For these reasons, stroke is not explored further in this thesis. However, the thesis does make use of the Framingham Stroke Risk Score (FSRS), as this composite measure of vascular risk has been less thoroughly investigated and provides another angle from which to explore the associations between vascular risk factors and depression.

1.5 Methodological approaches

The associations between depression, vascular risk factors and vascular disease are investigated using neuroimaging and epidemiological methods. This section provides an introduction to the principles underlying the MRI and epidemiological methods employed in this thesis. It also reviews the literature relating to previous studies that have employed this dual methodological approach.

1.5.1 Magnetic Resonance Imaging (MRI)

What is MRI?

Magnetic Resonance Imaging (MRI) is a non-invasive technique that uses principles of nuclear magnetic resonance to visualise body structures, including the brain. It provides excellent spatial and temporal resolution, and is able to detect subtle changes in brain structure and to investigate brain function. It has been used extensively in clinical practice and research,

offering reliable, validated protocols for data acquisition and analysis. While other techniques (e.g. magnetoencephalography, MEG) may provide superior temporal resolution, MRI provides excellent spatial resolution (e.g. better than Computed Tomography, CT), and, unlike Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) scanning, does not require an intravenous tracer. It therefore provides an excellent compromise in its ability to provide in vivo detailed structural and functional imaging data.

Crucial for its use in a research setting, MRI has an excellent safety record, with the advantage of being a non-invasive technique, which does not use ionising radiation. It is, however, not suitable for people with implanted metal devices (e.g. pacemakers), or those with a previous injury involving metal, in case metal fragments have been retained in the body. This is because ferromagnetic objects have the potential to cause serious injury through attraction, torque and heating effects within the strong magnetic field. Therefore, safety guidelines need to be carefully adhered to. MRI is very well tolerated by the majority of people, although the space limitation and noisy environment within the scanner may be difficult for a minority, including those with claustrophobia.

What are the principles behind MRI?

The human body comprises many millions of hydrogen nuclei, largely within water molecules. Hydrogen nuclei are usually orientated in random directions; however, when placed in a strong magnetic field (B_0) they tend to align with the field, precessing (spinning) at a frequency (ω), proportional to the magnetic field applied (Figure 1) (89-91). This frequency is called the Larmor frequency and can be represented using the following equation:

$$\omega = \gamma B_0$$

ω, Larmor frequency; γ, constant; B_0, main magnetic field strength

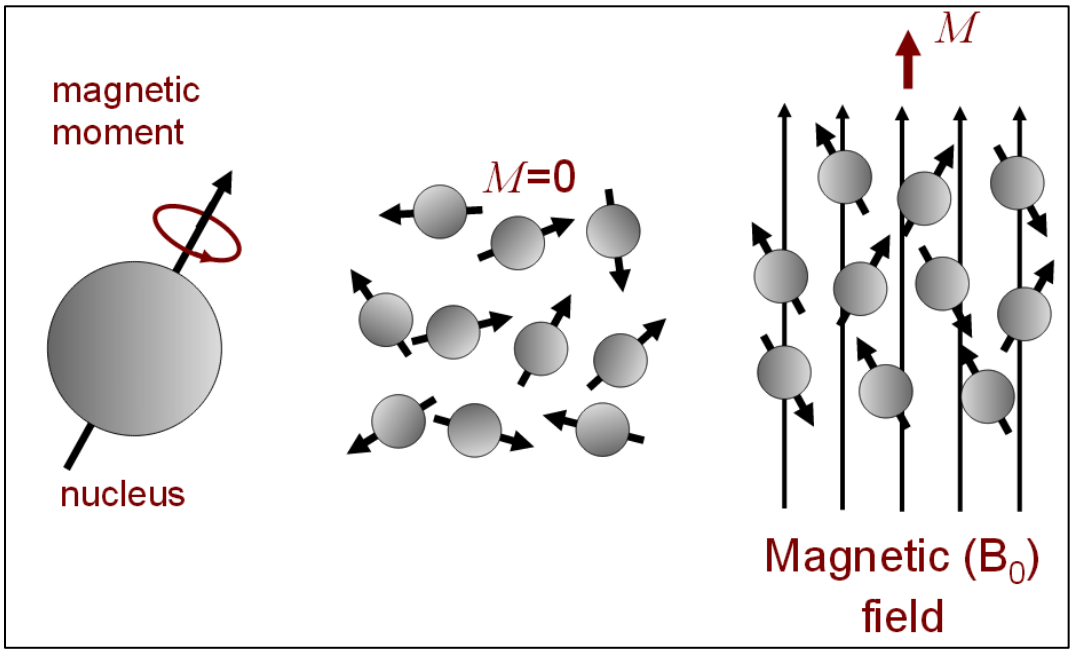
The alignment of nuclei with the main magnetic field (B_0) leads to a small change in the net magnetisation (magnetic moment). In order to measure this change in magnetisation a second, much smaller, magnetic field (B_1) is applied for a short period, at an angle to the first field, using a radio-frequency (RF) transmitter coil. This excites a proportion of the nuclei so that they flip out of alignment with B_0, precessing at an angle to it (Figure 2). The time that nuclei spend in this new energy state varies depending on the local environment, e.g. whether

the hydrogen nuclei are situated within cerebrospinal fluid (CSF), grey matter or white matter. When nuclei relax from their second position, back to their original position in alignment with the main magnetic field (B_0), they release energy in the form of a radio-frequency (RF) pulse, which can be detected and measured. The differential relaxation time that occurs in different tissues allows the generation of images that show contrasts between different tissue types. In order to acquire spatial information, i.e. information about the location of protons (and therefore of different tissue types), a magnetic field gradient is used. This field gradient provides graded variation in the magnetic field so that nuclei in different locations precess at different frequencies; the detection of different frequencies thus provides information about proton location.

The MRI scanner accordingly consists of a series of coils which generate a) the main magnetic field (B_0); b) the second magnetic field (B_1); and c) the magnetic field gradient. Additional shim coils, are used to improve field homogeneity, to help prevent artefacts.

Figure 1. Alignment of nuclei with main magnetic field

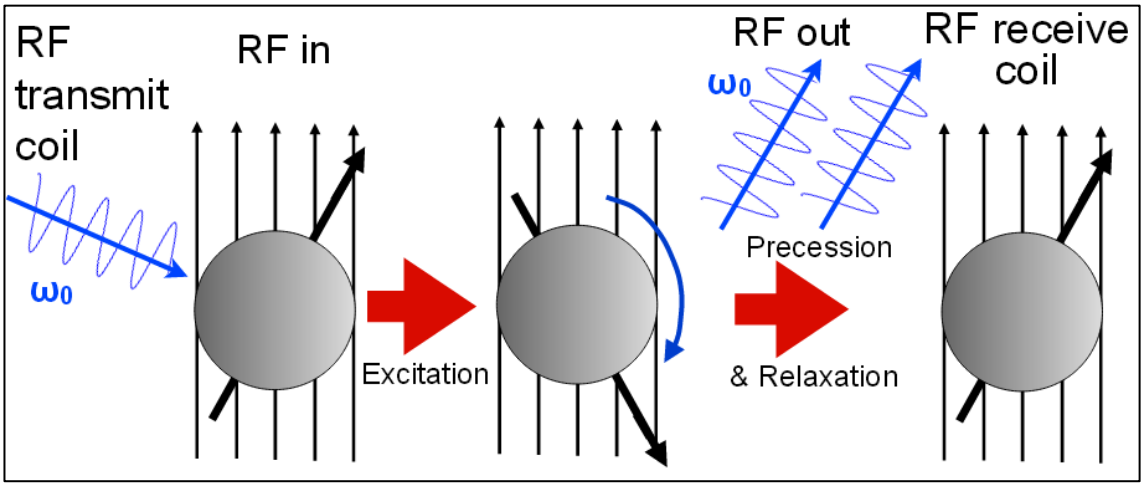
This figure is adapted from FMRIB resources and re-produced with permission of the author (92).



M=direction of magnetic moment; B_0=direction of main magnetic field

Figure 2. Excitation of nuclei

This figure is adapted from FMRIB resources and re-produced with permission of the author (92).



RF=radio frequency; ω_0=Larmor frequency

Structural imaging

Several different sequences can be used to investigate different aspects of brain structure. This thesis uses sequences for T1-weighted imaging, T2-weighted imaging and Diffusion Tensor Imaging.

T1-weighted imaging shows the density and type of brain tissue, providing a standard structural image that can be used to identify lesions (e.g. tumours) and atrophy, calculate whole-brain volumes, segment different tissue types (grey matter, white matter and CSF), investigate structure and shape of subcortical structures, and investigate cortical surfaces and thickness. While this can provide a great deal of information about brain structure, the disadvantages are that T1-weighted imaging does not measure tissue type directly, contrasts poorly between bone and air, and is susceptible to artefacts and "noise".

T1-weighted imaging uses a gradient echo sequence with short repetition times. T1 refers to the time it takes for nuclei to return to alignment in the B_0 direction, more specifically, the time it takes 63% of the longitudinal magnetisation to recover in the tissue (91). In T1-weighted structural scans, areas with high water molecule content (e.g. CSF) have a long T1 and appear dark in T1-weighted images. Grey and white matter have different T1 relaxation times: the shorter T1 in white matter means that it appears brighter than grey matter. By adjusting the repetition time for the RF pulse, it is possible to achieve different T1 weighting, providing different types of contrast.

T1-weighted MRI can be used to study structural changes in grey matter using a variety of analytic methods. Region of interest analysis can be used to assess the volumes of a-priori defined cortical and subcortical structures. While this provides an effective method of investigating structural brain changes, it is limited by the need for operator defined regions (volumes) of interest. This is intrinsically less reliable than considering changes in the whole brain and increases the risk of type II statistical error, where significant differences occurring outside or including only a part of these pre-defined volumes may not be identified. An alternative is to investigate the location and nature of changes in subcortical structures based on their shape. However, this approach has not been widely applied to investigation of depressive symptoms or disorder (93). A further option is to investigate grey matter across the whole brain using voxel based morphometry (VBM). This rapid, automated approach was chosen for this study, because it has the advantage of being able to assess global changes in

brain structure, does not require prior selection of regions of interest, and has been shown to be effective in studies of depression (36). The analysis pipeline for T1-weighted imaging using VBM involves brain extraction, segmentation of tissue type, segmentation of tissue structures, registration (alignment) and statistical comparisons to assess local changes between different groups.

The T2-weighted sequence measures the magnetic resonance signal after a longer period for decay of the signal than that used in T1-weighted imaging (i.e. longer repetition time). Modifications to the T2-weighted sequence provide Fluid Attention Inversion Recovery (FLAIR) images that suppress the high CSF signal, providing enhanced white matter contrast in regions adjacent to CSF, enabling pathology such as white matter hyperintensities to be seen more clearly (91). T2-weighted MRI or FLAIR images can be used to study brain structural changes in white matter (e.g. white matter hyperintensities) using visual or automated methods. Visual methods such as the Fazekas scale (94), have the advantage of not requiring further processing, that they can be used by trained clinicians or neuroscientists, and that they can be easily applied to individual data, making them potentially useful in clinical practice. However, they retain an element of subjectivity and do not provide the precision available with automated methods in terms of quantity and location of changes. Automated methods (e.g. FreeSurfer http://surfer.nmr.mgh.harvard.edu/) may be quicker to apply to large numbers of subjects and provide specific, objective and quantifiable data. However, there have been concerns about their ability to accurately determine white matter hyperintensities from other brain structures, and in separating periventricular from deep white matter changes (95, 96). In this study both methods are used, and the results between them are compared to more fully elucidate the advantages and disadvantages of each method.

Diffusion tensor imaging (DTI) investigates white matter structure and connectivity by considering the integrity and direction of fibres (97, 98). It does this by modelling the diffusion of water using a tensor model. If diffusion of water molecules is unrestricted, water molecules will spread out equally in all directions, in which case diffusion is termed *isotropic* and can be modelled as a sphere. However, in white matter tracts (axons) water molecules are constrained by myelin sheaths and the parallel direction of fibres. In this case a restricted pattern of diffusion would be expected, with more diffusion along the axon, and less diffusion across the axon. If diffusion of water molecules is restricted in any direction, the diffusion is termed *anisotropic* and is modelled as an ellipsoid. When water diffusion is constrained within

white matter tracts, the degree of anisotropy provides information about the structure and orientation of the white matter fibres.

The principal measures of diffusion used in DTI are fractional anisotropy (FA) and mean diffusivity (MD), which are used to measure the average diffusion in a group of white matter tracts. FA measures how elongated the ellipsoid model is, and is a measure of fibre integrity. In CSF, where there is free diffusion, FA would be very low (i.e. close to zero); in white matter tracts such as the corpus callosum, where diffusion is constrained and highly directional, FA would be higher (i.e. close to one). Mean diffusivity is a measure of the mean direction of diffusion averaged over all directions, and provides information about white matter microstructure. Mean diffusivity can be considered separately in its component parts: radial diffusivity (RD) and axial diffusivity (AD). If there is reduced white matter integrity, then tracts that would normally be expected to show highly directional patterns of diffusion may reveal more variable patterns. For example, FA may be reduced (closer to zero), and MD may be increased (closer to one). A disadvantage of DTI is that it is difficult to assess the diffusion patterns in regions where there are crossing fibres. This can lead to difficulties in interpreting the DTI measures of FA and MD. Additionally, since DTI uses fast echo planar imaging to acquire sufficient data, it is sensitive to artefacts such as distortion and eddy currents (98). These can be anticipated and compensated for during acquisition (e.g. by using field maps) and analysis (e.g. by using motion correction).

Diffusion Tensor Imaging data can be analysed using region of interest analysis. However, similar to use with T1-weighted imaging this has the disadvantage that a pre-defined region of interest is required, making it dependent on the operator and potentially failing to identify significant changes outside or only covering part of these regions. Another option is to use tractography; this provides the ability to reconstruct white matter tracts based on their direction and orientation. However, yet again user bias is a possibility as the operator needs to start by defining a seed or target region (99, 100). Voxel based analysis can be used to investigate white matter diffusivity, but is limited by confounding factors related to image registration and spatial smoothing of the data (101). A further option, and the one chosen for this study, is tract based spatial statistics (TBSS), a powerful, yet relatively conservative analysis tool for use with DTI (101). This technique assesses white matter integrity globally,

comparing voxel [1] by voxel differences across 'skeleton tracts' of the whole brain. It projects all participants' FA data onto a mean FA skeleton tract before applying voxelwise statistics. This approach ensures that values from the centre of the tract are compared between participants, therefore minimising the effects of misalignment and making it a more robust tool compared to other approaches, such as voxel based analysis (101). .

1.5.2 Epidemiological approaches

Epidemiology uses quantitative methods to study the distribution and determinants of disease in human populations (102). This provides information about the frequency, aetiology, and prognosis of a disease, informing strategies for prevention. Epidemiological studies focus on defined populations, based on e.g. geographical region, occupation, or disease status. Studies can be purely descriptive, exploring the patterns of disease or risk factors in a population using a case-control or cohort approach, either cross-sectionally or longitudinally. Alternatively, they may be analytical, either observing associations between risk factors, or observing the effect of an intervention.

Case-control studies are used to estimate the relative risk of disease associated with a given exposure. This is a particularly useful study design when the cases are relatively rare, since it allows retrospective identification of cases, which can be matched with controls. The validity of such a design relies on accurate identification of cases and controls (who are representative of an identified population from which the cases arise), accurate assessment of the exposure variable, and the ability to control for confounding factors. In a case-control study, comparability of cases and controls is crucial. For this reason the sample may focus on a complete population sample, or a random sample of a population, termed a 'population-based case-control study' (103). Alternatively, cases and controls can be drawn from a cohort study (a 'nested case-control study'). This has the advantage of ensuring that controls are drawn from the same population from which the cases arise.

[1] A voxel represents a unit of three dimensional volume. A three-dimensional object such as the brain can be divided into voxel units using a grid pattern, allowing comparison between subjects and groups.

A cohort study can be used to investigate the relationship between an exposure and the development of disease. It focuses on a defined sample (e.g. by population, geography or occupation) that is identified at the outset. Each participant is classified as exposed, or not exposed to a risk factor; follow-up assesses further exposure to this risk factor and the effect on incidence of a disease or outcome variable. The cohort can be identified prospectively and followed for several years, or defined retrospectively and followed up using previous records. Prospective identification allows the outcome to be defined and detected accurately using a systematic protocol, and is likely to be the best substitute where a true experiment is not possible (103). Data can be collected that may not be readily available in a participant's medical records (e.g. someone without hypertension is unlikely to have regular primary care records of blood pressure). The disadvantage of this type of study is the length of time over which studies take place, especially if there is a time lag between the risk factor (e.g. smoking) and the outcome (e.g. lung cancer). This has significant cost implications for the running of a study, and from a scientific perspective risks exposing the sample to potential bias through differential drop-out related to the exposure of interest. A further issue is that the variables of interest need to be clearly defined at the outset, and cannot be added or amended later. Retrospective cohort studies can be quicker to undertake, making use of data that has been previously collected. However, the reliance on previous data collection may limit the scope of the investigation, and may impair data accuracy since information pertaining to risk factor exposure and disease outcome may not be standardised.

In contrast to case-control and cohort studies, observational and experimental studies offer the possibility of intervening to change outcomes, for example, to establish the effects of interventions (103). Observational studies involve observing outcomes in patients who are, or are not, exposed to a specific variable. Similar to cohort studies, the advantage of observational studies is the ability to systematically collect data studying a range of risk factors; on the other hand, the disadvantage is that the risk of bias within different groups will lead to incorrect interpretation of results. In experimental studies, or clinical trials, selection of participants, treatment groups, follow-up and measurement of outcomes are all highly controlled, allowing careful investigation of the effect of treatment (103). The advantage of this rigorous methodology is that it is most likely to lead to conclusive results, provided a representative sample has been used. The disadvantages are the cost and logistics of organising such a study, and the potential for bias and confounding factors when dealing with a large number of people.

The Whitehall II Study follows an occupationally based cohort of civil servants; it is an observational, prospective cohort study in which risk factors are measured, and associations between risk factors and outcomes analysed (104). This study design is well suited to the present investigation of depression and vascular disease because it uses measurable outcomes that have an impact on health, and are informative of strategies to prevent disease and develop health policy (102). Depression and vascular disease are both complex conditions correlated with a range of biological, psychological and social factors; use of a well characterised epidemiological cohort such as Whitehall II enables investigation of their multi-factorial aetiology, and the bi-directional relationship between conditions. There are several reasons why depression and vascular risk factors lend themselves to this population approach. Firstly, risk factors leading to depression and cardiovascular disease have a significant impact on health, and can be measured and quantified. Secondly, risk factors may be present for a long time and the use of longitudinal methodology helps to determine the cumulative effect on outcome. Thirdly, depression and vascular diseases are both common conditions with a high prevalence, so they will be represented within a general population. Of interest from an epidemiological perspective is that the conditions will be present with a range of severity, allowing investigation of a spectrum of risk factors and outcomes.

1.5.3 Combined MRI and epidemiological approaches

There are a number of longitudinal population cohort studies with an observational, prospective design that investigate depression and vascular risk factors (105), but fewer studies that combine these data with MRI measures. Other cohort studies investigating depression using MRI include the Cardiovascular Health Study, Framingham Study, LADIS Study, Rotterdam Study and Three-City Study (106-112). In terms of diagnosing depression, most other epidemiological studies measure depressive symptoms according to the Centre for Epidemiological Studies Depression rating scale (CES-D), using either the standard 20 item version, or short 10 item version (106-108, 110-112); some studies additionally report use of antidepressant medication (107, 108, 110-112). The Rotterdam Study adopts a comprehensive approach to diagnosis of depression: participants scoring as CES-D cases undergo a more detailed assessment using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview, and in addition, medical records are searched (110, 111).

There are similarities between the Whitehall Imaging sub-study and these previous studies – for example, data is available on a similar range of cardiovascular risk factors and measures of

depressive symptoms. Compared with previous studies, the present study has the advantage of a particularly detailed characterisation of participants over a long follow-up period (28 years), combined with an MRI protocol that includes structural and functional methods using a higher strength (3 Tesla) scanner (106-112).

1.6 Summary

Depression is common and can have a significant adverse effect on individuals and their families. It has a multi-factorial aetiology based on biological, psychological and social factors. In those over 60 years old, depression is associated with cardiovascular disease, brain abnormalities and cognitive impairment. Relatively little is known about the effects of long-term exposure to vascular risk factors, and whether or not these lead to the development of depressive disorder and depressive symptoms. Combined imaging and epidemiological approaches provide a powerful tool with which to investigate the vascular aetiology of depression, offering potential insights into the long-term effect of vascular risk factors on clinical outcome, as well as on brain structure. Use of multi-modal MRI enables subtle effects on grey and white matter to be carefully considered.

Chapter 2. Review of MRI in relation to vascular risk and depression

2.1 Introduction

Chapter 2 provides a more detailed introduction and literature review of the key areas of investigation in this thesis. It focuses on vascular risk and depression, the MRI correlates of vascular risk factors and the MRI correlates of depression. This literature review will be used to highlight the gaps in current research in order to develop a rationale for the aims and hypotheses in this thesis, which will be described in Chapter 3.

2.2 Vascular risk and depression

Clinical observations that cardiovascular diseases including stroke and myocardial infarction, lead to an increased risk of depression were important in the development of the 'vascular depression hypothesis' (113, 114). This hypothesis proposes that vascular diseases may predispose to, precipitate or perpetuate depression. Older people, who are more likely to have vascular disease and multiple vascular risk factors, are particularly vulnerable (24). There may be a number of social and psychological factors which could explain the association between vascular disease and depression. However, the discovery that these relationships were bi-directional, and that elevated vascular risk factors (even in the absence of vascular disease) may also increase the risk of depression, strengthened the argument that vascular risk factors are an important component in the aetiology of depression.

A recent meta-analysis of cohort and case-control studies has provided a useful review of vascular risk factors and depression in later life (74). While individual studies investigating vascular risk and depression showed mixed and inconsistent results, overall the meta-analysis found that smoking, diabetes, cardiovascular disease and stroke were associated with increased risk for depression (Table 4). For diabetes, cardiovascular disease and stroke, some studies controlled for the effects of chronic illness; while controlling for this attenuated the effect-size, it still remained statistically significant. Other vascular risk factors including hypertension, dyslipidaemia and the Framingham Stroke Risk Score (FSRS) were not associated with a statistically significant increased risk of depression (Table 4) (74). This suggests that current vascular disease may be more important in the development of depression than generic vascular risk factors, or that depression may be related to severity of vascular disease

rather than to isolated cardiovascular risk factors. Alternatively, it may not be vascular disease itself which leads to depression, but rather a non-specific effect of being diagnosed with a serious progressive disease, such as cancer, arthritis, or neurological disorder. This possibility forces attention onto a consideration of alternative mechanisms leading to depression. For example, what is the effect of on brain structure and function, and what is the final common pathway (if any) leading to depression? In addition, do vascular risk factors increase vulnerability to depression, or are other precipitants needed in order for the clinical symptoms to develop?

From an epidemiological perspective, longitudinal follow-up of over 5000 participants in the Whitehall II cohort study found that diagnosed vascular disease was associated with an increased risk for depressive symptoms (odds ratios 1.5-2.0) (115). In this study, amongst participants without manifest vascular disease at baseline, none of the cardiovascular risk prediction scores in middle age were significantly associated with new-onset depressive symptoms in those aged over 65 (odds ratios 0.8-1.2) (115). Epidemiological studies are, however, limited by the lack of clinically-defined measures of depression, and this limitation may contribute to the discrepancy between case-control and prospective cohort studies.

Table 4. Vascular risk factors for depression
Adapted from Valkanova and Ebmeier, 2012 (74) with the authors permission

	Number of studies	Odds Ratio*	95% CI	p-value	Heterogeneity		
					Q	p	I^2
Hypertension	14	1.14	0.94 to 1.40	0.19	32.7	0.002	60.3
Dyslipidaemia	10	1.08	0.91 to 1.28	0.40	15.3	0.08	41.0
Framingham Stroke Risk Score	5	1.25	0.99 to 1.57	0.06	7.2	0.12	44.6
Smoking	10	1.35	1.00 to 1.81	0.05	27.1	0.001	36.5
Diabetes	15	1.51	1.30 to 1.76	<0 .001	18.7	0.18	25.0
Diabetes †	5	1.46	1.14 to 1.86	0.003	6.3	0.18	36.5
Cardiovascular disease	10	1.76	1.52 to 2.04	<0 .001	12.1	0.21	25.7
Cardiovascular disease †	6	1.40	1.08 to 1.80	0.01	10.6	0.06	53.0
Stroke	10	2.11	1.61 to 2.77	<0.001	21.9	0.01	58.9
Stroke†	5	1.80	1.24 to 2.62	0.002	7.3	0.12	45.4

* Pooled random-model odds ratio
† Studies which control for the effects of chronic illness

Blood pressure

In their meta-analysis Valkanova and Ebmeier (2013) (74) identified 14 studies comparing the prevalence or incidence of late-life depression in people with and without hypertension (116-129). When combined, these studies showed that there was no significant association between hypertension and increased risk of depression. However, other studies have found an association, and population studies demonstrate that patients with major depressive disorder have a higher prevalence and incidence of hypertension compared with the general population (130). In a large cross-sectional population study, people with controlled hypertension had an increased risk of depression (131). This effect was mediated by an increased burden of vascular disease, and not necessarily related to hypertension. Mid-life hypertension has been associated with depressive symptoms in late life, particularly in those with blood pressure variability (132). Although hypertension may be a marker of cardiovascular disease this could also suggest that it is variability in blood pressure which is important; hypotension, as well as

hypertension, could also lead to structural and functional brain changes. Finally, hypertension is an important component of risk prediction models that seek to identify individuals at risk of post-stroke depression (133). Therefore, there is conflicting evidence for the relationship between hypertension and depression, and this is a key vascular risk factor that warrants further investigation.

Cholesterol

A meta-analysis did not support an association between dyslipidaemia and increased risk of depression in the ten studies identified (74). This finding is disputed in a more recent single study (134). However, an investigation of 3564 people recruited through the Rotterdam study found no association between atherosclerosis and incident depressive disorder (135). This was a longitudinal study with a six-year follow up and the results support the theory that depression itself may contribute to vascular disease, rather than vice versa. In addition, a study of 5000 participants from the Gutenberg Health Study found no association between atherosclerosis (measured by intima-media thickness and carotid plaques) and depressive symptoms, again failing to support the vascular depression hypothesis (136). Taking these studies together, the relationship between atherosclerosis and dyslipidaemia as risk factors for depression seems doubtful. It is likely that there are complex mechanisms linking these two conditions, including dysfunction in the autonomic nervous system and the hypothalamic-pituitary axis as well as underlying vascular causes promoting chronic inflammation, endothelial dysfunction and platelet activation and aggregation (137). Given that there are relatively few previous studies in this area, this common risk factor would benefit from further investigation, utilising prospective data from the Whitehall II study to fully investigate longitudinal associations with depression.

Diabetes

There is likely to be a bi-directional relationship between depression and diabetes, but the exact mechanisms are unclear and a relative lack of longitudinal studies makes it difficult to confirm causality. Meta-analysis of 15 studies supports an association between diabetes and depression (74), however, only five of these studies adjusted for the effects of chronic illness. Depression is twice as common in people with type 2 diabetes compared to controls, and even pre-diabetes is associated with a small but significant association with increased rates of depression (138, 139). The association could be mediated by vascular changes, by the

psychological effects of living with a chronic disease, or by the effect that depression has on an individual's ability to monitor and manage a chronic disease.

Smoking

Smoking increases the risk of developing depression (74) (Table 4). There are several theories of how this effect might be mediated. For example, it may be that smoking causes increased atherosclerosis, thus increasing vascular risk and leading to depression. If this is the case it is an important modifiable risk factor for depression. However, the association may be due to confounding factors related to smoking, for example shared genetic risk (140) or environmental factors. Alternatively, some longitudinal studies have shown a direct causal link between smoking and depression (141, 142).

Framingham Stroke Risk Score

Framingham Stroke Risk Score has been associated with incident depressive symptoms in one study (127). In a further study, although FSRS was associated with depressive symptoms after one year of follow-up, this result became non-significant after controlling for medical co-morbidities (143). Other studies have not supported an association between depressive symptoms and FSRS (115, 117, 144), and overall it seems unlikely that there is an association between this composite risk score and depressive symptoms or disorder (74).

Coronary heart disease

Cardiovascular disease increases the risk of major depressive disorder (74) (Table 4). Single cardiovascular events such as myocardial infarction increase the risk of depression, and people who develop depression following myocardial infarction have an increased risk of all-cause mortality and cardiovascular events (114). There is also a modest association between lifetime coronary artery disease and major depression (odds ratio 1.3) (26), with evidence to suggest that lower cardiovascular fitness at age 18 is associated with an increased risk of depressive disorder in adulthood (145). Young people with a family history of depression, but no personal history of depression show altered cardiovascular risk profiles even in the absence of depressive symptoms, suggesting that vulnerability to vascular risk and depression starts many years before clinical symptoms become apparent (146). Given that there is substantial evidence linking coronary heart disease and depression, it is surprising that atherosclerosis does not appear to increase the risk of incident depression in older adults (135). This places

doubt on the nature of the common pathway linking these conditions. If it is not related to pathophysiology, its effects could be mediated through other psychological or social factors; alternatively it could be due to shared risk factors for cardiovascular disease itself, and not for atherosclerosis. A further reason for doubting the association between cardiovascular disease and depression is that the persistence and recurrence of depressive symptoms is not influenced by the presence of cardiovascular disease (147).

The predictive association of CHD with major depression is much stronger than that of depression with CHD (26), although depression is associated with an increased risk of myocardial infarction and cardiovascular disease (148, 149). It is possible that the relationship between these conditions is bi-directional, and even mutually re-enforcing (28, 150). A meta-analysis of longitudinal cohort and case-control studies of depression and cardiovascular diseases suggests that depression may be an independent risk factor for cardiovascular diseases (151). There was substantial heterogeneity between studies, especially for those including participants with depressive symptoms.

2.3 MRI correlates of vascular risk factors

If vascular disease and risk factors lead to increased risk of depressive disorder, it is plausible that changes in brain structure and function may mediate this association. This section reviews research on the MRI brain changes associated with vascular risk factors and diseases to explore the evidence related to this hypothesis.

Blood pressure

There have been relatively few studies considering the effect of hypertension on brain structure within non-clinical populations. There is some evidence that older, hypertensive subjects have smaller whole-brain volumes compared to normotensive individuals (152), and possibly an increased rate of whole-brain atrophy (153). In addition, subjects with untreated, raised blood pressure may have an increased risk for hippocampal atrophy (154, 155), although this is not a universal observation (152, 156). Hypertension also seems to be linked to age-related white matter changes, (157, 158) increased white matter lesion load (159-161), increased white matter hyperintensity volume (153, 162, 163) and reduced white matter integrity (164-167). However, these associations continue to be debated because of several shortcomings in the evidence: many studies are based on cross-sectional data (158, 162, 164)

or with short follow-up periods (155, 168); use small samples (166) or younger subjects with, due to their age, limited exposure to the effects of hypertension (164, 165); ignore the potential effects of antihypertensive drug treatment (152, 159, 162); use low-resolution MRI (159), without a fully automated MRI analysis technique (154), or focus only on white matter (157).

Dose-response patterns provide support for a causal association, but few studies have examined whether a longer exposure to hypertension is associated with greater changes in brain structure. Hypertension in mid-life is related to thinner cortex in several brain areas, including insular, frontal, and temporal cortices nearly 30 years later (169), a well as increased rate of progression of vascular brain injury, global atrophy and hippocampal atrophy (160). In a four year longitudinal study, subjects with hypertension at baseline had a significantly increased risk of severe white matter hyperintensities at follow-up (170). There is evidence that the effects of systolic blood pressure on white matter integrity are present even in young adults (164), and use of longitudinal data on hypertension, such as that available through the Whitehall II Study is therefore important to fully understand this association.

Cholesterol

Some studies have identified an association between reduced HDL levels and grey matter volume reductions in temporal regions (171) and the hippocampus (172). However, this is not a well-replicated finding: a further study found an association with hippocampal volume reductions in men but not in women (173), with other studies finding no association between grey matter volume and HDL cholesterol (174, 175). Cortical thickness has been used to investigate changes in global grey matter volume, and in a population sample of elderly people high HDL levels were associated with decreased cortical thickness (176). This finding contrasts with previous studies, and given that higher HDL levels are thought to be beneficial for cardiovascular health, is somewhat unexpected.

White matter hyperintensity volume is not generally associated with LDL cholesterol levels (177); however, increased HDL cholesterol and decreased LDL cholesterol are associated with progression of white matter lesions on serial MRI scans (178). One study reports that dyslipidaemia is associated with a lower risk of small vessel disease identified through MRI brain scans; however, this study did not account for the effects of medication, which are likely to significantly affect the results (179).

Familial hypercholesterolaemia is associated with increased white matter lesions and investigation of this patient group has provided further insights into the effect of dyslipidaemia on brain white matter. People with familial hypercholesterolaemia on high dose statin therapy are much less likely to develop increased white matter changes (180), even when plasma cholesterol levels remain high (181). This suggests that treatment can be effective in reducing the effect of raised cholesterol on the brain, but the fact that structural brain changes can be ameliorated even when plasma levels stay high indicates that the relationship between raised cholesterol and brain structure is far from straightforward.

Metabolic syndrome (comprising at least three of the following: hypertension, hyperglycaemia, hypertriglyceridemia, low HDL levels and central obesity) is associated with microstructural abnormalities in white matter, particularly in the frontal lobe (182). Research using neuropathological techniques supports an association between atherosclerosis and microvascular changes in frontal white matter (183). However, it still remains unclear to what extent this relationship is driven by dyslipidaemia rather than other vascular risk factors. In view of the findings described above, is seems more likely that the association is strongly influenced by hypertension rather than by dyslipidaemia.

There is a strong association between dyslipidaemia and cardiovascular disease. However, the relationship with cerebrovascular disease is disputed, and there is no clear consensus about the association between dyslipidaemia and MRI structural changes. The relationship is complicated by the protective and adverse effects of different types of cholesterol which lead to reduced and increased cardiovascular risk, respectively. It is further complicated by the widespread use of medication, and the confounding effects of multiple vascular risk factors. Finally, while dyslipidaemia may contribute directly to cerebrovascular pathology, its effects could be mediated through other factors, such as inflammation. If the relationship is indirect it may explain some of the discrepant results in the literature.

Diabetes

Cortical atrophy, hippocampal atrophy and increased ventricular size are more common in patients with type 2 diabetes mellitus, compared to controls (175, 184-191). Hippocampal atrophy is also found in people with elevated fasting blood glucose that does not meet the criteria for diabetes, suggesting that metabolic and vascular changes are a causal component of hippocampal atrophy (192). It is likely that macrovascular and microvascular factors (e.g.

fasting serum glucose and duration of hyperglycaemia) contribute to the extent of brain atrophy (193). Atrophy is more prominent in type 2, rather than type 1 diabetes, likely owing to the characteristics of patients with type 2 diabetes, who are older and have increased rates of co-morbidity, macrovascular disease and reduced insulin sensitivity (62). Type 2 diabetes is an independent risk factor for medial temporal lobe atrophy (156). However, observations from a longitudinal cohort found evidence for a causal relationship between alterations in glycaemic control and blood pressure, and subsequent brain ischemic and atrophic changes (194).

Although diabetes is related to increased brain atrophy, there is conflicting evidence about whether this is independent of depression and other vascular risk factors (195, 196), or exacerbated in those with depression in addition to diabetes (197). Those with diabetes have increased rates of cognitive decline (198, 199) and an increased incidence of dementia (200, 201). Accelerated cognitive decline in patients with type 2 diabetes is associated with progressive changes on brain MRI, including global atrophy and vascular damage (202).

White matter lesions and microstructural abnormalities in white matter tracts, thought to be due to vascular risk factors, are increased in people with type 2 diabetes (62, 187, 188). Deep white matter lesions are more common than periventricular lesions in patients with type 2 diabetes (203). However, despite biological plausibility, there have been a number of negative studies, and the relationship between type 2 diabetes and white matter lesions remains unresolved (189, 190).

Smoking

MRI studies have demonstrated significant grey matter abnormalities in cigarette smokers (204, 205) including ventricular enlargement, generalised atrophy, reduced grey matter density and sulcal enlargement (206-208). In a longitudinal study of cognitively intact adults (mean age 76 years), smokers showed greater atrophy in multiple brain regions (209). The prefrontal cortex, left dorsal anterior cingulate cortex, right cerebellum and corpus callosum are particularly affected (206, 210, 211). There is cross-over in the brain regions affected by smoking and those affected in early Alzheimer's disease (212). These structural changes may, therefore, explain why smokers show cognitive changes including impaired executive function, verbal learning, processing speed and working memory (205). On stopping smoking, grey matter volumes in regions related to habit learning and visual processing can increase, but

those related to long-term memory do not change (213). The length of smoking history, and number of cigarettes smoked contributes to grey matter changes and both are independent risk factors for MRI-defined small vessel disease (214). Smoking greatly increases the risk of cerebral and cardiovascular events in people aged over 75 years (215).

Smoking is associated with white matter changes with some, but not all, studies reporting greater periventricular white matter hyperintensities in smokers (204, 216). More recently, there has been a greater focus on the effect of smoking on white matter microstructure. A small case control study (n=20) showed that smoking is associated with reduced micro-structural integrity in white matter within the body and splenium of the corpus callosum (217). Smokers also show abnormal white matter integrity in the anterior corpus callosum, which is related to the duration of smoking (218).

Functional MRI studies have been used to demonstrate that smokers show greater activation than controls in regions linked to attention and motivation, in response to smoking related cues (216, 219, 220). The intensity of smoking craving is correlated with activation in frontal regions including the orbitofrontal cortex, dorsolateral prefrontal cortex and cingulate gyrus (216). The anterior and posterior cingulate cortex, medial and lateral orbitofrontal cortex, ventral striatum, amygdala, thalamus and insula are involved in the maintenance of smoking and nicotine withdrawal (221).

Smoking seems to be associated with reduced grey matter volumes, reduced white matter integrity and functional brain changes related to attention and motivation. The majority of studies in this field are small, and many are cross-sectional. However, longitudinal data is important, since length of exposure makes a difference to MRI measures.

Framingham Stroke Risk Score

There is a limited literature investigating the MRI correlates of the FSRS in otherwise healthy individuals. However, two studies arising from the Framingham study itself suggest that elevated FSRS is associated with reduced total cerebral brain volume (222) and increased total white matter hyperintensity volumes (223).

Coronary heart disease

Coronary heart disease has a major effect on the cerebrovascular system and the brain is an important end organ of cardiovascular disease (48). A history of CHD indicates significant atherosclerosis, which would be expected to affect the cerebrovascular system. Indeed, cortical grey matter changes, increased silent brain infarcts and increased white matter hyperintensities are all commonly associated with CHD (224, 225). Extensive white matter hyperintensities are particularly associated with symptomatic vascular disease (226). People who already have substantial white matter disease before a cardiovascular event would be expected to have a worse prognosis than those without established cerebrovascular changes prior to cardiovascular event (227). CHD and vascular risk factors may also have an effect on cerebral blood flow and vascular reactivity. One study found that the Framingham Cardiovascular Risk Profile was negatively correlated with vasoreactivity to hypercapnia (228). This suggests that elevated vascular risk is associated with changes in blood flow and reactivity throughout the cortex, and in the hippocampus in particular. This, and other studies have helped to highlight the links between CHD, altered brain structure and cognitive impairment (160, 229).

2.4 MRI correlates of depression

Magnetic resonance imaging has been used to investigate depression, particularly late-life depression where structural brain changes may be more common compared to depression with onset at younger ages. This section reviews the previously published literature which used MRI to identify structural changes in those with depressive symptoms and depressive disorder. This review of the literature provides the background to the development of the hypotheses pertinent to this thesis.

Grey matter

Depression is characterised by reduced grey matter brain volumes in areas involved in emotional processing and memory, including the frontal cortex, orbitofrontal cortex, subgenual cingulate cortex, hippocampus and striatum (38, 230-233). In late-life depression, grey matter abnormalities tend to be more widespread, and many studies report volume reductions in the orbitofrontal cortex, amygdala, hippocampus, putamen, and thalamus (36, 52, 234). In older subjects even sub-threshold depressive symptoms have been associated with frontal-temporal volume reductions (235). While many studies find widespread changes in

grey matter, some case-control studies of late-life depression find no differences in grey matter volumes (16). Differing imaging methodology and analysis, as well as variations in current symptoms, may explain the conflicting results. Overall, previous studies support the notion of regional grey matter reductions in depressive disorder in areas related to emotional processing and memory. The latter is of particular interest in late-life depression as this may explain the association with cognitive impairment and increased risk for the development of dementia (236).

White matter

Cross-sectional analyses show that increased white matter hyperintensity volumes are found in people with unipolar depression (230). This finding is well replicated in older people, with several studies finding that white matter hyperintensities in frontal and temporal regions are correlated with late-life depressive symptoms (237-239). Late-life depression is characterised by more frequent and severe white matter abnormalities, compared to early-onset depression, suggesting that aetiology may differ depending on age at onset (240). Given that white matter hyperintensities can be ischaemic in origin, these studies offer support for the theory that vascular disease and risk factors are more likely to contribute to the development of depression later in life (40, 41, 241). Deep white matter hyperintensities (affecting the frontal-subcortical circuits), rather than periventricular white matter hyperintensities, are more important in the aetiology of late-life depression (39, 41, 242).

The longitudinal data on white matter hyperintensities and depression are less consistent, with some studies showing that the progression of white matter hyperintensities is greater in those with depression at baseline (239), and others finding that baseline depressive symptoms, development of depressive symptoms and greater duration of depressive symptoms do not have an impact on white matter hyperintensities (240, 243, 244). The relationship between white matter hyperintensities and depressive symptoms therefore remains uncertain.

Imaging data on white matter hyperintensities has helped to support the vascular depression hypothesis. However, these use visual ratings that give an indication of lesion severity, but do not quantify lesion load precisely, and also lack anatomical specificity. The advent of more sophisticated techniques to investigate white matter structure (e.g. DTI using Tract Based Spatial Statistics) has provided tools which are more sensitive and better suited to detecting and quantifying subtle structural differences and their location (245). In meta-analyses of DTI

studies of affective disorders, reduced FA within frontal and temporal lobes is a consistent finding (246, 247). This suggests that abnormalities within white matter tracts connecting the pre-frontal cortex within cortical and subcortical areas underlie the network dysfunction in major depressive disorder (246, 247). In major depressive disorder, as well as late-life depression, white matter integrity is widely reduced within the limbic system, frontal cortex and the thalamus, when compared to controls (16, 245, 248). Changes in white matter integrity are evident in major depressive disorder and are associated with increasing severity of depressive symptoms (249).

2.5 Limitations of published research related to vascular risk, depression and MRI

There is a good deal of evidence for the vascular depression hypothesis. However, individual studies continue to show inconsistent results, particularly in relation to vascular risk factors such as hypertension and dyslipidaemia. It is surprising that there is limited evidence in support of these risk factors, because if micro-vascular changes are relevant to depression then these may represent common pathways by which CHD, diabetes and stroke exert their effects. Vascular risk factors therefore warrant further investigation, particularly to consider whether they may affect brain structure, and thereby predispose to increased vulnerability to depression.

Many studies considering vascular risk and depression are cross-sectional, or based on only a short follow-up period. This means that it is not possible to distinguish between short-term and long-term exposure to vascular risk factors. This approach may underestimate the association with vascular risk factors and depression, which would be expected to have a cumulative effect on the risk of depression if present over a period of years. While some results indicate that current vascular disease may be more important in the aetiology of depression than previous disease, only the use of prospective, longitudinal data is capable of measuring the cumulative effect on depression and brain structure. Many studies have focussed specifically on patient groups; by contrast, the use of a prospective cohort such as the Whitehall II Study offers the valuable opportunity to consider the effects of vascular risk factors amongst a population sample, rather than a sample specifically selected for depression, or cognitive impairment.

There are relatively few studies focussing specifically on the MRI correlates of vascular risk factors, partly because of the difficulty in controlling for confounding variables. It seems important to fully understand the effect and contribution of vascular risk on brain structure and function before drawing conclusions linking vascular risk and depression. Thorough investigation of the MRI correlates of vascular risk factors might confirm that there are anatomical changes underlying the association, or (if these are absent) stimulate investigation into alternative mechanisms.

Few studies have used data on vascular risk and depression collected across the adult life-course, in conjunction with high-resolution MRI. Many MRI studies utilise small sample sizes, and are cross-sectional in nature, without robust longitudinal data. Some studies of depression utilise a clinical diagnosis, whereas many measure depressive symptoms only, which may or may not equate to a clinical diagnosis. One strength of the present study using participants from the Whitehall II cohort study is the opportunity it affords of comparing DSM-IV diagnosis of depression with use of rating scales for depressive symptoms, to investigate whether both are identifying similar neurobiological changes through structural and functional imaging.

2.6 Summary

There may be a bi-directional relationship between vascular risk and depression, with the strongest evidence for associations with cardiovascular disease, stroke, smoking and diabetes. These effects are most evident in late life. There are inconsistent results for other vascular risk factors including hypertension and dyslipidaemia, and their associations with depression, and these warrant further investigation. The mechanisms linking vascular disease and depression are still unclear; use of neuroimaging would allow investigation of changes in brain structure to determine both risk and resilience factors.

There have been relatively few studies focussing on the effects of individual vascular risk factors on brain structure. There has been most investigation of hypertension and smoking, with studies suggesting that these factors are associated with increased whole-brain atrophy, regional atrophy and white matter changes. There are more studies considering the effects of diabetes, stroke and CHD on brain structure, but apart from a few large trials, these are limited by being largely cross-sectional, or of limited longitudinal duration.

There is a wide range of literature describing the MRI correlates of depression, which include reduced grey matter volumes in areas involved in emotional processing and memory, and white matter changes. Depression is associated with increased white matter hyperintensities and reduced white matter integrity, particularly in frontal-limbic regions.

Chapter 3. The present study

3.1 Study aims

The principal aim of this study is to explore the vascular aetiology of depression and depressive symptoms using neuroimaging and epidemiological methods. This combined approach addresses important limitations in previous studies (for example, cross-sectional designs with short-term exposure to vascular risk factors and low-resolution MRI, or lack of sophisticated analysis techniques) by analysing a large data-set of (3 Tesla (T)) MRI scans with sophisticated analysis measures, and combining this with high-quality cross-sectional and prospective longitudinal data collected over a 28-year period, relating to depression and vascular risk. Participants included in this study are recruited from the Whitehall II Study conducted at University College London (UCL) and represent the first phase of the Whitehall Imaging sub-study being conducted at the University of Oxford. Given that all participants are over the age of 60, where depressive symptoms and cardiovascular disease are common but rates of dementia and frailty remain low, this represents an ideal window of opportunity to explore the vascular aetiology of depression.

3.2 Study objectives and hypotheses

The objectives of this thesis are to examine the following questions:

1. Are long-term vascular risk factors associated with changes in grey and white matter brain structure?
2. Are current and previous depressive symptoms associated with changes in grey and white matter brain structure?
3. Are there common MRI correlates for vascular risk and depression that could explain the mechanisms linking these conditions?
4. Do long-term vascular risk factors lead to increased risk of depressive disorder (defined using DSM-IV criteria) and depressive symptoms (defined using CES-D)?

An additional focus for this thesis consists of two methodological elements. First, to compare visual and automated MRI analysis techniques, to consider whether visual techniques can be useful in quantifying structural brain changes in an epidemiological sample over the age of 60, and used to distinguish mood-related structural brain changes. Second, to compare whether depression diagnosed using a self-reported rating scale, and DSM-IV criteria have similar

underlying anatomical correlates. If these are similar, this would strengthen the rationale for using self-reported measures to diagnose depression in the context of epidemiological studies.

Following the literature review in Chapter 2 the study hypotheses are as follows:

1. Visual rating scales for global atrophy, hippocampal atrophy and white matter hyperintensities can provide objective and reliable measures of brain structure in this cohort.
2. Visual and automated techniques can be cross-validated and used to distinguish structural brain changes and cognitive changes in an occupationally-based sample.
3. Long-term exposure to vascular risk factors (hypertension, dyslipidaemia, diabetes, smoking and Framingham Stroke Risk Score) are associated with reduced grey matter volumes and reduced white matter integrity particularly in frontal-subcortical regions.
    a. White matter brain changes are more pronounced than grey matter changes.
    b. Specifically, diabetes, smoking and coronary heart disease will have the most significant effects on brain structure; dyslipidaemia the least. Hypothesis generation is more difficult for hypertension and FSRS due to inconsistencies in previous findings and the limited previous studies (see Chapter 2).
4. Depressive symptoms and depressive disorder are associated with reduced grey matter volumes (e.g. in the hippocampus) and reduced white matter integrity, particularly in frontal-subcortical regions.
    a. Correlations with brain structure will be more pronounced in those with persistent depressive symptoms.
5. Common brain structures are affected by exposure to long-term vascular risk factors and to depressive symptoms.
6. Long-term exposure to vascular risk factors is associated with increased prevalence of depressive disorder and depressive symptoms, in accordance with the vascular depression hypothesis.

3.3 Summary

Compared to previous work, the advantages of the present study are the use of a large sample size, with 28 years of prospective data over the adult life-course relating to vascular risk factors and depressive symptoms, coupled with high resolution, multi-modal imaging. This will enable exploration of the hypotheses that vascular risk factors and disease are associated with MRI brain changes, and that depressive symptoms and depressive disorder are associated with MRI brain changes. This will ultimately allow the identification of common structural MRI correlates between depression and vascular risk.

Chapter 4. Whitehall Imaging sub-study: methods

4.1 Introduction

The ongoing Whitehall Imaging sub-study, based at the University of Oxford, is recruiting 800 participants who are already enrolled in the Whitehall II Study, UCL. Recruitment and participant testing for this sub-study will take place over a four year period (2012 – 2016) with participants having detailed characterisation of brain and behavioural measures underlying cognitive and physical functioning in ageing. This thesis is based on phase 1 of the Whitehall Imaging sub-study which recruited over 200 participants in the period April 2012 – June 2013. Chapter 4 describes how these participants were recruited, introduces the study protocol, and outlines the study measures which are relevant to investigation of vascular risk and depression used later in this thesis.

The overall aim of the Whitehall Imaging sub-study is to explore the brain-related factors linked to risk and resilience in ageing, and common mental disorders in late-life. This will be achieved by combining longitudinal, prospective data collected over 28 years, with high-resolution MRI brain measures, detailed cognitive testing, and clinical measures. Investigations arising from this study will focus on, amongst others, depression, cognitive impairment, resilience and stress.

Utilising data obtained during phase 1 of the Whitehall Imaging sub-study, in conjunction with previous longitudinal data, this thesis explores the structural brain changes associated with vascular risk factors and depression. This will enable common MRI correlates for vascular risk and depression to be identified, in order to explore the biological mechanisms linking these conditions. There are two key methodological elements to be investigated as part of this study: first, whether clinically applicable, visual ratings are comparable with automated measures used in research; second, whether clinical measures of depression are comparable with simple depression rating scales commonly used in research.

Table 5. Summary of prospective data collected through the Whitehall II Study

Measures	**Phase 1** 1985-88	**Phase 2** 1989-90	**Phase 3** 1991-93	**Phase 4** 1995-96	**Phase 5** 1997-99	**Phase 6** 2001	**Phase 7** 2003-04	**Phase 8** 2006	**Phase 9** 2007-09	**Phase 10** 2011	**Phase 11*** 2012-13	**Oxford** 2012-13
Age range, *years*	35 – 55	37 – 59	39 – 62	42 – 64	45 – 67	48 – 70	50 – 72	53 – 75	55 – 77	58 – 80	60 – 85	60 - 82
Participants	10308	8133	8637	8629	7830	7344	6967	7180	6755	277	6035	229
Social circumstances and behaviours												
Social circumstances	x	x	x	x	x	x	x	x	x	x	x	x
Smoking, alcohol	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**	x	**X**
Exercise, sleep	x		x		x		x		x		x	x
Diet			x		x		x		x		x	x
Biological measures												
BP, BMI, waist, lipids, glucose, insulin	**X**		**X**		**X**		**X**		**X**		x	BP and BMI only
Inflammatory markers			x				x		x		x	x
Genetic material							x		x			
MRI brain scan												**X**
Health outcomes												
CHD, stroke, diabetes, cancer, mortality	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	x	**X**
Medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	x	**X**
Psychosocial factors												
Social support & work	x	x	x		x		x	x	x	x	x	x
Employment status	x		x	x	x	x	x	x	x	x	x	x
Functioning												
Questionnaire	x	x	x	x	x	x	x	x	x	x	x	x
Cognitive tests					**X**		**X**		**X**		x	**X**
CES-D / GHQ	**X**		**X**		**X**		**X**		**X**		x	**X**

* Phase 11 data were not available at the time this thesis was prepared

Measures used in this thesis are highlighted in red with a capital **X**

4.2 Participants

4.2.1 The Whitehall II study

All participants have taken part in the Whitehall II Study, UCL since 1985 (104). The Whitehall II Study is a prospective longitudinal cohort originally established to investigate the social gradient in health and disease (250). All civil servants age 35-55 working in the London offices of 20 Whitehall departments in 1985-1988 were invited to participate. The response rate was 73% and a sample of 10 308 people (6895 men, 3413 women) was recruited. Although they represent a group of people in established employment, who may have more favourable risk factor profiles and disease incidence compared with the general population, standard risk factor-cardiovascular disease associations are in close agreement with those observed in a UK-wide general population study (British Regional Heart Study) and the community-based Framingham study (251). In addition, these participants were employed in a wide variety of roles from clerical work, through to senior administration grades (salaries ranging from £7 387 to £87 620), reflecting a diverse social gradient as seen in the general population (104).

Extensive data were collected through face-to-face contact with all participants at phases 1 (1985-1988), 3 (1991-1993), 5 (1997-1999), 7 (2003-2004), 9 (2007-2009) and 11 (2012-2013); intervening phases consisted of postal questionnaires, or face-to-face contact with a smaller proportion of the total sample (Table 5). Ethical approval for this study was provided by the UCL/UCLH Committees on the Ethics of Human Research (Committee Alpha, reference: 85/0938) with written informed consent obtained from each participant at each phase of data collection.

The original focus of the Whitehall II Study was to investigate the social and occupational influences on health and illness, with data collected on a range of measures including cardiovascular risk, psychological and social functioning, and quality of life (104). Investigation of this well-characterised cohort has made an important contribution to research, as well as to national and international public health policy (252, 253). As the cohort has aged, the focus of Whitehall II has shifted from ‘stress and health’, to a study investigating normal ageing, as well as risk and resilience factors for common mental illness of late-life. The extensive prospective longitudinal data means that the Whitehall II Study is ideally placed to investigate mid-life antecedents to ageing. In particular, previous data collection regarding cardiovascular illness and risk factors means that the cohort can be used to determine whether cardiovascular

disease and risk factors result in increased prevalence of depression and greater cognitive dysfunction, and whether there is an interaction between these two outcomes. Since phase 10 (2011), all participants are over 58 years of age, providing an ideal window of opportunity to explore the association between vascular disease and risk factors, with common mental disorder in later life.

4.2.2 The Whitehall Imaging sub-study

For the Whitehall Imaging sub-study, based in Oxford, participants are recruited from phases 10 and 11 of the Whitehall II Study. Participants from Whitehall phase 10 (2011) represent an enriched sample, selected for the presence of late-onset depressive symptoms. They were identified as having normal Centre for Epidemiological Studies Depression Scale (CES-D) and General Health Questionnaire (GHQ) scores at age <60 and late-onset depressive symptoms with high scores at age ≥60 (254-257). Participants from phase 11 (2012-13) were selected at random from the whole Whitehall cohort. The Whitehall Imaging sub-study plans to recruit 800 participants over four years from 2012 to 2016. Phase 1, of the Whitehall Imaging sub-study took place from April 2012 to June 2013, with just over one quarter of the total number of participants recruited. All participants recruited during phase 1 of the Whitehall Imaging sub-study in Oxford are included in this thesis. Ethical approval for this study was provided through the Oxford NHS Research Ethics committee (Reference: 10/H0606/71) and the Central University Research Ethics Committee (Reference: MSD/IDREC/C1/2011/71).

4.3 Recruitment for the Whitehall Imaging sub-study

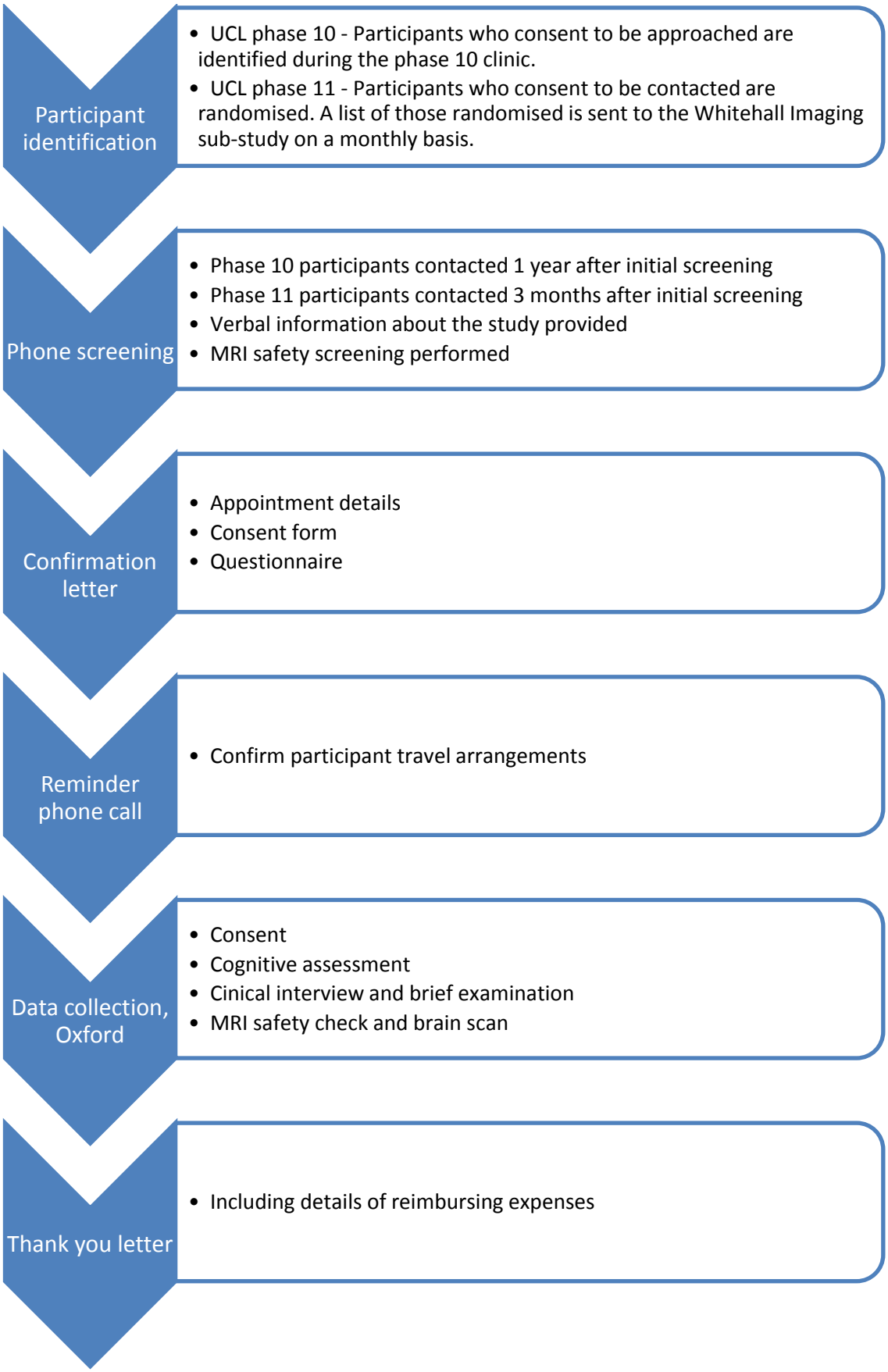
The recruitment and assessment protocol is summarised in Figure 3. During phase 10, a pilot study for the new measures due to be used at phase 11, participants gave consent to be approached by researchers to discuss an MRI brain imaging study. Participants who agreed to be approached were provided with written and verbal information about the study, gave their contact details, and were re-contacted one year later by phone. The majority of participants were recruited from Whitehall phase 11. During the phase 11 clinic participants were asked to give their consent to be contacted about an MRI brain imaging study. Those who agreed to this were randomised, and each month a list of participants was sent to the Whitehall Imaging sub-study research team in Oxford; in total a list of 1380 names was sent. This oversampling was designed to allow for those who declined to participate, or were unable to participate because safety reasons precluded participation in the MRI scan.

Where possible, participants were contacted by phone within one month of the Whitehall phase 11 visit to confirm their interest in the study, to provide them with further information about it, and to invite them to participate. An MRI safety screening was conducted by phone. As required by standard MRI safety protocols, individuals with contraindications to MRI scanning were excluded, including those with pacemakers, certain metallic implants, previous metallic injury to the eye or a history of claustrophobia. Those who agreed to participate were sent written confirmation of their appointment, a consent form, details of practicalities (e.g. travel directions) and the questionnaire. Participants were phoned a second time one or two days prior to their visit to Oxford to confirm their travel arrangements and answer any questions. Table 6 provides further detail about the number of participants identified from Whitehall II at UCL, and the numbers included and excluded up to the end of June 2013. The most common reasons for exclusions related to MRI safety concerns, or participants choosing not to take part in the MRI sub-study.

Table 6. Participant recruitment for the Whitehall Imaging sub-study 2012-2013

	Phase 10	**Phase 11**	**Total**
Number of participants, *n*			
Identified	51	1380	1431
Included	29	200	229
Excluded	22	98	120
Pending for subsequent phases of Whitehall Imaging sub-study	0	1082 - 20 phone screened, appointment offered - 15 phone screened, no appointment - 13 awaiting phone screening - 1034 will be re-contacted in 1 year	1082

Figure 3. Summary of Whitehall Imaging sub-study recruitment and assessment protocol



4.4 Data acquisition for the Whitehall Imaging sub-study

All participants were assessed at the FMRIB Centre (Functional Magnetic Resonance Imaging of the Brain, http://www.fmrib.ox.ac.uk/), University of Oxford using an assessment protocol that lasted approximately four hours. On arrival participants were asked to provide written consent. The questionnaire was reviewed with the participant to ensure it had been completed accurately. After this, basic demographic details were documented, and a detailed cognitive assessment was performed. A brief physical examination followed, taking blood pressure and heart rate, before performing a structured clinical interview. Participants were briefed about the MRI scan and the MRI safety screening was repeated prior to the scan.

4.4.1 Questionnaire

Participants were asked to complete the questionnaire (see Appendix 1) in the week prior to their visit to Oxford. This included questions in five domains: background (including education and employment), medical history, mood and life events, activity and sleep. Background information included details of past education and employment; medical history focussed on past medical history, current prescribed and non-prescribed medication, drug, alcohol and smoking history. The mood and life events section included the CES-D, which has been used previously in Whitehall II Study phases 7, 9, 10 and 11.

4.4.2 Cognitive assessment

All participants had a comprehensive cognitive assessment administered by trained psychology graduates and psychiatrists. The choice of cognitive tests was informed by a systematic review and previous experience within the Department of Psychiatry in testing participants of this age group (16, 35). Table 7 lists the cognitive tests performed, in the order they were administered. These covered the following cognitive domains: processing speed, executive function, visuospatial memory, visuospatial skills, verbal learning, episodic memory, semantic memory and language skills (Table 8).

Table 7. List of tests performed during Whitehall Imaging sub-study cognitive assessment

	Cognitive Test	Abbreviated name	Maximum score	Normal cut-off †
1.	Montreal Cognitive Assessment	MOCA	30	≥26
2.	Trail Making Test A and B	TMT A TMT B	-	-
3.	Rey-Osterrieth Complex Figure – copying	RCF Copy	36	-
4.	Category Fluency (animals)	-	-	≥11
5.	Rey-Osterrieth Complex – immediate recall*	RCF Immediate	36	-
6.	Hopkins Verbal Learning Test Revised – immediate recall	HVLT Immediate	36	≥19
7.	60-item Boston Naming Test	BNT	60	-
8.	Digit Span Forward Digit Span Backward Digit Span Sequencing	DSFW DSBW DSS	14 14 14	-
9.	Digit Coding	DC	135	-
10.	Test of Pre-morbid Functioning	TOPF	70	-
11.	Hopkins Verbal Learning Test Revised – delayed recall	HVLT Delay	12	-
12.	Hopkins Verbal Learning Test Revised – recognition	HVLT Recognition	12	-
13.	Rey-Osterrieth Complex – delayed recall*	RCF Delay	36	-
14.	Rey-Osterrieth Complex – recognition	RCF Recognition	24	-
15.	Cambridge Neuropsychological Test Automated Battery Reaction Time	CANTAB RTI	-	-

*Total score on RCF delayed and immediate recall <40 indicates impairment
† Where applicable

The *Montreal Cognitive Assessment* (MOCA) is a 30-point cognitive screening test which includes measures of executive function, verbal recall, lexical fluency (with letter F), attention and naming (258, 259). The *Trail Making Test* requires participants to "join the dots" between consecutive numbers (TMT A), and then to alternating numbers and letters (TMT B) as rapidly as possible (260, 261). In the *Rey-Osterrieth Complex Figure* (RCF), participants are asked to

copy a complex geometric design; they are asked to repeat this from memory twice more, 1 minute and 10 minutes later (262, 263). Finally, they are shown composite parts of the complex design, together with similar shapes, and are asked to recognise which components formed part of the original figure. In c*ategory fluency*, participants are asked to name as many animals as possible in 1 minute (264). For the *Hopkins Verbal Learning Test Revised* (HVLT), participants are asked to recall a list of 12 words; this is repeated 3 times (265). In the second part of the HVLT, a list of 24 words is read to the participant, and they are asked if they recognise the 12 words included in the original list. For the 60-item *Boston Naming Test* (BNT) participants are shown pictures of 60 objects and are asked to name them (266, 267). In the *digit span tasks* participants are read a list of numbers and asked to recall them forwards (digit span forwards, DSFW), backwards (digit span backwards, DSBW) and then by rearranging them in ascending order (digit span sequencing, DSS); in each case the task increases in difficulty by using a longer list of digits each time (268). In *digit coding* (part of the Wechsler Adult Intelligent Scale-IV), participants have to transcribe as many numbers as possible using the appropriate symbol from a key; this is done under time pressure with participants asked to complete as much as possible of the task in 2 minutes (269). During the *Cambridge Neuropsychological Test Automated Battery Reaction Time* participants have to touch a series of crosses and circles on the screen (270, 271). This computerised task measures both speed and accuracy of completion. In the *Test of Pre-morbid Functioning* (TOPF) participants are asked to read a list of written words, and are scored according to their pronunciation (272). The raw TOPF score, together with age, sex and years of education is used to estimate the pre-morbid IQ.

Table 8. Cognitive domains tested during Whitehall Imaging sub-study

Cognitive domain	Test	
Cognitive screening	Montreal Cognitive Assessment	MOCA
Processing speed	Trail Making Test A Digit Span Sequencing Digit Coding Cambridge Neuropsychological Test Automated Battery Reaction Time	TMT A DSS DC CANTAB
Executive function	Trail Making Test B Digit Span Forward Digit Span Backward Digit Span Sequencing	TMT B DSFW DSBW DSS
Visusospatial skills	Rey-Osterrieth Complex Figure	RCF copy
Visuospatial memory	Rey-Osterrieth Complex Figure	RCF immediate RCF delay RCF recognition
Verbal learning and episodic memory	Hopkins Verbal Learning Test Revised	HVLT total HVLT immediate HVLT delayed HVLT recognition
Semantic memory and language skills	Category fluency 60-item Boston Naming Test	Category fluency BNT
Estimate of pre-morbid intelligence	Test of Pre-morbid Functioning	TOPF

4.4.3 Structured clinical interview

A structured clinical interview was administered using screening and mood disorders modules from the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID), non-patient version (273). The interview lasted approximately 30 minutes and enabled the identification of participants with a current or previous diagnosis of a DSM-IV mood disorder.

4.4.4 Brain MRI

Multi-modal MRI brain scans were acquired at the FMRIB centre, University of Oxford with a 3 Tesla, Siemens Verio scanner with a 32-channel head coil, using a sequence which lasted less than one hour (Table 9). This state-of-the-art sequence was designed to rapidly acquire data relating to brain structure. The protocol included T1-weighted, Fluid Attenuated Inversion Recovery (FLAIR) and diffusion tensor imaging sequences, which are considered in this thesis. In addition, T2*, resting state functional and magnetic resonance spectroscopy sequences were acquired; these are beyond the scope of this thesis but are described elsewhere (274) .

Table 9. MRI Protocol for Whitehall Imaging sub-study

Purpose	Sequence	Time taken (min:secs)
Anatomical reference points for sequences	Localizer 1	00:13
	Localizer 2 (MOCO)	00:29
T1-weighted	Structural	06:12
FLAIR	FLAIR	04:14
T2*	T2*	04:17
Resting State functional MRI	MB6 Resting	10:10
	MB1	00:07
	Fieldmap	01:11
Magnetic Resonance Spectroscopy	MRS	08:48
	MRS_Water_suppressed	00:46
Diffusion tensor imaging	DTI 1st direction	09:56
	DTI 2nd direction	00:36

T1-weighted structural images were acquired using a high-resolution three-dimensional rapid gradient echo sequence with repetition time 2530 ms, echo time 7.37 ms, flip angle 7°, field of view 256mm and voxel dimensions 1.0mm isotropic (275, 276). FLAIR, used to characterise white matter lesions or hyperintensities, used the following parameters: repetition time 9000 ms, echo time 73.0 ms, flip angle 150°, field of view 220 mm and voxel dimensions 0.9x0.9x3.0 mm. Diffusion tensor images were acquired with an echoplanar imaging sequence (60

directions, b-value 1500 s/mm^2) with the following parameters: repetition time 8900ms, echo time 91ms, field of view 192mm and voxel dimensions 2.0mm isotropic. Different sequences were used with regard to motion correction (MOCO) and this parameter was added as a co-variate in analysis. This ensured that differences in image quality did not affect the final results. Acquisition of DTI data employed a recently developed sequence with complementary information included in pairs of diffusion images acquired with reversed phase-encoding directions, enabling estimation of susceptibility-induced distortions to correct images for artefacts (especially motion–related artefacts) (274, 277).

4.5 Measures used

This section describes measures of depression and vascular risk used during the Whitehall Imaging sub-study, as well as those used in the Whitehall II Study (Table 10). Data in this thesis is based on phases 1-9; phase 11 data was not available at the time of writing.

4.5.1 Depressive symptoms

The widespread prevalence of depression makes it amenable to investigation using population and epidemiological studies. However, unlike a condition such as diabetes which can be diagnosed through quantitative blood measures, there is no objective investigation that can be used to provide a rapid, objective diagnosis. The gold-standard diagnostic tool, an unstructured clinical assessment, is often too time-consuming to form part of an epidemiological approach. Investigation of depression in a large group of people is best performed using a structured assessment, with high inter-rater reliability. Structured diagnostic instruments such as the Structured Clinical Interview for DSM-IV diagnosis (SCID) or Schedules for Clinical Assessment in Neuropsychiatry (SCAN) have good evidence for their reliability, but may still be too time-consuming and labour intensive when applied to large population studies. For this reason, large cohort studies frequently employ shorter, structured questionnaires to elicit depressive symptoms, such as the Center for Epidemiologic Studies Depression (CES-D) questionnaire. This is a validated measure (278), but does not equate to a clinical diagnosis. Thus, it is not clear whether a high CES-D score indicates similar underlying neurobiological and structural changes on MRI to those identified in people with a clinical diagnosis of depression. This is an issue which will be explored in this thesis.

Current depressive symptoms

As part of the Whitehall Imaging sub-study current depressive symptoms are measured using the CES-D, a 20-item self-reported questionnaire measuring the frequency of depressive symptoms during the previous week on a four-point ordinal scale (254, 278) (see appendix 1). The CES-D focuses on six domains: mood, guilt and worthlessness, helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance. The maximum score is 60, and those scoring ≥16 are categorised as cases with clinically significant depressive symptoms (254). The questionnaire used as part of the Whitehall Imaging sub-study asked details of current medication. Current use of antidepressant medication (British National Formulary, (BNF), chapter 4.3) was recorded as an additional indicator of current depressive disorder.

History of depressive symptoms

In order to confirm lifetime diagnosis of DSM-IV mood disorder the SCID semi-structured clinical interview was used. This has good reliability between interviewers and good validity compared to gold-standard clinical interview techniques (279). It includes demographic details, screening questions for mental disorder and mental illness, and detailed questions in relation to past mood disorders (including depressive symptoms, hypomania and mania) and associated clinical symptoms. This enables an accurate diagnosis of mood disorder to be reached, including the DSM-IV categories of: dysthymia, minor depressive disorder, major depressive disorder, recurrent major depressive disorder, hypomania (current or previous), mania (current or previous) and bipolar disorder.

Previously, the presence of depressive symptoms has been measured through Whitehall II Study data collection using the CES-D rating scales at phases 7 and 9. CES-D score was also measured at phase 10 for a small number of individuals, and at phase 11. At previous phases the General Health Questionnaire (GHQ), has also been used (255, 256). This is a self-administered questionnaire which is a well-validated screening tool to identify those with symptoms of depression or anxiety (278). It is scored out of 30, and those scoring ≥5 are considered cases. Although caseness does not equate to a diagnosis of depression, it does provide a measure of psychological distress.

4.5.2 Vascular risk factors and disease

Vascular risk factors were measured prior to the MRI scan as part of the Whitehall Imaging sub-study (Oxford). Long-term exposure to vascular risk factors was recorded during face-to-face data-collection phases as part of the Whitehall II Study (UCL), with further details given below.

Blood pressure

a) Whitehall Imaging sub-study

The Whitehall Imaging sub-study measured blood pressure using an OMRON HEM 907 sphygmomanometer. Systolic and diastolic blood pressure was measured twice in the sitting position after five minutes of rest and the average of the two readings recorded. High blood pressure was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. The postal questionnaire asked for self-report of hypertension, and current medication. This meant that use of anti-hypertensive medication (BNF, chapter 2.5) could be documented as an additional indicator of hypertension.

b) Whitehall II Study

Data relating to long-term exposure to high blood pressure was acquired during past phases of the Whitehall II Study. Systolic and diastolic blood pressure was measured twice in the sitting position after five minutes of rest with the Hawksley random-0 sphygmomanometer (phases 1, 3 and 5) and OMRON HEM 907 (phases 7 and 9). The average of the two readings was taken to be the measured systolic and diastolic blood pressure. High blood pressure was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. At all phases of the Whitehall II Study self-reported data on doctor-diagnosed hypertension and use of anti-hypertensive medication was recorded.

When considering long-term exposure to elevated blood pressures, the 'Mean Arterial Pressure' (MAP) was calculated. This combines systolic and diastolic blood pressures into a single composite measure using the formula: mean arterial pressure = ((2*mean diastolic pressure) + mean systolic blood pressure))/3.

Cholesterol

a) Whitehall Imaging sub-study

The Whitehall Imaging sub-study postal questionnaire asked for self-report of dyslipidaemia, and current medication. Use of lipid-regulating medication (BNF, chapter 2.12) was recorded as an additional indicator of dyslipidaemia.

b) Whitehall II Study

The Whitehall II Study measured blood cholesterol levels following a venous blood sample at phases 1, 3, 5, 7 and 9 and was classified according to standardised criteria: high triglycerides ≥2 mmol/L and low HDL as <1.0 mmol/L.

Diabetes and fasting glucose

a) Whitehall Imaging sub-study

The Whitehall Imaging sub-study postal questionnaire asked for self-report of diabetes and current medication. Current use of diabetic medication (BNF, chapter 6.1) was documented as an additional indicator of diabetes.

b) Whitehall II Study

Diabetes was investigated at phases 3, 5, 7 and 9 of the Whitehall II Study following a fasting venous blood sample, and a standard two-hour oral glucose tolerance test using 75g oral glucose. Diabetes was defined as fasting glucose ≥7.0 mmol/L or a two-hour, post-load glucose ≥11.1 mmol/L. Fasting glucose was measured in non-diabetic participants who had fasted for at least five hours. Glucose samples were drawn into fluoride monovette tubes and centrifuged on site within one hour. Blood glucose was measured using the glucose oxidase method (280). Participants who self-reported doctor-diagnosed diabetes or use of diabetic medication were classified as having diabetes, regardless of their blood test results.

Smoking

a) Whitehall Imaging sub-study

Self-reported smoking status (yes, no, occasional) was recorded using the Whitehall Imaging sub-study postal questionnaire.

b) Whitehall II Study

Data on cigarette smoking was recorded following self-report on a questionnaire at Whitehall II Study phases 1, 3, 5, 7 and 9. Participants were classified into three groups: current smoker, ex-smoker or never smoked, at baseline and at phase 9 follow-up.

Framingham Stroke Risk Score

a) Whitehall Imaging sub-study

The Whitehall Imaging sub-study used the FSRS as a measure of cardiovascular disease (281-283). This was calculated for all participants based on their age, systolic blood pressure, diabetes mellitus status, smoking status, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and use of hypertensive medication (281). These data were obtained by self-report, apart from blood pressure which was measured as described above.

b) Whitehall II Study

The FSRS was recorded at phases 1, 3, 5, 7 and 9 using the criteria defined above, and data collected at each face-to-face data-collection phase. Atrial fibrillation and left ventricular hypertrophy were recorded following ECG measurements.

Coronary heart disease

a) Whitehall Imaging sub-study

Coronary heart disease was measured cross-sectionally using the Whitehall Imaging sub-study postal questionnaire. This asked for self-report of history of coronary heart disease including myocardial infarction and angina.

b) Whitehall II Study

Coronary heart disease measurements recorded for the Whitehall II Study were not used as part of this thesis.

Table 10. Summary of measures used to identify depression and vascular risk

	Whitehall Imaging sub-study, Oxford	Whitehall II Study, London
Depression		
Current depressive symptoms	CES-D Antidepressant medication use	CES-D GHQ
Lifetime depressive disorder	SCID	-
Vascular risks		
Blood pressure	Systolic ≥140 mm Hg, or diastolic ≥90 mm Hg Medication use	Systolic ≥140 mm Hg, or diastolic ≥90 mm Hg Medication use
Cholesterol	Medication use Self-reported dyslipidaemia	Triglycerides ≥1.7 mmol/L HDL as <1.0 mmol/L (men) or <1.2 mmol/L (women)
Diabetes	Medication use Self-report	Fasting glucose ≥7.0 mmol/L or a two-hour, postload glucose ≥11.1 mmol/L Medication use Self-report
Smoking	Self-report	Self-report
CHD	Self-report	-

4.6 Data processing and analysis

4.6.1 Questionnaire and cognitive assessment

Data from questionnaires, cognitive assessments and clinical interviews were inputted into a study-specific online database. Data checking was performed at the end of phase 1 Whitehall Imaging sub-study data collection to ensure accuracy. All data were analysed using IBM SPSS version 20 for PC (284) or SAS software version 9.2 for PC (285).

4.6.2 Brain MRI

MRI data were analysed using automated and visual methods (see Table 11 for summary). Automated analysis used FSL tools (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl), a comprehensive library of analysis tools for MRI (286-288). Visual MRI assessments used standardised visual rating scales.

Table 11. Summary of analysis measures for structural MRI data

MRI Sequence	Automated analysis	Visual analysis
T1-weighted	Voxel based morphometry (VBM)	General atrophy Scheltens scale
FLAIR	-	Fazekas scale
Diffusion tensor imaging	Tract based spatial statistics (TBSS)	-

Structural MRI

Structural T1-weighted images were processed using the anatomical processing script, fsl_anat (beta version) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat) which provides a pipeline for processing T1-weighted scans. This uses standard FSL tools, but has improved bias-field correction, which is useful for high-field scanners. In this pipeline the images are reoriented to the standard MNI (Montreal Neurological Institute) orientation, automatically cropped, bias field corrected, registered to standard space using linear (FLIRT) and non-linear registration (FNIRT) and brain-extracted before applying tissue-type segmentation (289, 290). FIRST (FMRIB's Integrated Registration and Segmentation Tool) was used to segment sub-cortical structures and calculate hippocampal volumes (291). Differences in grey matter were analysed with FSL-VBM (Voxel Based Morphometry), an optimised VBM protocol (292). Statistical analysis was applied using a voxelwise general linear model using permutation-based non-parametric testing, correcting for multiple comparisons across space using the threshold-free cluster enhancement option.

Diffusion-weighted images were processed using TBSS to assess FA and MD, measures of white matter connectivity. This technique allows voxelwise statistical analysis of the FA data (288), thereby avoiding the problems of registration and smoothing associated with voxel-based approaches (101). First, 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 (289). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (293, 294) , which uses a b-spline representation of the registration warp field (295). Next, the mean FA image was created and thinned to create a mean FA skeleton representing the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.

White matter hyperintensity segmentation was undertaken using FreeSurfer software version 5.2.0 (https://surfer.nmr.mgh.harvard.edu/). This provides a fully automated pipeline for segmentation and calculation of white matter hyperintensity volumes (296). This open source software provides a series of tools that can be used for sub-cortical segmentation as well as other methods for processing and analysing brain MRI.

Visual rating scales for MRI measures

In order to bridge the gap between the computerised, automated measures used in research, and clinically applicable methods of analysis that can be utilised in practice, three visual rating scales were used to assess MRI data. Scales chosen had been previously validated, had high inter- and intra-rater reliability, and adopted a straightforward approach which could be used by those with minimal training as well as by experienced raters. T1-weighted images were assessed for global and medial temporal lobe atrophy; FLAIR images were assessed for white matter hyperintensities. For each scale, ratings were made by three independent raters (Charlotte Allan, Anya Topiwala and Vyara Valkanova) blind to participant demographics. Raters used reference images to increase consistency; where there were discrepancies between ratings, the modal value was used. If this was not possible the scans were reviewed again in conjunction with a fourth rater (Klaus Ebmeier) to reach a final rating score. For all visual ratings a higher score represents increased severity of structural brain changes. When using visual ratings in analysis no adjustments were made for total brain size or white matter volume, as these are automatically taken into account when looking at the images visually.

Global atrophy was assessed on axial and coronal sections of T1-weighted images. It was measured on a four-point ordinal scale from 0-3 (Figure 4), based on a rating scale used for analysis of regional atrophy (297, 298). *Medial temporal lobe atrophy* was assessed on coronal sections of T1-weighted images measured using the Scheltens' scale (299). This is a composite score based on width of the choroid fissure, width of the temporal horn and height of the hippocampal formation, measured using a five-point ordinal scale from 0-4 (Figure 5). Left and right sides were rated separately. *White matter hyperintensities* were assessed using axial FLAIR images, measured using the Fazekas' scale (94). This rates periventricular and deep white matter hyperintensities separately, each based on a four-point ordinal scale from 0-3 (Figure 6). These two ratings were summed, leading to the total Fazekas score, which is an integer from 0-6. This was done to enable comparison with the automated measure of white matter hyperintensities, which does not distinguish between periventricular and deep white matter changes.

Figure 4. Visual rating of global atrophy

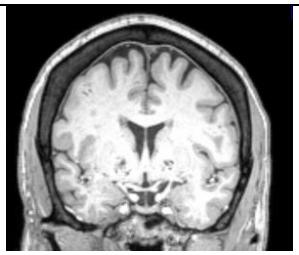
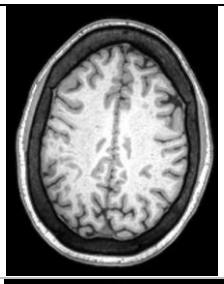
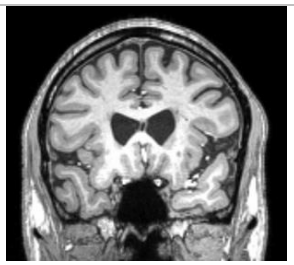
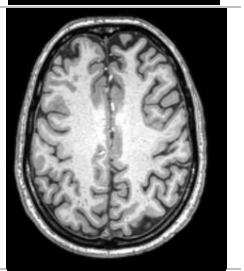
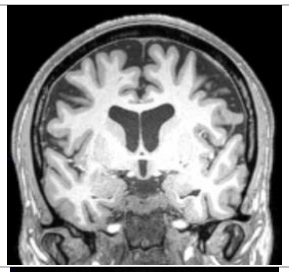
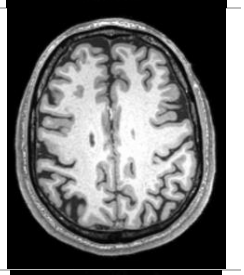
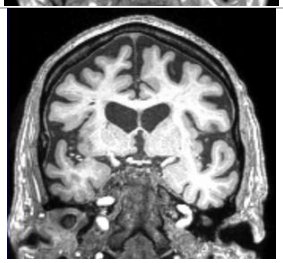
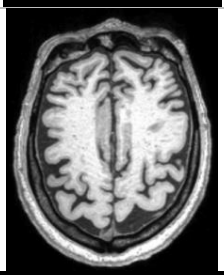
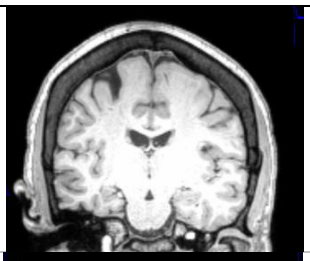
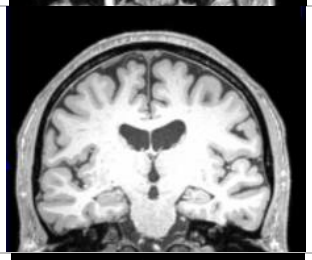
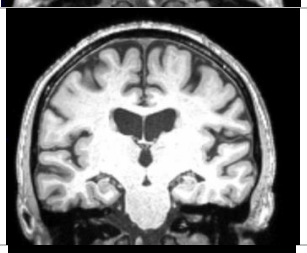
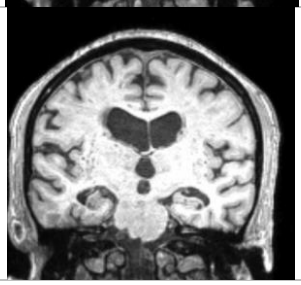
Score	Global atrophy	Coronal view	Axial view
0	Absent		
1	Mild		
2	Moderate		
3	Severe		

Figure 5. Visual rating of medial temporal lobe atrophy based on Scheltens scale

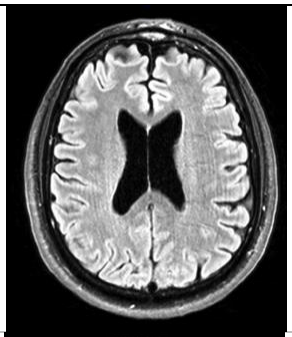
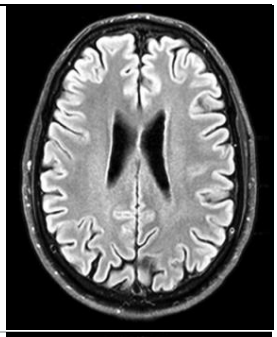
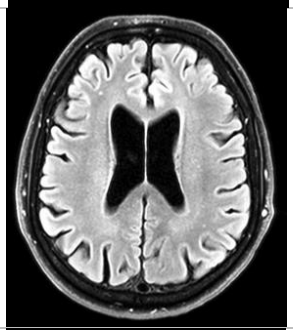
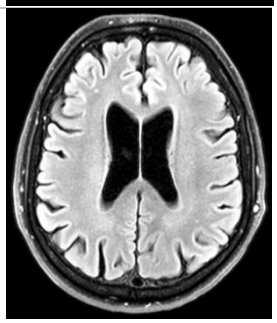
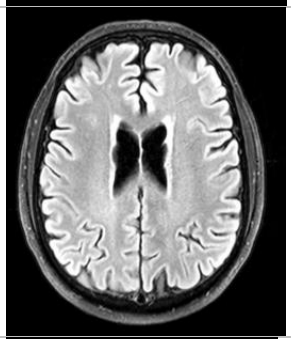
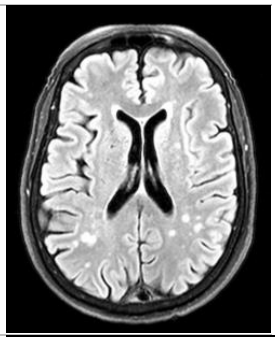
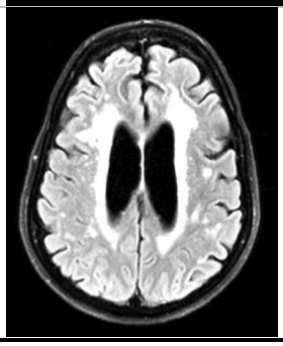
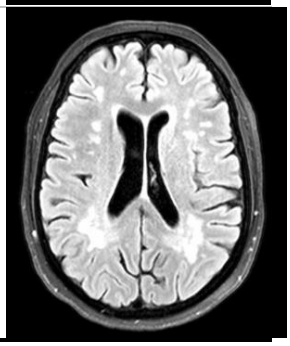
The Scheltens scale is discussed in more detail by Scheltens et al., 1992 (299).

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampal formation	Coronal view
0	Normal	Normal	Normal	
1	Slight increase	Normal	Normal	
2	Moderate increase	Slight increase	Slight decrease	
3	Severe increase	Moderate increase	Moderate decrease	
4*	Severe increase	Severe increase	Severe decrease	

*There were no participants with a rating of 4 on the Schelten's scale

Figure 6. Visual rating of white matter hyperintensities based on Fazekas scale

The Fazekas scale is discussed in more detail by Fazekas et al., 1987 (94).

Score	Periventricular white matter hyperintensities		Deep white matter hyperintensities	
0	Absent		Absent	
1	Caps or pencil-thin lining		Punctate foci	
2	Smooth halo		Beginning confluence of foci	
3	Irregular, extending to the deep white matter		Large confluent areas	

4.7 Summary

The ongoing Whitehall Imaging sub-study aims to recruit 800 participants from the Whitehall II Study (2012-2016) who have over 25 years of longitudinal data available from phases 1 – 9 inclusive. Phase 1 of the Whitehall Imaging sub-study was completed in June 2013 for 229 participants, with information collected about their medical history, cognitive function and brain structure; this group of participants is studied in this thesis. Data-collection has been based on a questionnaire, cognitive assessment, clinical interview and multi-modal MRI scan. This allows detailed characterisation of current and previous mood disorder, as well as vascular disease and risk factors, complementing prospective data previously acquired through the Whitehall II Study.

Chapter 5. Sample description

5.1 Introduction

Chapter 5 presents an overview of the sample of participants recruited during phase 1 of the Whitehall Imaging sub-study (2012-2013), who are studied in this thesis. The key demographic data and characteristics of the sample relating to cognitive measures, depressive symptoms and vascular risk factors are outlined. These data are used for analysis in subsequent chapters.

5.2 Participant demographics

Between April 2012 and June 2013 the Whitehall Imaging sub-study recruited 229 participants, and excluded 120 participants. This represents approximately one quarter of participants expected to be recruited to the Whitehall Imaging sub-study (2012 to 2016). The mean age of participants was 69.2 ± 5.3 years and the majority were male (82.5%) (Table 12). This is, on average, a well-educated sample with above-average IQ. In comparison with the original Whitehall II sample (Table 13), the mean age at baseline was similar; however, the Whitehall Imaging sample had a greater proportion of men, and a greater proportion of people with higher occupational status at baseline.

Table 12. Participant demographics: phase 1 Whitehall Imaging sub-study

	n	%	Mean ± SD	Min.	Max.
Recruitment					
Phase 10	29	12.7	-	-	-
Phase 11	200	87.3	-	-	-
Sex					
Men	189	82.5	-	-	-
Women	40	17.5	-	-	-
Age, *years*	229	-	69.2 ± 5.3	60.3	82.0
Education, *years*	229	-	14.1 ± 3.1	7.0	23.0
Pre-morbid IQ*	229	-	118.0 ± 10.0	78.0	146.2

*Estimated from the Test of Premorbid function (TOPF), education and sex

Table 13. Baseline (1985-1988) characteristics of participants in the present study and of all Whitehall II study participants

Baseline characteristic in 1985-1988	Whitehall Imaging sub-study sample (Phase 1) (n=229)	Whitehall II sample (n=10 308)
Age, *years, mean (SD), range*	43.2 (5.3), 35-55	44.4 (6.1), 35-55
Sex, *n (%)*		
Women	40 (17.5)	3413 (33.1)
Men	189 (82.5)	6895 (66.9)
Occupational group, *n (%)*		
Administrative	102 (44.5)	3028 (29.4)
Professional/executive	112 (48.9)	4942 (47.7)
Clerical/support	15 (6.6)	2337 (22.7)

5.3 Cognitive assessment

A complete cognitive assessment was performed on 98% of participants. The mean scores confirm that this is a group without significant cognitive impairment (mean MOCA 27 ± 2.4), as would be expected from a population sample in which participants are required to travel a significant distance to participate in research (Table 14). However, the range of scores across tests of processing speed, executive function, visuospatial skills, visuospatial memory, verbal learning and episodic memory, and semantic memory and language skills indicate that this is a population exhibiting significant variation, despite having above-average pre-morbid intelligence. Scores at the lower end of the ranges are consistent with symptoms of clinically significant mild-moderate cognitive impairment.

Table 14. Summary results of cognitive testing, phase 1 Whitehall Imaging sub-study

	n	Mean	SD	Min.	Max.
Cognitive screening					
MOCA	229	27.0	2.4	17.0	30.0
Processing Speed					
TMTA, *secs*	227	32.0	13.6	13.0	125.0
DSS	229	10.2	2.7	0.0	16.0
CANTAB_RTI	224	341.5	48.8	257.9	585.9
CANTAB_MOT	224	287.4	75.7	122.8	598.0
Executive Function					
TMTB, *secs*	226	67.9	34.2	27.0	289.0
DSFW	229	10.9	2.3	6.0	16.0
DSBW	229	9.8	2.6	4.0	16.0
DC	228	61.4	14.2	13.0	98.0
Visuospatial skills					
RCF copy	228	30.0	4.6	7.0	36
Visuospatial memory					
RCF immediate recall	228	14.6	6.4	0.0	32.0
RCF delayed recall	228	14.1	6.2	1.0	27.0
RCF recognition	227	10.0	1.7	2.0	12.0
Verbal learning and episodic memory					
HVLT immediate recall	229	26.9	5.0	10.0	36.0
HVLT delayed recall	229	8.9	3.0	0.0	12.0
HVLT recognition	229	10.5	1.6	2.0	12.0
Semantic memory and language skills					
Category fluency	229	21.5	5.9	3.0	40.0
BNT	229	57.1	5.0	15.0	60.0
Estimate of pre-morbid intelligence					
TOPF	229	61.0	9.5	17.0	70.0

5.4 Depressive symptoms

Within the total sample (n=229) 10% had significant current depressive symptoms, as defined by CES-D score (Table 15). In participants randomly selected from Whitehall II phase 11 the prevalence of elevated CES-D scores was 8.5%. In the phase 10 group the prevalence of elevated CES-D scores was 20%. Previous studies have found the prevalence of depression in older adults to be in the range 10-15% (4-6). The prevalence in the randomly selected phase 11 group is slightly lower than might be expected for participants of this age; that in the phase 10 group slightly higher. This is to be expected given the recruitment criteria: phase 10 participants were an enriched group selected for having elevated CES-D scores at age >60 years. There was a statistically significant difference (p=0.002) between the mean CES-D score in phase 11 and phase 10 participants. In both groups the proportion of participants taking antidepressant medication was lower than the proportion with significant depressive symptoms as defined by CES-D score. Given that depressive symptoms as defined by CES-D do not equate to an exact diagnosis of minor or major depressive disorder, and that antidepressants should lower the CES-D score, this discrepancy is also to be expected.

One third of participants had a lifetime diagnosis of DSM-IV mood disorder, with a higher rate (38%) amongst phase 10 participants (Table 16). Major and minor depressive disorders were the most common, with a much smaller proportion having recurrent depressive disorder or other conditions (e.g. bipolar disorder). There was a significant correlation between use of antidepressant medication and depressive symptoms defined using CES-D (p=0.003) and DSM-IV criteria (p<0.001).

Participants recruited at phase 10 had later onset of DSM-IV mood disorder (mean age 53 ± 16.5 years), compared to phase 11 (mean age 39 ± 14.4 years). This difference was significant (p=0.006) and reflects recruitment criteria (phase 10 participants were selected on the basis of late-onset depressive symptoms). However, it shows that selection on the basis of CES-D symptoms alone does not detect all previous mood episodes. This is to be expected given that the CES-D reviews mood-related symptoms in the week prior to completion of the questionnaire. There was a significant correlation between current depressive symptoms defined using CES-D and a past history of mood disorder diagnosed using DSM-IV criteria (p<0.001). This suggests that participants selected for having late-onset depressive symptoms, may also have had previous depressive symptoms that were not diagnosed by CES-D, but which could be identified using the SCID.

Table 15. Frequency of current depressive symptoms, phase 1 Whitehall Imaging sub-study

	Total n=229	Phase 10 n=29	Phase 11 n=200
CES-D score			
Mean ± SD	5.9 ± 6.8	9.7 ± 7.5	5.39 ± 6.6
Range	0 to 39	0 to 32	0 to 39
CES-D cases			
%	10.0	20.7	8.5
n	23	6	17
Antidepressant use			
%	7.0	10.3	6.5
n	16	3	13

Table 16. Frequency of lifetime DSM-IV diagnosis, phase 1 Whitehall Imaging sub-study

	Total n=229	Phase 10 n=29	Phase 11 n=200
	% (n)	% (n)	% (n)
Any DSM-IV diagnosis	31.4 (72)	37.9 (11)	30.5 (61)
Mood disorder	30.6 (70)	37.9 (11)	29.5 (59)
Dysthymia	0.9 (2)	3.4 (1)	0.5 (1)
Minor depressive disorder	9.6 (22)	13.8 (4)	9.0 (18)
Major depressive disorder	16.6 (38)	13.8 (4)	17.0 (34)
Recurrent major depressive disorder	2.6 (6)	3.4 (1)	2.5 (5)
Bipolar disorder	0.9 (2)	3.4 (1)	0.5 (1)
Other	0.9 (2)	0 (0)	1.0 (2)

5.5 Vascular risk

Vascular risk factors are common amongst participants of the Whitehall Imaging sub-study, as would be expected in a sample of people with mean age of 69 years. Over half the sample had hypertension defined as systolic blood pressure ≥140 mm Hg, and one third of participants were on treatment for hypertension (Table 17). This is slightly lower than the prevalence of hypertension in this age group nationally (Table 3), reflecting a group from an occupational cohort likely to be more health-conscious and able to modify vascular risk factors after over 25 years of regular follow-up through the Whitehall II Study. Cholesterol was not measured directly in this sample, but self-reported information shows that 54% have a history of dyslipidaemia, with 34% using lipid-regulating medication (Table 17), similar to national prevalence rates.

Rates of diabetes (approximately 10% of the sample) and smoking (approximately 6% of the sample) are lower than the national average (Table 17; Table 3) again reflecting a bias toward health promotion and prevention. A small number of participants reported having suffered a previous stroke or TIA (4.4%); half of these cases were definitely TIAs, resulting in only 2.2% of participants having had a possible stroke. The proportion with CHD was much lower than the national average (Table 3).

Table 17. Frequency of vascular risk factors, phase 1 Whitehall Imaging sub-study

	n	% (n)	Mean	SD	Range	
					Min.	Max.
Blood pressure						
Systolic BP, *mm Hg*	228	-	142.6	17.7	99.0	195.0
Diastolic BP, *mm Hg*	227	-	77.9	9.9	56.0	114.0
Systolic BP ≥140 mm Hg	228	54.8 (125)	-	-	-	-
Diastolic BP ≥90 mm Hg	227	11.5 (26)	-	-	-	-
Anti-hypertensive medication	229	33.6 (77)	-	-	-	-
Cholesterol						
Self-reported dyslipidaemia	229	54.1% (124)	-	-	-	-
Lipid-regulating medication	229	34.1 (78)	-	-	-	-
Diabetes						
Self-reported diabetes	229	9.6 (22)	-	-	-	-
Diabetic medication	229	12.7 (29)	-	-	-	-
Smoking						
Smoker	13	5.7 (13)	-	-	-	-
Non-smoker	216	94.3 (216)	-	-	-	-
FSRS						
FSRS, *% risk per 10yr*	229	-	10.7	3.9	4.0	24.0
Coronary Heart Disease						
Yes	229	6.1 (14)	-	-	-	-
No	229	93.9 (215)	-	-	-	-

5.6 Summary

This thesis is based on data collected during phase 1 of the Whitehall Imaging sub-study, which recruited 229 participants between April 2012 and June 2013. This sample of older adults has a mean age of 69 years, is predominantly male and has above average IQ. Mild cognitive impairment was common, with a small proportion scoring within the range for moderate impairment on cognitive tests. Current depressive symptoms were present in 10% of the total sample, and 20% of the Phase 10 group who were selected to be at higher risk of late-onset depression. Over 30% of the total sample had a lifetime diagnosis of DSM-IV mood disorder, predominantly major and minor depressive disorders. Elevated vascular risk factors were widespread, particularly hypertension and dyslipidaemia. Overall, however, prevalence rates for vascular risk factors were lower than population averages, likely reflecting a more health-conscious cohort who had participated in regular health screening over the course of their adult life.

Chapter 6. Study of agreement between visual and automated MRI measures

6.1 Introduction

Visual and automated approaches to MRI analysis can be used to investigate global atrophy, hippocampal atrophy and white matter hyperintensities. However, there is little research to bridge the gap between these methods of interpreting MRI brain scans. Clinicians report individual MRI images qualitatively – and also sometimes quantitatively – using standardised visual rating scales. If visual rating scales prove to be comparable with high-precision automated techniques then the use of visual rating scales in clinical practice would be further supported, to assist clinicians in reporting the degree of observed changes (rather than the simple presence of a change). Visual rating scales that identify and describe early structural changes, regardless of patient age, could be genuinely useful to clinicians, since reduced brain volumes and white matter brain changes have clinical significance in terms of progression to mild cognitive impairment and dementia (300-302). Furthermore, using quantitative descriptions of brain changes that are usually labelled 'normal for age' (303-306) (307-309), may start adding useful diagnostic information to the overall clinical assessment (310).

Automated assessments of MRI scans provide precise assessments of brain structure, but are not routinely used in clinical settings. These techniques have been developed over a number of years, with validation work based on comparisons with expert manual labels to confirm accuracy of automated techniques (311). They may therefore be viewed as the gold-standard approach to MRI analysis. Automated analysis techniques are usually used for groups of people, rather than for individuals. Although they have been simplified for ease of use, they still require a certain amount of technical expertise. For these reasons, their use is largely confined to research settings. It remains unclear how well an 'automated assessment of global brain atrophy' correlates with a 'clinical radiological report of global brain atrophy'.

This chapter considers the utility of visual methods of rating MRI scans in relation to their automated equivalents. Using the Whitehall Imaging sub-study data enables investigation of two hypotheses: first, that visual rating scales for global atrophy, hippocampal atrophy and white matter hyperintensities can be used meaningfully in this cohort, providing objective and reliable measures; second, that both visual and automated techniques can be cross-validated

and used to distinguish structural brain changes and cognitive changes in an occupationally-based sample.

6.2 MRI methods

Visual MRI ratings were performed as described in Chapter 4.6, in order to assess global atrophy, medial temporal lobe atrophy and white matter hyperintensities.

Automated analysis methods were selected which assessed similar structural differences to these visual ratings, and used well-validated MRI processing and analysis techniques. *Global atrophy* was estimated by measuring total cerebrospinal fluid volume normalised to whole-brain volume, as a measure of the amount of whole-brain atrophy. Values were obtained after partial volume segmentation, using FMRIB's Automated Segmentation Tool (FAST), which segments a 3D image of the brain into different tissue types (grey matter, white matter, CSF), as well as correcting for spatial intensity variations (291). *Medial temporal lobe atrophy* was calculated by segmenting sub-cortical structures using 'FIRST', a fully automated, model-based segmentation and registration tool, based on multivariate Gaussian assumptions (290) (i.e. the automated measure of medial temporal lobe atrophy equated to hippocampal volume). Right and left hippocampal volumes were calculated separately, and were normalised for whole-brain volume. *White matter hyperintensity* volume was calculated using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), a fully automated method of segmenting white matter hyperintensities, allowing calculation of total white matter hyperintensity volume. White matter hyperintensity volumes were normalised for total white matter volume.

6.3 Results

6.3.1 Reliability of visual measures

The first step in use of visual scales was to perform a reliability analysis to confirm inter- and intra-rater reliability, to justify use of these scales. To determine consistency between the three raters, inter-rater reliability analysis used a single-measures Intra-Class Correlation Coefficent (ICC) with a two-way random-effects model with absolute agreement. This can be used instead of a weighted-kappa which is usually used for ordinal variables, and provides increased flexibility when comparing three or more variables (312, 313). To determine the internal consistency of raters an intra-rater reliability analysis was performed based on repeat

measures of a random 10% of the total sample. Scans were selected for re-assessment by generating a list of random numbers. Repeat ratings were made blind to the original score and demographic details, and were compared using an ICC. These (and other) correlations were classified as follows: weak correlation, 0.10 to 0.29; moderate correlation, 0.30 to 0.49; strong correlation, >0.50 (314).

For visual rating scales the inter-rater and intra-rater reliability comparing all three raters showed strong agreement for global atrophy, medial temporal lobe atrophy and white matter hyperintensities (Table 18).

Table 18. Reliability of visual MRI ratings

	Inter-rater reliability			Intra-rater reliability		
	ICC	95% CI	p	ICC	95% CI	p
Global atrophy	0.71	0.65 to 0.77	<0.001	0.75	0.61 to 0.87	<0.001
Medial temporal lobe atrophy						
Left	0.64	0.56 to 0.71	<0.001	0.67	0.51 to 0.82	<0.001
Right	0.63	0.55 to 0.71	<0.001	0.75	0.61 to 0.87	<0.001
White matter hyperintensities						
Total	0.72	0.65 to 0.77	<0.001	0.78	0.65 to 0.88	<0.001
Periventricular	0.53	0.45 to 0.62	<0.001	0.68	0.52 to 0.82	<0.001
Deep	0.73	0.67 to 0.79	<0.001	0.71	0.57 to 0.85	<0.001

6.3.2 Sample overview

Of 229 participants recruited through the Whitehall Imaging sub-study, 190 were included in this analysis. Participants were excluded due to conditions that would affect MRI registration or analysis. The following exclusions were made: neurological conditions including stroke and TIA (n=25), incomplete MRI data (n=7), and inadequate MRI processing or grey matter segmentation (n=7). Similar to participant demographics in the Whitehall Imaging sub-study, this sample had mean age 69.3 ± 5.4 years, the majority were male, and were not cognitively impaired (Table 19). There were no significant differences between included and excluded participants.

Table 19. Participant demographics: visual and automated MRI measures study

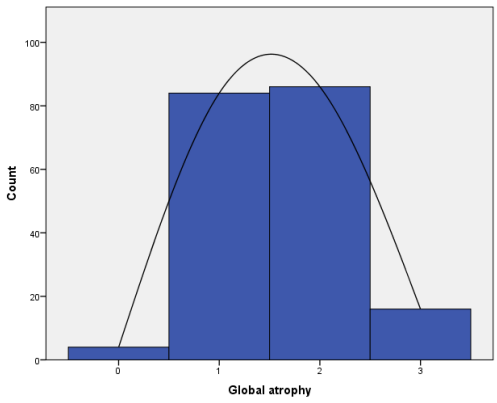
	Whole sample	Inclusions	Exclusions	p-value*
n	229	190	39	-
Sex, males *n (%)*	189 (82.5%)	155 (81.6%)	34 (87.2%)	0.40†
Age, *years* *Mean ± SD*	69.2 ± 5.3	69.3 ± 5.4	68.8 ± 4.6	0.60
Education, *years* *Mean ± SD*	14.1 ± 3.1	14.1 ± 3.2	14.2 ± 2.9	0.91
Pre-morbid IQ *Mean ± SD*	118.0 ± 10.0	117.9 ± 9.8	118.1 ± 11.3	0.93
MoCA *Mean ± SD*	27.0 ± 2.4	26.9 ± 2.4	27.2 ± 2.3	0.43
HVLT *Mean ± SD*	26.9 ± 5.0	26.7 ± 5.1	27.5 ± 4.3	0.39
CES-D score *Mean ± SD*	5.9 ± 6.8	6.1 ± 7.2	5.0 ± 4.7	0.35
SCID diagnosis (any) *n (%)*	72 (31.4%)	59 (31.1%)	13 (33.3%)	0.78†

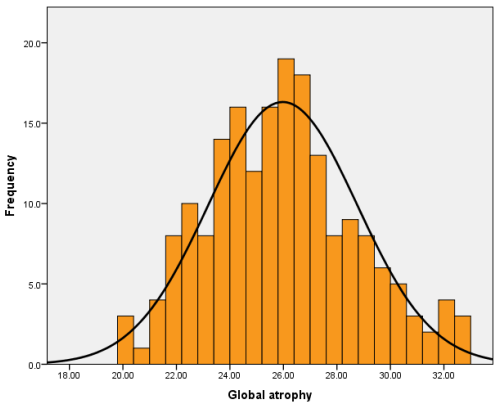
* Comparing inclusions (n=190) and exclusions (n=39) using t-test for continuous variables
† Chi-squared used for ordinal variables

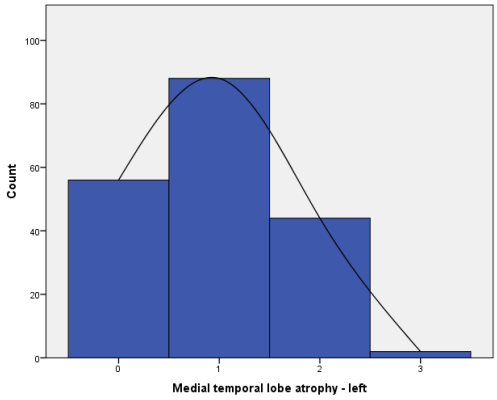
Visual and automated measures of global and hippocampal atrophy were approximately normally distributed (Figure 7). Visual and automated measures of white matter hyperintensities were positively skewed (Figure 7). There were no participants with the most severe visual rating of medial temporal lobe atrophy (a score of 4), yet despite this the scores could still be used to distinguish participants with mild-moderate brain changes, suggesting that these scales are useful even in a population sample for which most ratings were in the lower mid-range of scores. Images included in Figures 4, 5 and 6 demonstrate that the visual ratings in this study were consistent with previous studies.

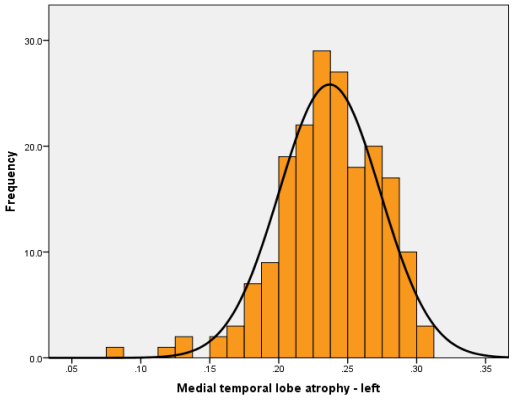
Figure 7. Distribution of visual and automated MRI measures

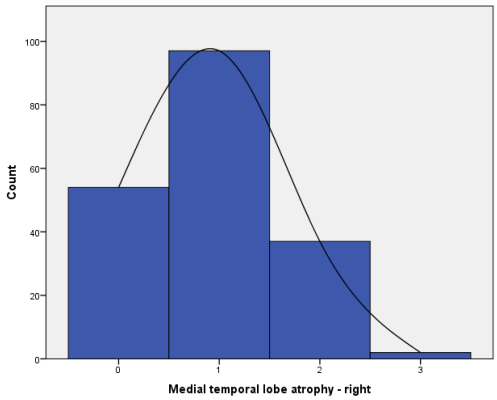
Visual measures (blue) Automated measures (orange)

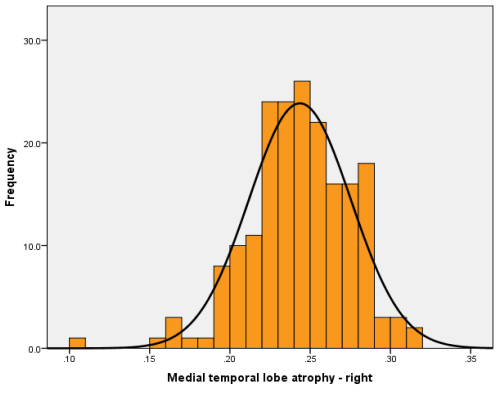


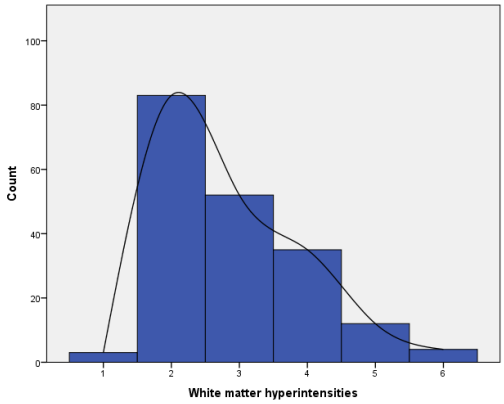


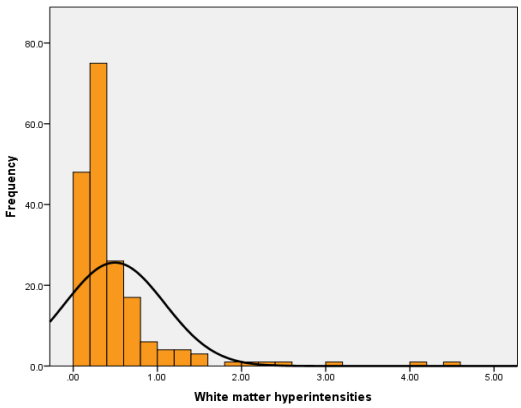












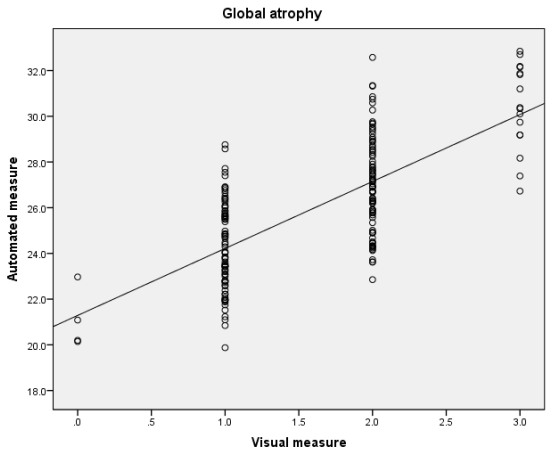
MRI measures were correlated with age using Pearson's correlations with two-tailed significance. Visual ratings were significantly correlated with age for global atrophy ($r=0.42$, $p<0.001$), medial temporal lobe atrophy (left, $r=0.41$, $p<0.001$; right, $r=0.44$, $p<0.001$) and total white matter hyperintensities ($r=0.27$, $p<0.001$). Likewise, automated ratings were significantly correlated with age for global atrophy ($r=0.59$, $p<0.001$), medial temporal lobe atrophy (left, $r=-0.20$, $p=0.007$; right, $r=-0.21$, $p=0.004$) and total white matter hyperintensities ($r=0.31$, $p<0.001$). For visual ratings of white matter hyperintensities, deep and periventricular changes were rated separately. Deep white matter hyperintensities ($r=0.32$, $p<0.001$), but not periventricular white matter hyperintensities ($r=0.14$, $p=0.06$), were significantly correlated with age.

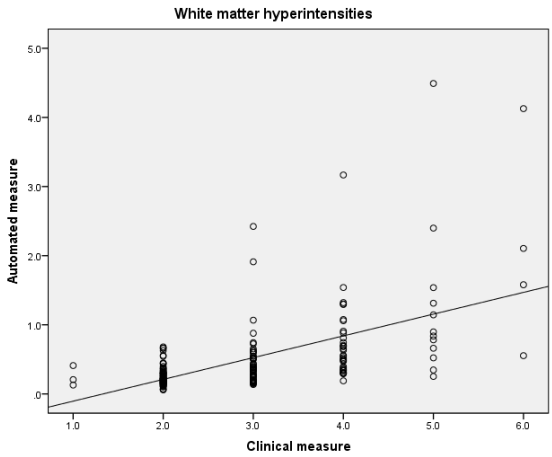
6.3.3 Comparison between visual and automated MRI analysis

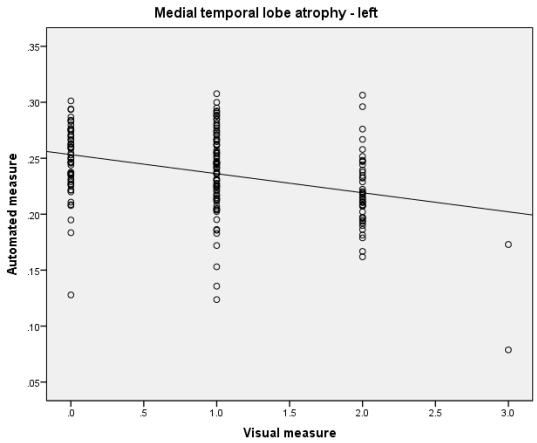
Visual and automated measurements of global atrophy, medial temporal lobe atrophy and white matter hyperintensities were correlated using Pearson's correlations (with two-tailed significance). Visual and automated methods were significantly correlated for global atrophy ($r=0.71$, $p<0.001$), medial temporal lobe atrophy (left $r=-0.35$, $p<0.001$; right, $r=-0.29$, $p<0.001$) and white matter hyperintensities ($r=0.56$, $p<0.001$). This demonstrates that increased global and hippocampal atrophy measured with visual scales is related to lower automated brain volumes, and that increased severity of white matter hyperintensities is related to increased automated white matter hyperintensity volumes. Graphical comparison using scatterplots to review the distribution of scores (Figure 8) confirms this relationship, but also highlights the range of automated volumes corresponding to each visual measure, revealing that automated methods are not linearly associated with the visual assessments made by trained clinical raters.

Visual and automated measures were correlated with selective cognitive tests (MOCA, HVLT-R, TMTA and TMTB) using uncorrected Pearson's correlations. These cognitive measures were chosen for their clinical applicability. Visual and automated MRI measures both showed significant correlations with cognitive tests (Table 20). Most correlations were weak in strength, though some were moderate. Visual rating scales showed greater sensitivity to differences in cognitive tests. Visual ratings of deep white matter hyperintensities were significantly correlated with cognitive tests, in contrast to periventricular hyperintensity scores, which were not correlated. Consequently, the correlation with total white matter hyperintensity volume was weaker, and less significant, although still present.

Figure 8. Scatterplots to compare visual and automated MRI measures







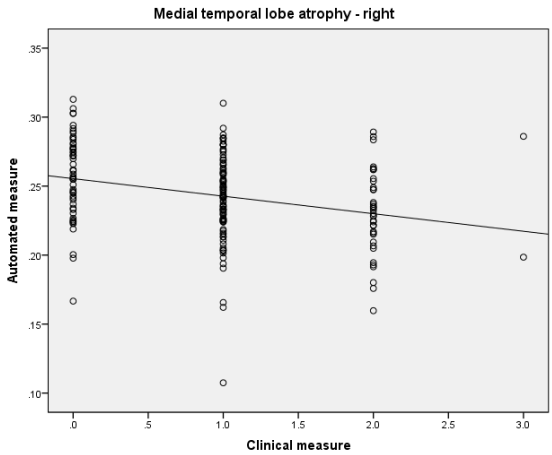


Table 20. Cognitive correlates of visual and automated MRI measures

	Visual measures				**Automated measures**			
	Correlation, Pearson's r				**Correlation, Pearson's r**			
	MoCA	HVLT	TMT A	TMT B	MoCA	HVLT	TMT A	TMT B
Global atrophy	-0.20 **p=0.007**	-0.22 **p=0.002**	0.28 **p<0.001**	0.06 p=0.44	-0.27 **p<0.001**	-0.24 **p=0.001**	0.29 **p<0.001**	0.08 p=0.26
Medial temporal lobe atrophy								
Left*	-0.17 **p=0.02**	-0.20 **p=0.01**	0.07 p=0.32	0.04 p=0.58	0.11 p=0.13	0.08 p=0.29	-0.05 p=0.54	0.03 p=0.68
Right *	-0.24 **p=0.001**	-0.26 **p<0.001**	0.18 **p=0.01**	0.06 p=0.40	0.18 **p=0.01**	0.16 **p=0.03**	-0.02 p=0.77	-0.06 p=0.45
White matter hyperintensities								
Total †	-0.16 **p=0.03**	-0.21 **p=0.003**	0.16 **p=0.03**	0.07 p=0.34	-0.12 p=0.08	-0.20 **p=0.005**	0.19 **p=0.008**	0.04 p=0.60
Periventricular	-0.05 p=0.51	-0.06 p=0.41	0.03 p=0.67	0.03 p=0.73				
Deep	-0.22 **p=0.002**	-0.31 **p<0.001**	0.25 **p=0.001**	0.10 p=0.19				

* Automated measures normalised for whole-brain volume
† Automated measures normalised for total white matter volume

Significant results highlighted in **bold**

6.4 Discussion

Synopsis

In this sample of older adults from the Whitehall Imaging sub-study, visual rating scales for global atrophy, medial temporal lobe atrophy and white matter hyperintensities could be used effectively and had acceptable reliability. Visual and automated methods could be used to identify structural brain changes and cognitive changes. Visual ratings were closely related to automated ratings and provided a valid measure for quantifying subtle changes in brain structure, which were associated with impairment in cognitive tests. This study comparing visual and automatic measures therefore demonstrates a clear link between rating scales that are readily used in clinical practice, and sophisticated, automated measures used in quantitative research.

Comparison with previous studies

The reliability of visual ratings was comparable to (306, 315-317), and in some cases higher than previous studies (298, 318, 319), possibly due to use of higher resolution MRI and a larger sample size. Agreement between ratings for medial temporal lobe atrophy was lower than for other measures; however, values were similar to a previous population study of older adults (315). One reason for this might be that visual assessments of medial temporal lobe atrophy utilised coronal sections only, whereas the automated assessment measured the whole hippocampal volume.

Visual ratings of deep white matter hyperintensities were associated with impaired function on cognitive tests; this was not replicated with periventricular scores. Deep white matter hyperintensities have a stronger association with physical decline (320, 321) and depression, compared with periventricular white matter hyperintensities (39). These results are consistent with previous studies that have found an association between subcortical white matter lesions and memory performance (322, 323), but are at odds with others that show that periventricular white matter hyperintensities, but not deep white matter hyperintensities, are associated with reduced cognitive performance (321, 324, 325). Mild periventricular changes alone are thought to reflect ageing phenomena (326); as white matter hyperintensities develop they become more confluent, making differentiation between deep and periventricular changes difficult in those with severe changes. This may help to explain the lack of correlation between periventricular scores and cognitive measures. While automated

measures of white matter hyperintensities behaved similarly to Fazekas total white matter intensity, if functional changes are largely driven by deep white matter changes, the ability of visual scales to distinguish between the two offers an advantage over automated measures.

Strengths and weaknesses

Strengths of this study include the use of 3 Tesla MRI in a large sample of older adults. Visual ratings were performed using validated, clinically relevant scales, by three independent raters who had received training in these instruments and used them with good inter and intra-rater reliability. The automated techniques involved complex computerised techniques, but have the advantage of being objective and non-operator dependent, as well as being able to generate large amounts of data analysis rapidly. The automated techniques in this study were chosen to map closely onto the visual ratings employed, but are not as sensitive as other analysis methods, particularly for white matter where DTI may be preferable in terms of describing white matter tract integrity and connectivity. The study was limited by focussing on only three measures of structural brain changes: global atrophy, hippocampal atrophy and white matter hyperintensities. While visual ratings can be usefully used for these and other aspects of brain structure, they lack the range and variety of analysis techniques that can be employed using automated measures. When considering correlations between brain structure and cognitive changes, the focus of this study was to compare visual and automated methods; therefore these analyses were not adjusted for age, sex or other variables, which would be necessary if associations with functional changes were to be considered in more detail.

Conclusion

These results show that visual MRI assessments can be used in this sample to quantify structural brain changes. While these measures are more subjective than automated measures, this study shows that they can be used with a high degree of reliability. It is therefore justifiable to use these visual measures in further analyses in relation to depression and vascular risk factors.

More widespread use of visual rating scales of MRI scans in clinical practice has the potential to increase accurate communication between clinicians, and to aid clinical diagnosis. Importantly for clinicians without routine access to MRI scans, these visual scales can be used to assess CT brain scans for both grey and white matter changes (297). More systematic,

widespread use of such scales across clinical services could be valuable in helping to increase consistency and to improve quality and standards of neuroimaging reporting, particularly in memory clinics.

6.5 Summary

Visual rating scales can be used effectively and have acceptable inter- and intra-rater reliability. This justifies their further use in analyses relating to depression and vascular risk factors. Visual and equivalent automated measures were significantly correlated and both provided a valid measure for quantifying structural changes, which were associated with impairment in cognitive tests. Visual ratings had the advantage of differentiating deep from periventricular white matter hyperintensities, which was not possible using automated measures. Visual ratings of MRI scans could be useful in clinical practice when automated measures are not available. They would allow clinicians to quantify structural brain changes in older adults and bridge the gap between sophisticated, computerised methods and routine clinical practice.

Chapter 7. Study of MRI correlates of vascular risk

7.1 Introduction

Chapter 7 investigates the structural MRI correlates of individual vascular risk factors that have been determined prospectively at five data-collection phases between 1985 and 2009. This use of prospective data enables vascular risk factors to be identified accurately and with confidence over several decades of the adult life-course. In addition, the chapter considers the cross-sectional association between coronary heart disease, identified at the time of the MRI scan, and structural brain changes. Combining these data on vascular risk factors and vascular disease with high-resolution MRI enables evaluation and localisation of any associations with structural changes in grey and white matter.

The aim of this chapter is to identify structural brain changes (using visual techniques as well as detailed automated MRI techniques) that are associated with longitudinal vascular risk factors and coronary heart disease. If similar brain regions prove to be affected by vascular risk and disease, and by depression, then this would provide support for the vascular depression hypothesis. If this is the case, then common structural changes may represent a mediating mechanism that could account for why these conditions commonly co-exist. The hypotheses are that elevated vascular risk factors will be associated with reduced grey matter volumes and reduced white matter integrity, particularly in frontal-subcortical regions. Based on the literature review in Chapter 2, hypertension and diabetes would be expected to have the most significant effects on brain structure, particularly on white matter.

7.2 Methods

For this analysis participants were drawn from phase 1 of the Whitehall Imaging sub-study. Of 229 participants recruited for this phase, exclusions were made on the basis of neurological conditions (n=25), incomplete MRI data (n=7), and inadequate MRI processing or grey matter segmentation (n=7). Therefore, 190 participants were considered for inclusion in this analysis (the same sample as described in Chapter 6). Details and reasons for further exclusions are discussed below.

The continuous variables (blood pressure, cholesterol, fasting glucose and FSRS) were investigated by considering the correlations with brain structure across the whole group of

participants. Ordinal variables (presence or absence of diabetes, smoking status, and presence or absence of coronary heart disease) were investigated using a case-control approach.

For continuous variables, to assess long-term exposure to vascular risk factors the mean of each score was calculated incorporating data from each of the five data collection phases between 1985 – 2009. This effectively incorporated all available data, allowing it to be used as a continuous variable in regression models with visual and automated MRI variables as outcomes. An alternative method would have been to use area under the curve analysis, which takes into account the time interval between repeat measurements. However, since the data collection phases were approximately equally spaced (every five years) in the Whitehall II, the simple mean of the measures is likely to correlate reasonably well with the area under the curve method as a measure of 'risk factor load'. A further possibility is to dichotomise participants' data at each time point (e.g. hypertensive or not hypertensive) and to sum the total score based on each of the five data collection phases. However, when modelling continuous vascular risk factors this approach would have reduced the statistical power compared to the use of the simple mean of measures.

7.2.1 Assessment of long-term exposure to vascular risk factors

All participants were required to have complete MRI data of good quality, and no major neurological conditions. Participants meeting these criteria were considered for inclusion based on long-term exposure to vascular risk. Further inclusion and exclusion criteria are detailed below.

Blood pressure

Blood pressure was measured at phases 1 (1985-1988), 3 (1991-1993), 5 (1997-1999), 7 (2003-2004) and 9 (2007-2009). When considering longitudinal associations the Mean Arterial Pressure (MAP) was calculated. This combines systolic and diastolic blood pressures into a single, composite measure using the formula: mean arterial pressure = ((2*mean diastolic pressure) + mean systolic blood pressure))/3. The MAP from each of these five phases was combined to form a single measure that was included as a continuous variable and correlated with structural MRI measures. Further exclusions were made on the basis of incomplete blood pressure data.

Cholesterol

Total cholesterol was measured at phases 1, 3, 5, 7 and 9. The mean total cholesterol level from each of these five phases was included as a continuous variable and correlated with structural MRI measures. Further exclusions were made on the basis of incomplete data on total cholesterol.

Diabetes and fasting glucose

Fasting glucose was measured across phases 3 to 9 (i.e. four times between 1991 and 2009) in those who did not already have a diagnosis of diabetes. The mean fasting glucose level from each of these phases was calculated and these measures were combined to form a single measure which was included as a continuous variable and correlated with structural MRI measures. Further exclusions were made on the basis of incomplete data on fasting glucose.

Type 2 diabetes was measured as a categorical variable (present or absent) in those who developed diabetes in the follow-up period i.e. from phase 5 onwards. Participants with type 2 diabetes were classed as cases, and were compared to controls drawn from the cohort. Controls were systematically excluded on the basis of age range and mean age, mean years of education and mean TOPF score, to create a comparable group to the cases.

Smoking

Smoking status was measured as a categorical variable. Participants who were smokers at the follow-up study (phase 9) were classed as cases. Controls were systematically excluded on the basis of age range and mean age, mean years of education and mean TOPF score, to create comparable groups to the cases.

Framingham Stroke Risk Score

The FSRS was measured at phases 1, 3, 5, 7 and 9. The mean score from each of these five phases was combined to form a single measure that was included as a continuous variable and correlated with structural MRI measures. Further exclusions were made on the basis of incomplete FSRS data.

Coronary heart disease

Coronary heart disease was defined on the basis of the presence or absence of angina and/or previous myocardial infarction. Control participants were required to have no history of coronary heart disease (including: angina, MI, hypertension, arrhythmias) according to definitions in ICD-10 Chapter IX (diseases of the circulatory system) (2). These data on CHD were obtained from participants' self-reported medical history using the questionnaire (see Appendix 1). Controls were systematically excluded on the basis of age range and mean age, mean years of education and mean TOPF score, to create comparable groups to the cases.

7.2.2 Brain MRI analysis

MRI analysis investigated the correlation between long-term exposure to vascular risk factors and differences in MRI brain structure using clinical, visual techniques and equivalent automated measures as described previously (Chapter 6.2 MRI methods). More detailed MRI analysis explored correlations using VBM and TBSS, both applied to whole-brain data. Continuous variables were correlated with structural MRI brain measures; categorical variables were investigated using a case-control approach.

Structural differences in grey matter were analysed using FSL-VBM (292), (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised VBM protocol (327) which uses FSL tools (288). First, structural images were brain-extracted and grey matter-segmented before being registered to the MNI152 standard space using FMRIB's Non-linear Image Registration Tool (FNIRT) (293, 294). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic gaussian kernel with a sigma of 3mm. Finally, voxelwise statistics were applied using 'randomise', a permutation-based method (using 5000 permutations) for non-parametric testing, which corrects for multiple comparisons across space. The significance threshold for group differences was set at $p<0.05$ using the threshold-free cluster enhancement (TFCE) option. The TFCE option maintains the sensitivity benefits of cluster-based thresholding, but avoids the problem of needing to pre-define an initial cluster-forming threshold, or to carry out a large amount of data-smoothing. It provides greater sensitivity than other methods, and richer, more interpretable output than cluster-based thresholding (328). For continuous

variables age, years of education (defined as years of continuous full-time education) and sex were included as confound regressors. For categorical variables, cases and controls were matched for age, years of education (defined as years of continuous full-time education) and sex. For both continuous and ordinal variables motion correction (MOCO) was included as a confound regressor, as this was used for some (but not all) scans, and can affect the structural images.

Changes in white matter were investigated using DTI and analysed using TBSS. TBSS is part of FSL (288) and allows voxelwise statistical analysis of the FA and MD data (101). First, 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 (289). All participants' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (293, 294), which uses a b-spline representation of the registration warp field (295). Next, the mean FA image was created and thinned to create a mean FA skeleton representing the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. The latter stages were repeated using measures of MD, RD, and AD. Finally, voxelwise statistics were applied using 'randomise', a permutation-based non-parametric testing (using 5000 permutations), which corrects for multiple comparisons across space. The significance threshold for group differences was set at $p<0.05$, using the TFCE option. Group differences in FA, MD, RD and AD were investigated across the whole skeleton. For continuous variables, age, years of education (defined as years of continuous full-time education) and sex were included as confound regressors. For categorical variables cases and controls were matched for age, years of education and sex.

To examine whether prevalent coronary heart disease explained the associations between risk factors and MRI parameters further analysis was undertaken where there were positive associations between vascular risk and MRI brain changes. For any positive findings, the main analyses were repeated after excluding participants who had a current or previous diagnosis of coronary heart disease.

7.3 Results

7.3.1 Blood pressure

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made on account of poor-quality MRI data which would have prevented analysis with VBM or TBSS. Therefore, in this analysis 171 participants were included. All had data on hypertension collected at phases 1, 3, 5, 7 and 9. The majority of participants were male with mean age 69.4 ± 5.5 years, with above-average mean IQ of 118. There were no significant differences in demographic data between included and excluded participants (Table 21). The MAP was 89.8 ± 8.2 mm Hg (Table 22).

Table 21. Participant demographics for analysis of blood pressure and cholesterol

	Included cases		Excluded cases		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	139 (81.3%)	-	50 (86.2%)	-	0.40
Age, *years*	171	69.4 ± 5.5	58	68.6 ± 4.7	0.26
TOPF	171	60.8 ± 9.5	58	61.7 ± 9.5	0.56
Education, y*ears*	171	14.1 ± 3.3	58	14.1 ± 2.7	0.94
MOCA	171	26.9 ± 2.5	58	27.2 ± 2.1	0.43

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

Table 22. Long-term vascular risk factors

Vascular risk factor	n	Mean ± SD
Mean arterial pressure, *mm Hg*	171	89.8 ± 8.2
Mean total cholesterol, *mmol/L*	171	5.76 ± 0.8
Mean fasting glucose, *mmol/L*	155	5.15 ± 0.36
Mean FSRS, *% risk per 10 years*	169	2.1 ± 1.8

Visual measures

Visual and equivalent automated measures were correlated with MAP across the whole sample using Pearson's correlation. There was a weak but significant association with left and right medial temporal lobe atrophy; this was not replicated using the equivalent automated measures (Table 23). Automated measures showed a weak but significant correlation between MAP and measures for general atrophy and white matter hyperintensities.

Table 23. Correlation between MRI measures and mean arterial pressure

	Mean arterial pressure (n=171)	
	Pearson's correlation, *r*	p-value
Visual measures		
Global atrophy	0.07	0.35
Medial temporal lobe atrophy		
Left	0.17	0.03
Right	0.27	<0.001
White matter hyperintensities		
Total	0.09	0.27
Periventricular	0.02	0.822
Deep	0.13	0.10
Automated measures		
Global atrophy	0.16	0.04
Medial temporal lobe atrophy		
Left	-0.12	0.11
Right	-0.10	0.18
White matter hyperintensities	0.20	0.01

Grey matter

For grey matter using VBM, there were no significant correlations with longitudinal MAP at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, there were no significant correlations with longitudinal MAP in FA, MD, RD or AD, at the threshold of $p<0.05$ using TFCE. Values for FA and AD approached, but did not reach significance.

7.3.2 Cholesterol

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made due to poor-quality MRI data which would have prevented analysis with VBM or TBSS. Therefore, in this analysis 171 participants were included. All had data on total cholesterol collected at phases 1, 3, 5, 7 and 9. Participant demographic details are displayed in Table 21. The majority of participants were male with mean age 69.4 ± 5.5 years and above-average mean IQ of 118. There were no significant differences in demographic data between included and excluded participants (Table 21). The mean total cholesterol level was 5.76 ± 0.8 mmol/L (Table 22).

Visual measures

Visual and equivalent automated measures were correlated with mean total cholesterol level across the whole sample using Pearson's correlation. There was a weak but significant association with global atrophy, but this was not replicated using the equivalent automated measures (Table 24). There were no other significant correlations for visual or automated measures.

Grey matter

For grey matter using VBM, there were no significant correlations with longitudinal mean total cholesterol at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, there were no significant correlations with longitudinal mean total cholesterol in FA, MD, RD or AD, at the threshold of $p<0.05$ using TFCE.

Table 24. Correlation between MRI measures and mean total cholesterol

	Mean total cholesterol (n=171)	
	Pearson's correlation, *r*	p-value
Visual measures		
Global atrophy	0.16	0.04
Medial temporal lobe atrophy		
Left	0.03	0.66
Right	-0.002	0.98
White matter hyperintensities		
Total	0.01	0.87
Periventricular	-0.9	0.24
Deep	0.11	0.16
Automated measures		
Global atrophy	0.12	0.12
Medial temporal lobe atrophy		
Left	-0.02	0.81
Right	-0.12	0.12
White matter hyperintensities	0.14	0.08

7.3.3 Diabetes

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made due to poor-quality MRI data which would have prevented analysis with VBM or TBSS. Lack of data on fasting blood glucose led to a further 16 exclusions. Therefore, when investigating mean fasting glucose level 155 participants were included. The majority of participants were male with mean age 69.3 ± 5.5 years, with above-average mean IQ of 119. There were no significant differences in demographic data between included and excluded participants (Table 25). The mean fasting glucose level was 5.15 ± 0.36 mmol/L.

Table 25. Participant demographics for analysis of mean fasting glucose

	Included cases (n=155)		**Excluded cases (n=74)**		**p-value***
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	128 (82.6%)	-	61 (82.4%)		0.98
Age, *years*	155	69.3 ± 5.5	74	69.1 ± 4.9	0.83
TOPF	155	61.2 ± 9.2	74	60.7 ± 10.0	0.70
Education, *years*	155	14.2 ± 3.3	74	13.9 ± 2.8	0.39
MOCA	155	27.0 ± 2.3	74	26.8 ±2.6	0.64

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

When investigating participants with type 2 diabetes compared to controls, cases were drawn from the same sample (i.e. the original 190 participants minus those excluded due to lack of DTI data and poor-quality MRI data, n=171). From this sample 12 cases were identified. Further exclusions were made in order to create a control group with comparable characteristics to the cases. Exclusions were made on the basis of lack of data related to diabetes status (n=8), age (n=50), education (n=11), sex (n=15). Therefore, 75 controls were included. The majority of cases were male, with mean age of 71.1 ± 4.7 years, mean IQ of 110. Demographic characteristics in both groups were similar (Table 26).

Table 26. Participant demographics for analysis of type 2 diabetes

	Diabetic cases (n=12)		Controls (n=75)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	8 (66.7%)	-	63 (84.0%)	-	0.15
Age, *years*	12	71.1 ± 4.7	75	70.9 ± 4.2	0.85
TOPF	12	54.3 ± 11.5	75	61.3 ± 8.9	0.07
Education, *years*	12	13.3 ± 2.6	75	13.5 ± 3.0	0.86
MOCA	12	24.8 ± 4.0	75	26.9 ± 2.2	0.10

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

Visual measures

There was no correlation between mean fasting glucose and visual or equivalent automated measures (Table 27). When comparing cases with diabetes and controls, there were no significant differences between groups for visual or automated measures (Table 28).

Grey matter

For grey matter using VBM, there were no significant correlations with longitudinal mean fasting glucose at the threshold of $p<0.05$ using TFCE. For type 2 diabetes, there were no significant differences between cases and controls.

Table 27. Correlation between MRI measures and mean fasting glucose

	Mean fasting glucose (n=155)	
	Pearson's correlation, *r*	p-value
Visual measures		
Global atrophy	0.002	0.98
Medial temporal lobe atrophy		
Left	0.07	0.38
Right	0.07	0.36
White matter hyperintensities		
Total	-0.12	0.14
Periventricular	-0.13	0.10
Deep	-0.07	0.36
Automated measures		
Global atrophy	-0.02	0.79
Medial temporal lobe atrophy		
Left	0.02	0.80
Right	0.08	0.31
White matter hyperintensities	-0.05	0.52

Table 28. Group differences in MRI measures: type 2 diabetes and controls

	Cases (n=12)		Controls (n=75)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	1 (8.3)	-	0 (0.0)	-	0.62†
1 (mild)	4 (33.3)	-	32 (42.7)	-	
2 (moderate)	5 (41.7)	-	37 (49.3)	-	
3 (severe)	2 (16.7)	-	6 (8.0)	-	
Automated	-	27.7 ± 3.8	-	26.3 ± 2.4	0.09†
Left medial temporal lobe atrophy					
0 (normal)	2 (16.7)	-	18 (24.0)	-	0.48†
1 (slight increase)	8 (66.7)	-	36 (48.0)	-	
2 (mod. increase)	2 (16.7)	-	20 (26.7)	-	
3 (severe increase)	0 (0.0)	-	1 (1.3)	-	
Automated	-	0.25 ± 0.03	-	0.24 ± 0.04	0.23†
Right medial temporal lobe atrophy					
0 (normal)	2 (16.7)	-	19 (25.3)	-	0.76
1 (slight increase)	7 (58.3)	-	42 (56.0)	-	
2 (mod. increase)	3 (25.0)	-	14 (18.7)	-	
3 (severe increase)	0 (0.0)	-	0 (0.0)	-	
Automated	-	0.25 ± 0.03	-	0.24 ± 0.03	0.59†
Deep white matter hyperintensities (DWM)					
0 (absent)	0 (0.0)	-	1 (1.3)	-	0.67†
1 (punctate foci)	7 (58.3)	-	44 (58.7)	-	
2 (beginning confluence of foci)	5 (41.7)	-	26 (34.7)	-	
3 (large confluent areas)	0 (0.0)	-	4 (5.3)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.50
1 (caps or pencil thin lining)	6 (50.0)	-	50 (66.7)	-	
2 (smooth halo)	5 (41.7)	-	22 (29.3)	-	
3 (irregular and extending to DWM)	1 (8.3)	-	3 (4.0)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	0.78†
1	0 (0.0)	-	1 (1.3)	-	
2	5 (41.7)	-	36 (48.0)	-	
3	3 (25.0)	-	20 (26.7)	-	
4	3 (25.0)	-	13 (17.3)	-	
5	1 (8.3)	-	4 (5.3)	-	
6	0 (0.0)	-	1 (1.3)	-	
Automated	-	0.68 ± 0.65	-	0.45 ± 0.43	0.11

* p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

For white matter using TBSS, there were significant correlations between long-term exposure to high fasting glucose and reduced FA within the right posterior corona radiata, right corticospinal tract, and in the splenium and body of the corpus callosum, at the threshold of $p<0.05$ using TFCE (Figure 9). For AD there was a very small, significant cluster in the posterior limb of the internal capsule.

There were significant correlations between long-term exposure to high fasting glucose and increased RD in multiple regions, including those where reduced FA was observed. There was increased RD within the right superior longitudinal fasciculus, right superior and anterior corona radiata, right and left posterior corona radiata, right corticospinal tract, and in the splenium and body of the corpus callosum, when using the threshold of $p<0.05$ using TFCE (Figure 9). Given that there were minimal changes in AD, correlations with MD were seen to a lesser degree. However, significant clusters were again seen in regions where reduced FA was observed, including the splenium and body of the corpus callosum as well as within the right superior corona radiata. The correlation between longitudinal mean fasting glucose and white matter changes is further illustrated in Figures 10 and 11. These scatterplots show the correlation between longitudinal mean fasting glucose and significantly different FA and RD values ($p=<0.05$).

TBSS results for mean fasting glucose were re-analysed following exclusion of CHD cases (n=8). This resulted in 147 participants (mean age 69.2 ± 5.4 years, 83% male, mean education 14.2 ± 3.3 years, mean TOPF score 61.1 ± 9.4). Again, using thresholds of $p<0.05$ and TFCE, FA remained significantly reduced in the right posterior corona radiata, and in the splenium and body of the corpus callosum. There were no significant differences in AD. RD was significantly increased within similar regions, including the right superior corona radiata, left posterior corona radiata, and in the splenium and body of the corpus callosum. There were fewer correlations with MD, but there were significant clusters in the right superior corona radiata, left posterior corona radiata, and in the splenium and body of the corpus callosum.

For type 2 diabetes there were no significant differences between cases and controls in FA, MD, RD or AD at the threshold of $p<0.05$ using TFCE.

Figure 9. Correlation between long-term exposure to elevated fasting glucose and white matter

Regions in which there are significant correlations in Fractional Anisotropy (red), Mean Diffusivity, Radial Diffusivity and Axial Diffusivity (blue) at a threshold of $p<0.05$, overlaid on the mean FA skeleton (green). Significant regions are dilated for illustrative purposes.
R=right; L=left; P=posterior; A=anterior

Slice locations:
X 84, Y 94, Z 89 and Z 99

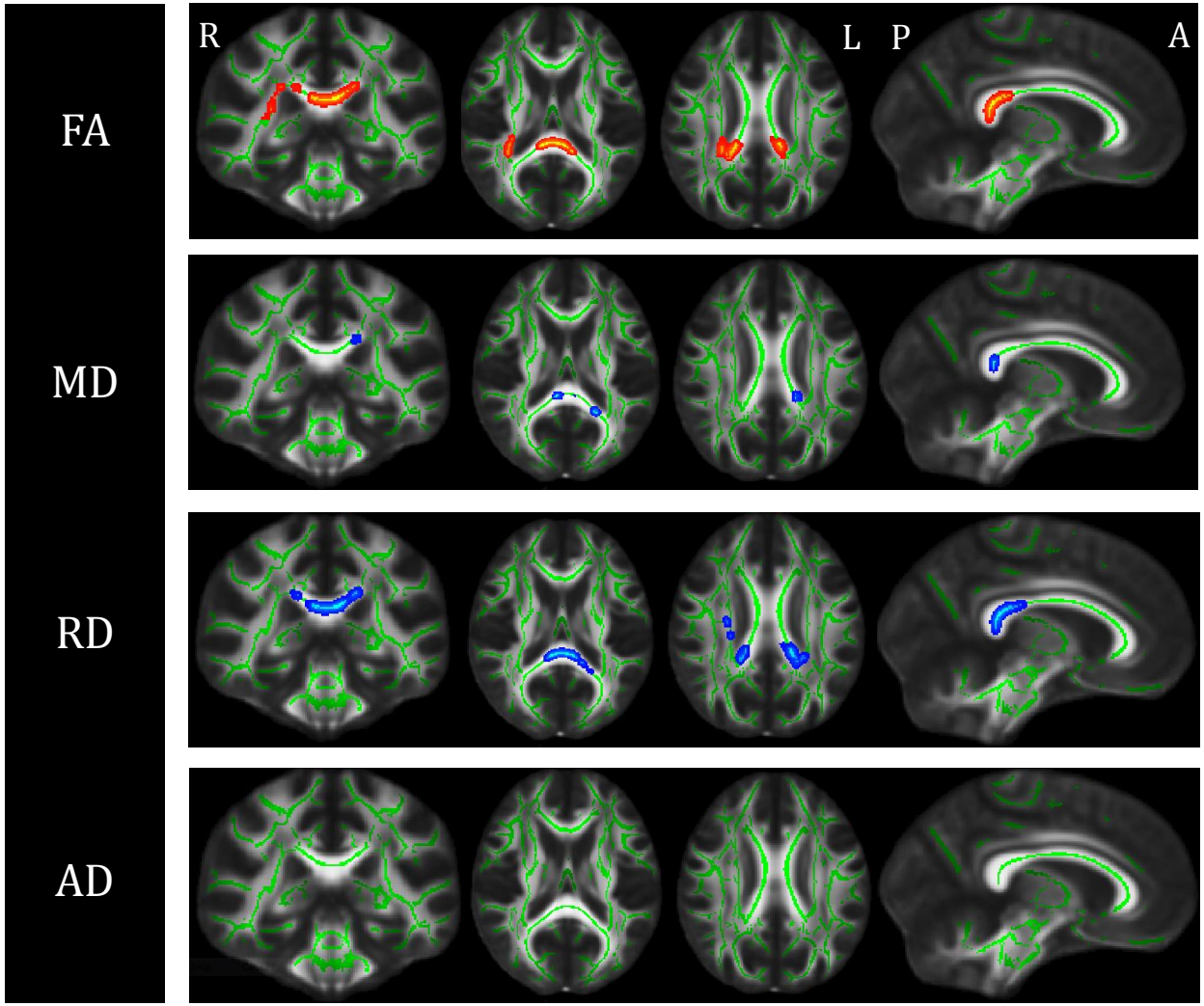


Figure 10. Scatterplot to show the correlation between mean fasting glucose and fractional anisotropy in regions of statistically significant difference (p<0.05)

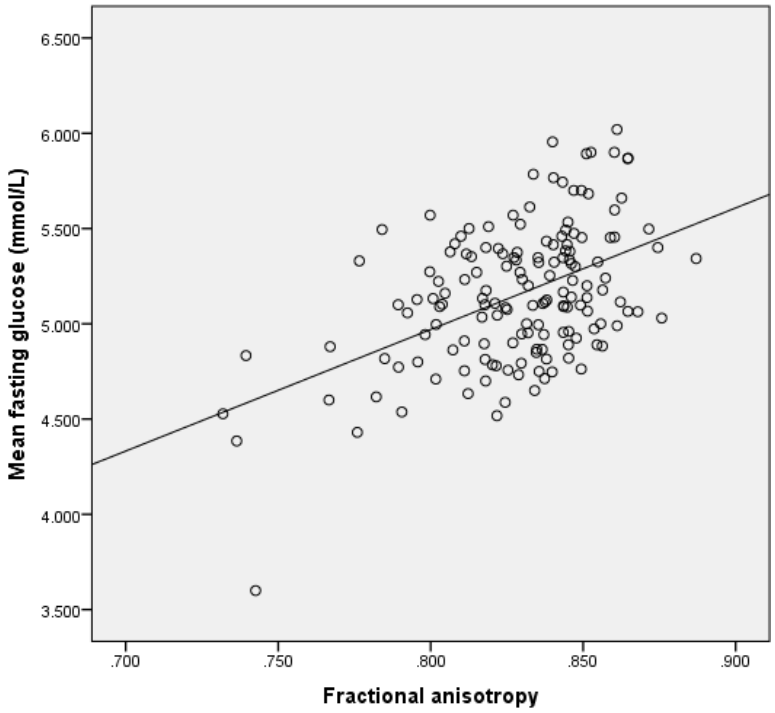
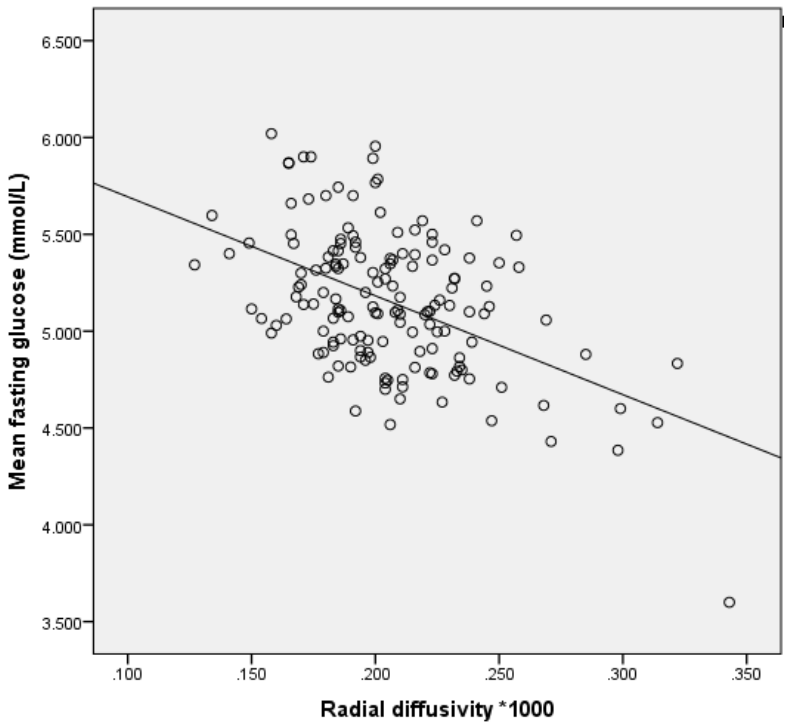


Figure 11. Scatterplot to show the correlation between mean fasting glucose and radial diffusivity in regions of statistically significant difference (p<0.05)



7.3.4 Smoking

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made due to poor-quality MRI data which would have prevented analysis with VBM or TBSS. From this sample of 171 participants there were 14 current smokers who were included as cases. Further exclusions were made in order to create a control group with comparable characteristics to the cases. Exclusions were made on the basis of age (n=12) and education (n=27). Controls who were smokers at baseline (n=9) were also excluded. Therefore, 109 controls were included. The majority of cases were male with mean age 68.2 ± 4.9 years and with mean IQ of 115. Cases and controls were well matched for demographic characteristics, with no significant differences between groups (Table 29).

Table 29. Participant demographics for analysis of smoking status

	Cases (n=14)		**Controls (n=109)**		**p-value***
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	11 (78.6%)	-	88 (80.7%)	-	0.85
Age, *years*	14	68.2 ± 4.9	109	68.6 ± 5.1	0.82
TOPF	14	62.1 ± 5.1	109	60.0 ± 10.2	0.21
Education, *years*	14	12.9 ± 2.1	109	13.1 ± 2.7	0.68
MOCA	14	27.3 ± 1.8	109	27.1 ± 2.5	0.72

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

Visual measures

Visual and equivalent automated measures were compared between cases and controls. For visual measures there was a significant group difference for left medial temporal lobe atrophy; this was not replicated using the equivalent automated measures (Table 30). There were no significant group differences for other visual measures or equivalent automated measures.

Grey matter

For grey matter using VBM, there were no significant group differences between cases and controls in terms of their smoking status, using a threshold of $p<0.05$ with TFCE.

White matter

For white matter using TBSS there were no significant group differences between cases and controls in terms of smoking status for FA, MD, RD or AD, at the threshold of $p<0.05$ using TFCE.

Table 30. Group differences in MRI measures: smoking status

	Cases (n=14)		Controls (n=109)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	0 (0.0)	-	4 (3.7)	-	0.72
1 (mild)	6 (42.9)	-	52 (47.7)	-	
2 (moderate)	7 (50.0)	-	50 (45.9)	-	
3 (severe)	1 (7.1)	-	3 (2.8)	-	
Automated	-	26.4 ± 2.9	-	25.5 ± 2.6	0.23†
Left medial temporal lobe atrophy					
0 (normal)	4 (28.6)	-	38 (34.9)	-	0.01
1 (slight increase)	3 (21.4)	-	55 (50.5)	-	
2 (mod. increase)	7 (50.0)	-	16 (14.7)	-	
3 (severe increase)	0 (0.0)	-	0 (0.0)	-	
Automated	-	0.23 ± 0.04	-	0.24 ± 0.03	0.20†
Right medial temporal lobe atrophy					
0 (normal)	3 (21.4)	-	37 (33.9)	-	0.08
1 (slight increase)	6 (42.9)	-	58 (53.2)	-	
2 (mod. increase)	5 (35.7)	-	14 (12.8)	-	
3 (severe increase)	0 (0.0)	-	0 (0.0)	-	
Automated	-	0.25 ± 0.03	-	0.25 ± 0.03	0.92†
Deep white matter hyperintensities (DWM)					
0 (absent)	0 (0.0)	-	3 (2.8)	-	0.70
1 (punctate foci)	9 (64.3)	-	72 (66.1)	-	
2 (beginning confluence of foci)	5 (35.7)	-	29 (26.6)	-	
3 (large confluent areas)	0 (0.0)	-	5 (4.6)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.66
1 (caps or pencil thin lining)	9 (64.3)	-	64 (58.7)	-	
2 (smooth halo)	5 (35.7)	-	39 (35.8)	-	
3 (irregular and extending to DWM)	0 (0.0)	-	6 (5.5)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	0.69†
1	0 (0.0)	-	3 (2.8)	-	
2	7 (50.0)	-	52 (47.7)	-	
3	4 (28.6)	-	28 (25.7)	-	
4	3 (21.4)	-	17 (15.6)	-	
5	0 (0.0)	-	8 (7.3)	-	
6	0 (0.0)	-	1 (0.9)	-	
Automated	-	0.43 ± 0.39	-	0.39 ± 0.35	0.71†

*p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

7.3.5 Framingham Stroke Risk Score

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made due to poor-quality MRI data which would have prevented analysis with VBM or TBSS. Lack of complete data on FSRS led to a further two exclusions. Therefore, in this analysis 169 participants were included. The majority of participants were male with mean age 69.5 ± 5.5 years and above-average mean IQ of 118. There were no significant differences in demographic data between included and excluded participants (Table 31). The mean FSRS was 2.1 ± 1.8.

Table 31. Participant demographics for analysis of Framingham Stroke Risk Score

	Included cases (n=169)		**Excluded cases (n=60)**		**p-value***
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	138 (81.7 %)	-	51 (85.0%)	-	0.56
Age, *years*	169	69.5 ± 5.5	60	68.5 ± 4.6	0.20
TOPF	169	60.8 ± 9.5	60	61.8 ± 9.4	0.48
Education, *years*	169	14.2 ± 3.2	60	13.9 ± 2.8	0.62
MOCA	169	26.9 ± 2.5	60	27.2 ± 2.1	0.35

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

Visual measures

Visual and equivalent automated measures were correlated with FSRS across the whole sample using Pearson's correlation. Using visual measures there were significant correlations with global atrophy, right and left medial temporal lobe atrophy and with deep white matter hyperintensities (Table 32). This was replicated using equivalent automated measures. When correlations with visual measures were additionally adjusted for age most became non-significant, apart from left medial temporal lobe atrophy (r=0.16, p=0.04). When correlations with automated measures were additionally adjusted for age, most remained statistically significant (global atrophy r=0.23, p=0.002; left medial temporal lobe atrophy r=-0.16, p=0.04; right medial temporal lobe atrophy r=-0.19, p=0.02), although that with total white matter

hyperintensities attenuated to the null (r=0.06, p=0.46). These findings suggest that longitudinal FSRS is unlikely to be associated with structural changes in grey and white matter.

Table 32. Correlation between MRI measures and Framingham Stroke Risk Score

	Mean FSRS (n=169)	
	Pearson correlation, *r*	p-value
Visual measures		
Global atrophy	0.33	<0.001
Medial temporal lobe atrophy		
Left	0.33	<0.001
Right	0.32	<0.001
White matter hyperintensities		
Total	0.15	0.05
Periventricular	0.07	0.40
Deep	0.20	0.01
Automated measures		
Global atrophy	0.48	<0.001
Medial temporal lobe atrophy		
Left	-0.26	0.001
Right	-0.27	<0.001
White matter hyperintensities	0.23	0.002

Grey matter

For grey matter using VBM, there were no significant correlations with longitudinal mean FSRS at the threshold of p<0.05 using TFCE.

White matter

For white matter using TBSS, there were no significant correlations between longitudinal FSRS and FA, MD, RD or AD, at the threshold of p<0.05 using TFCE.

7.3.6 Coronary heart disease

From the sample of 190 participants from the Whitehall Imaging sub-study, a further four exclusions were made due to lack of DTI data, and a further 15 exclusions were made due to poor-quality MRI data which would have prevented analysis with VBM or TBSS. From this sample of 171 participants there were 10 people with CHD (five with angina, four with previous MI and one with angina and a previous MI). The majority of cases were male with mean age 71.5 ± 6.9 years and mean IQ of 117. The remaining 161 participants were considered for inclusion in the control group. From this group 71 participants were excluded due to the presence of CHD as defined by ICD-10 Chapter IX (diseases of the circulatory system) (2) and 22 were excluded based on age in order to create a control group with comparable characteristics to the cases. Therefore, in total there were 68 controls. Cases and controls were well matched for demographic characteristics, with no significant differences between groups (Table 33).

Visual measures

Visual and equivalent automated measures were compared between cases and controls. There were no significant group differences for visual measures or equivalent automated measures (Table 34).

Grey matter

For grey matter using VBM, there were no significant group differences in grey matter between cases and controls, using a threshold of $p<0.05$ with TFCE.

White matter

For white matter using TBSS there were no significant group differences between cases and controls for FA, MD, RD or AD at the threshold of $p<0.05$ using TFCE.

Table 33. Participant demographics for analysis of coronary heart disease

	Cases (n=10)		Controls (n=68)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Sex, *male*	7 (70.0%)	-	49 (72.1%)	-	0.89
Age, *years*	10	71.5 ± 6.9	68	70.2 ± 5.0	0.47
TOPF	10	60.9 ± 7.3	68	60.3 ± 11.0	0.86
Education, *years*	10	14.2 ± 2.7	68	14.4 ± 3.5	0.83
MOCA	10	25.7 ± 2.0	68	26.9 ± 2.6	0.15

* p-value from chi-squared test (sex) or analysis of variance (all other variables)

Table 34. Group differences in MRI measures: coronary heart disease

	Cases (n=10)		Controls (n=68)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	0 (0.0)	-	2 (2.9)	-	0.62†
1 (mild)	4 (40.0)	-	24 (35.3)	-	
2 (moderate)	4 (40.0)	-	35 (51.5)	-	
3 (severe)	2 (20.0)	-	7 (10.3)	-	
Automated	-	26.9 ± 3.4	-	26.3 ± 2.8	0.53†
Left medial temporal lobe atrophy					
0 (normal)	1 (10.0)	-	26 (38.2)	-	0.21†
1 (slight increase)	6 (60.0)	-	26 (38.2)	-	
2 (mod. increase)	3 (30.0)	-	15 (22.1)	-	
3 (severe increase)	0 (0.0)	-	1 (1.5)	-	
Automated	-	0.24 ± 0.03	-	0.24 ± 0.03	0.73†
Right medial temporal lobe atrophy					
0 (normal)	2 (20.0)	-	22 (32.4)	-	0.63†
1 (slight increase)	5 (50.0)	-	33 (48.5)	-	
2 (mod. increase)	3 (30.0)	-	12 (17.6)	-	
3 (severe increase)	0 (0.0)	-	1 (1.5)	-	
Automated	-	0.24 ± 0.02	-	0.25 ± 0.03	0.90†
Deep white matter hyperintensities (DWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.79
1 (punctate foci)	7 (70.0)	-	44 (64.7)	-	
2 (beginning confluence of foci)	3 (30.0)	-	21 (30.9)	-	
3 (large confluent areas)	0 (0.0)	-	3 (4.4)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.79
1 (caps or pencil thin lining)	5 (50.0)	-	41 (60.3)	-	
2 (smooth halo)	4 (40.0)	-	23 (33.8)	-	
3 (irregular and extending to DWM)	1 (10.0)	-	4 (5.9)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	0.92†
1	0 (0.0)	-	0 (0.0)	-	
2	5 (50.0)	-	34 (50.0)	-	
3	2 (20.0)	-	17 (25.0)	-	
4	2 (20.0)	-	12 (17.6)	-	
5	1 (10.0)	-	3 (4.4)	-	
6	0 (0.0)	-	2 (2.9)	-	
Automated	-	0.53 ± 0.42	-	0.51 ± 0.67	0.92†

*p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

7.4 Summary

For visual MRI measures there were correlations between long-term exposure to vascular risk factors (mean arterial pressure, mean total cholesterol, smoking status and mean FSRS) and structural MRI correlates, particularly for left medial temporal lobe atrophy (Table 35). However, most of the significant correlations were weak in strength. It is possible that a more robust association would be seen with a larger sample size, particularly for type 2 diabetes and smoking status, which both had small numbers of cases. Framingham Stroke Risk Score was the only variable to have a significant association with visual measures of global atrophy, medial temporal lobe atrophy and deep white matter hyperintensities. Although these results were replicated using equivalent automated measures, correlations with visual measures did not remain significant following adjustment for age. However, it may be the case that this composite measure is better able to predict structural MRI brain changes than the single vascular risk factors.

On the basis of associations with visual measures, it was hypothesised that grey matter changes would also be found using more sensitive analysis of grey matter using VBM. However, contrary to this hypothesis, long-term exposure to vascular risk factors was not correlated with VBM measures of grey matter.

Analysis of associations between long-term exposure to vascular risk factors and white matter integrity using TBSS produced largely negative results. However, mean fasting glucose was associated with significant differences in white matter, particularly in FA and RD. Reduced FA and increased RD was seen in the splenium and body of the corpus callosum, right posterior corona radiata and right corticospinal tract. RD was increased in other frontal-subcortical areas including right superior and anterior corona radiata and right superior longitudinal fasciculus. Contrary to the original hypothesis, hypertension did not have a significant effect on white matter.

Table 35. Summary of significant MRI correlates of vascular risk

Vascular risk / disease	MRI measure		
	Visual	**Grey matter (VBM)**	**White matter (TBSS)**
Blood pressure	Left and right medial temporal lobe atrophy	-	-
Cholesterol	Global atrophy	-	-
Diabetes / fasting glucose	-	-	Reduced FA and increased RD in corpus callosum, increased RD in other frontal-subcortical tracts including posterior corona radiata and right corticospinal tract
Smoking	Left medial temporal lobe atrophy	-	-
FSRS	Global atrophy Left and right medial temporal lobe atrophy Deep white matter hyperintensities	-	-
CHD	-	-	-

Chapter 8. Study of MRI correlates of depression

8.1 Introduction

Chapter 8 focuses on the structural MRI correlates of depressive symptoms, identified using the CES-D rating scale, and depressive disorder, following diagnosis using the SCID in accordance with DSM-IV criteria. This allows MRI correlates of depressive symptoms to be identified based on: current depressive symptoms (current CES-D score), late-onset depressive symptoms (raised CES-D score over the age of 60), lifetime diagnosis of DSM-IV major depressive disorder (using the SCID), and long-term exposure to depressive symptoms (cumulative CES-D score).

The aim of this chapter is to identify structural brain changes associated with depressive symptoms using visual techniques as well as detailed automated MRI techniques. The different approaches to defining depressive symptoms taken by CES-D and DSM-IV diagnosis is of particular interest, and one aim of this study is to determine whether these different clinical methods for identifying symptoms are associated with similar underlying pathophysiological changes. This is an important question in the context of epidemiological studies: if depressive symptoms identified using the CES-D equate to neurobiological changes associated with major depression, then this strengthens the case for using this simple and straightforward measure, particularly when there are constraints on time. The longitudinal nature of the data additionally allows investigation of whether late-onset depressive symptoms are associated with MRI brain changes, and whether persistent depressive symptoms over the course of adult life lead to increased structural brain changes later in life. The hypotheses were that there would be group differences between controls and participants with current depressive symptoms, late-onset depressive symptoms, or a previous DSM-IV diagnosis of major depressive disorder, who would show reduced grey matter volumes (particularly in the hippocampus) and reduced white matter integrity, particularly in frontal-subcortical regions. Furthermore, it was hypothesised that long-term exposure to depressive symptoms would show a more pronounced correlation with structural brain changes.

8.2 Methods

The investigations of current depressive symptoms, late-onset depressive symptoms and major depressive disorder each adopt a case-control approach with all participants drawn from phase 1 of the Whitehall Imaging sub-study. Investigation of long-term exposure to depressive symptoms considers the correlation between depressive symptoms and structural MRI measures across the whole group. Criteria for defining these groups are summarised in Table 36.

8.2.1 Current depressive symptoms

Current depressive symptoms were measured using the self-reported CES-D scale. Cases were classified as participants with a CES-D score ≥16, which equates to clinically significant depressive symptoms (254). Participants in this category were compared with controls who had a score <16 on CES-D, had no history of depression (measured using CES-D and SCID), and were not currently using antidepressant medication. Exclusions were made on the basis of incomplete or poor-quality MRI data and major neurological conditions including stroke and TIA. Additionally, controls were excluded systematically on the basis of age to ensure that mean age and age range, mean years of education and mean TOPF scores were similar, in order to create comparable groups.

8.2.2 Late-onset depressive symptoms

Cases were identified during phase 10 of the Whitehall II Study on the basis of normal CES-D and GHQ scores at age <60 and high CES-D scores at age ≥60, indicating late-onset depressive symptoms. Controls had current and previous CES-D symptoms <16 and were not taking antidepressant medication. SCID diagnosis of major depressive disorder was not used as an inclusion or exclusion criterion, since the aim was to determine whether changes could be identified purely on the basis of CES-D score alone. Both cases and controls were required to have complete MRI data of good quality, and no major neurological conditions. Controls were systematically excluded on the basis of age range and mean age, mean years of education and mean TOPF score to create comparable groups.

8.2.3 Major depressive disorder

Cases were identified on the basis of a clinical diagnosis of major depressive disorder identified through the SCID semi-structured interview performed at the time of the MRI scan. Controls had no current or previous SCID diagnosis of mental illness (including major depressive disorder, mood disorder not otherwise specified, dysthymia and bipolar disorder), no significant current or previous depressive symptoms as measured by CES-D (CES-D<16), and were not taking antidepressant medication. Both cases and controls were required to have complete MRI data of good quality, and no major neurological conditions. Controls were systematically excluded on the basis of age range and mean age, mean years of education and mean TOPF score to create comparable groups.

8.2.4 Long-term exposure to depressive symptoms

The effects of long-term exposure to elevated depressive symptoms were studied to determine whether persistently elevated depressive symptoms in mid-life might alter brain structure in late-life, therefore predisposing to late-life depression. The 'cumulative CES-D score' was calculated by summing the CES-D scores from phase 7 (2003 - 2004), phase 9 (2007 – 2009) and the Whitehall Imaging sub-study (2012 – 2013), and calculating the mean. The use of CES-D provides a continuous measure of depressive symptoms, and therefore CES-D scores of all participants were used to correlate depressive symptoms and MRI measures. To investigate the spectrum of depressive symptoms, all participants were included, and a range of depressive symptoms identified using CES-D (and therefore with a range of diagnoses identified using the SCID interview). Exclusions were made only on the basis of major neurological conditions, incomplete MRI data or poor-quality MRI data.

8.2.5 Brain MRI analysis

For current depressive symptoms, late-onset depressive symptoms and major depressive disorder, MRI analysis used a case-control approach to identify group differences. This utilised clinical, visual techniques and equivalent automated measures as described previously (Chapters 4.6 and 6.2). Further MRI analysis explored group differences in grey matter using VBM and TBSS as described in Chapter 7.2.

For long-term exposure to depressive symptoms, the cumulative CES-D score was correlated with structural measures: visual measures, VBM and TBSS. Analysis of MRI correlations for this continuous variable used the same methods as described in Chapter 7.2.2.

Table 36. Criteria used to define depressive symptoms and disorder

	CES-D score	DSM-IV diagnosis	Current antidepressant medication
Current depressive symptoms (n=20)			
Cases	≥16 at MRI scan		
Controls	<16 at MRI scan No previously elevated CES-D scores	None	None
Late-onset depressive symptoms (n=26)			
Cases	≥16 at age ≥60 normal CES-D and scores at age <60		
Controls	current and previous CES-D score <16		None
Major depressive disorder (n=32)			
Cases	-	DSM-IV criteria for major depressive disorder	
Controls	current and previous CES-D score <16	No previous DSM-IV diagnosis	None
Long-term exposure to depressive symptoms (n=171)			
Inclusions	Mean of CES-D scores at three phases from 2003 - 2013	-	-

8.3 Results

8.3.1 Current depressive symptoms

In Chapter 6 a group of 190 participants was identified who did not have major neurological conditions and had adequate-quality MRI data. This group included 21 participants with current depressive symptoms (CES-D ≥16). One participant was excluded due to missing DTI data, leaving 20 cases and a potential 169 controls. Further exclusions were made in the control group on account of a previous SCID diagnosis (n=30), previous high CES-D score (n=27), missing previous CES-D score (n=1), current use of antidepressant medication (n=8) and incomplete or poor-quality MRI data (n=15). Five further participants were excluded on the basis of age, to ensure that the control group was comparable with the cases. At this stage the control group was comparable with cases for age, as well as for years of education and TOPF score; no further exclusions were necessary in relation to the latter two variables. The final control group included 83 participants.

The mean CES-D score within the cases was 22.5 ± 7.0, and within the controls was 3.0 ± 3.1. There were no significant differences between cases and controls for age, years of education, and TOPF, although the proportion of men among the cases was lower (Table 37). Performance on cognitive assessments was similar between groups. The only significant difference was on the TMTB (this remained significant when making additional adjustment for the effect of gender).

Visual measures

Visual, ordinal measures were compared using the chi-squared test; equivalent automated, continuous measures were compared using independent samples t-tests. Visual measures of MRI brain structure showed no differences between groups. However, there was a significant difference using equivalent automated measures for total white matter hyperintensity volume (p=0.02) (Table 38).

Table 37. Participant demographics: current depressive symptoms and controls

	Cases (n=20)		Controls (n=83)		p-value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Demographics					
Sex, *male*	13 (65.0%)		71 (85.5%)		0.03
Age, *years*	-	70.4 ± 5.5	-	69.3 ± 5.0	0.41
Education, *years*	-	14.5 ± 4.2	-	13.8 ± 3.0	0.38
TOPF	-	61.9 ± 11.2	-	60.3 ± 8.9	0.51
Pre-morbid IQ*	-	116.8 ± 12.5	-	116.6 ±9.9	0.94
Cognitive testing					
MOCA	-	26.7 ± 3.0	-	27.1 ± 2.4	0.47
HVLT	-	25.3 ± 6.4	-	27.1 ± 5.0	0.19
TMTB, *secs*	-	84.7 ± 62.3	-	62.5 ± 26.9	0.02
DSFW	-	10.4 ± 2.5	-	11.3 ± 2.3	0.10
DSBW	-	10.2 ± 3.1	-	9.9 ± 2.7	0.70
DC	-	55.9 ± 14.7	-	62.9 ± 14.3	0.05
Depressive symptoms					
CES-D	-	22.5 ± 7.0	-	3.0 ± 3.1	<0.001
Current antidepressant medication	3 (15.0 %)	-	0 (0 %)	-	<0.001

* Estimated from the Test of Premorbid function (TOPF), education and sex

Table 38. Group differences in MRI measures: current depressive symptoms and controls

	Cases (n=20)		Controls (n=83)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	1 (5.0)	-	0 (0.0)	-	
1 (mild)	8 (40.0)	-	36 (43.4)	-	0.99†
2 (moderate)	10 (50.0)	-	43 (51.8)	-	
3 (severe)	1 (5.0)	-	4 (4.8)	-	
Automated	-	25.8 ± 2.5	-	25.9 ± 2.7	0.84†
Left medial temporal lobe atrophy					
0 (normal)	8 (40.0)	-	21 (25.3)	-	
1 (slight increase)	7 (35.0)	-	44 (53.0)	-	0.31†
2 (mod. increase)	5 (25.0)	-	17 (20.5)	-	
3 (severe increase)	0 (0.0)	-	1 (1.2)	-	
Automated	-	0.25 ± 0.04	-	0.24 ± 0.04	0.28†
Right medial temporal lobe atrophy					
0 (normal)	6 (30.0)	-	22 (26.5)	-	
1 (slight increase)	9 (45.0)	-	45 (54.2)	-	0.74†
2 (mod. increase)	4 (20.0)	-	16 (19.3)	-	
3 (severe increase)	1 (5.0)	-	0 (0.0)	-	
Automated	-	0.25 ± 0.04	-	0.25 ± 0.03	0.79†
Deep white matter hyperintensities (DWM)					
0 (absent)	0 (0.0)	-	2 (2.4)	-	
1 (punctate foci)	11 (55.0)	-	55 (66.3)	-	0.22†
2 (beginning confluence of foci)	6 (30.0)	-	22 (26.5)	-	
3 (large confluent areas)	3 (15.0)	-	4 (4.8)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	
1 (caps or pencil thin lining)	9 (45.0)	-	47 (56.6)	-	0.60
2 (smooth halo)	9 (45.0)	-	31 (37.3)	-	
3 (irregular and extending to DWM)	2 (10.0)	-	5 (6.0)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	
1	0 (0.0)	-	2 (2.4)	-	0.41†
2	7 (35.0)	-	39 (47.0)	-	
3	6 (30.0)	-	21 (25.3)	-	
4	3 (15.0)	-	14 (16.9)	-	
5	3 (15.0)	-	6 (7.2)	-	
6	1 (5.0)	-	1 (1.2)	-	
Automated	-	0.70 ± 0.7	-	0.43 ± 0.4	0.02†

*p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

Grey matter

For grey matter using VBM, there were no significant group differences between those with current depressive symptoms and controls, at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, the patient group showed reduced FA compared with the control group in parts of the right corticospinal tract, indicating less uniform patterns of diffusion in these areas in the patient group (i.e. better white matter integrity in the controls) (Figure 12).

The patient group showed increased MD in widespread regions, indicating reduced white matter integrity in the patient group, compared with the controls. The difference in MD was driven by changes in RD (Figure 12) that showed significant differences in the body of the corpus callosum, bilaterally within the corticospinal tract, superior longitudinal fasciculus and anterior thalamic radiation, and in the right posterior and superior corona radiata. The patient group showed smaller areas of AD which were significantly different. Clusters were significantly different bilaterally in the superior longitudinal fasciculus, in the left inferior frontal-occipital fasciculus, left anterior thalamic radiation, left uncinate fasciculus and right corona radiata.

The correlation between current depressive symptoms and white matter changes is further illustrated in Figures 13 and 14. These scatterplots show the correlation between current depressive symptoms and significantly different FA and RD values ($p=<0.05$) for cases and controls.

Figure 12. Group differences in white matter: current depressive symptoms

Regions in which there are significant group differences in Fractional Anisotropy (red), Mean Diffusivity, Radial Diffusivity and Axial Diffusivity (blue) at a threshold of $p<0.05$, overlaid on the mean FA skeleton (green). Significant regions are dilated for illustrative purposes.
R=right; L=left; P=posterior; A=anterior

Slice locations:
X 64, Y 104, Z 105 and Z 120

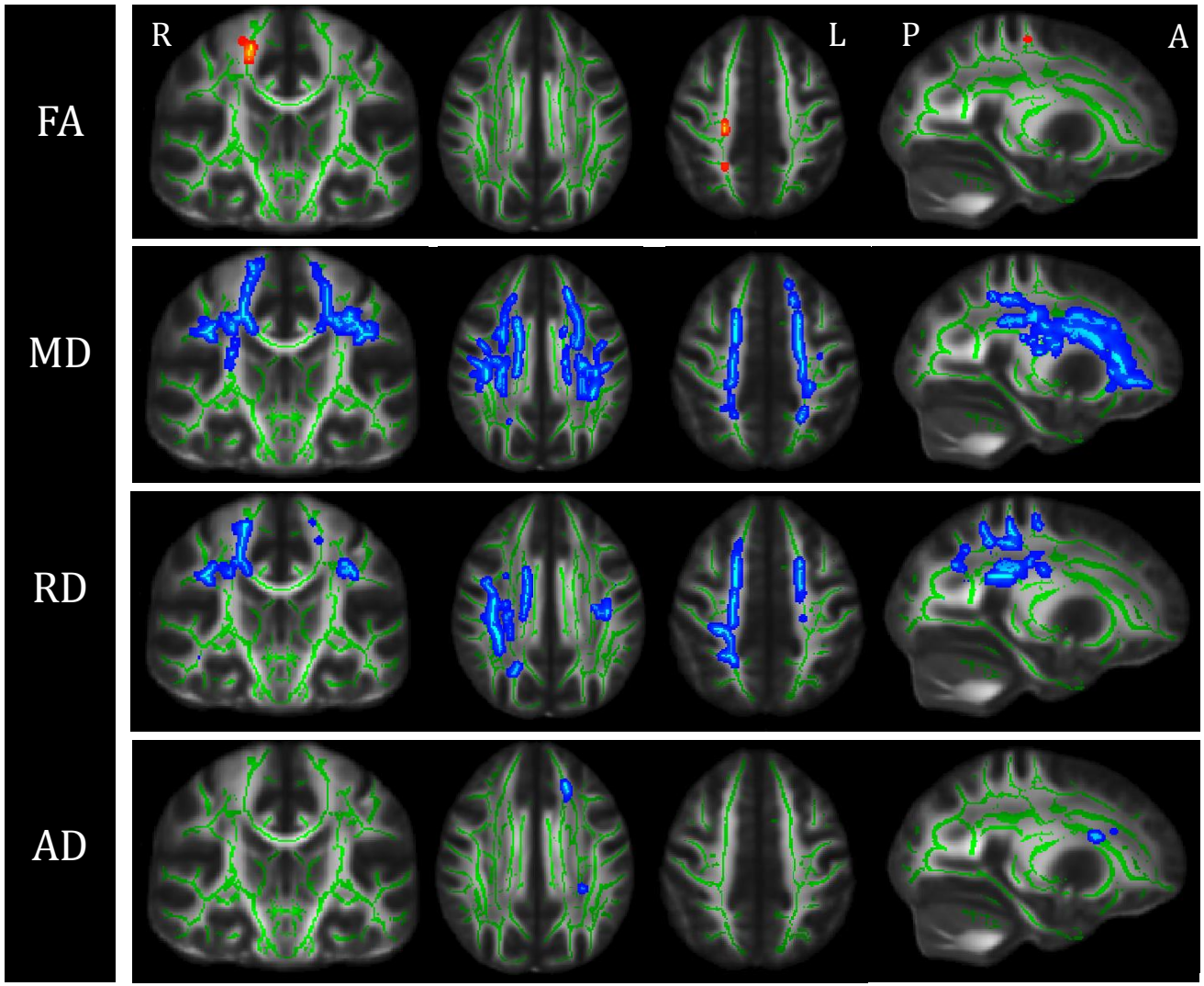


Figure 13. Scatterplot to show the correlation between current depressive symptoms and fractional anisotropy in regions of statistically significant difference (p<0.05)

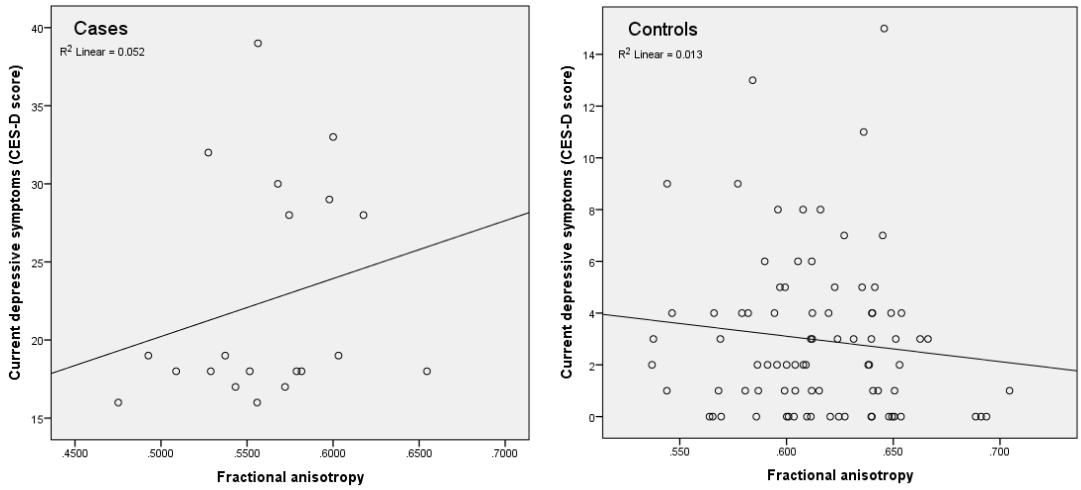
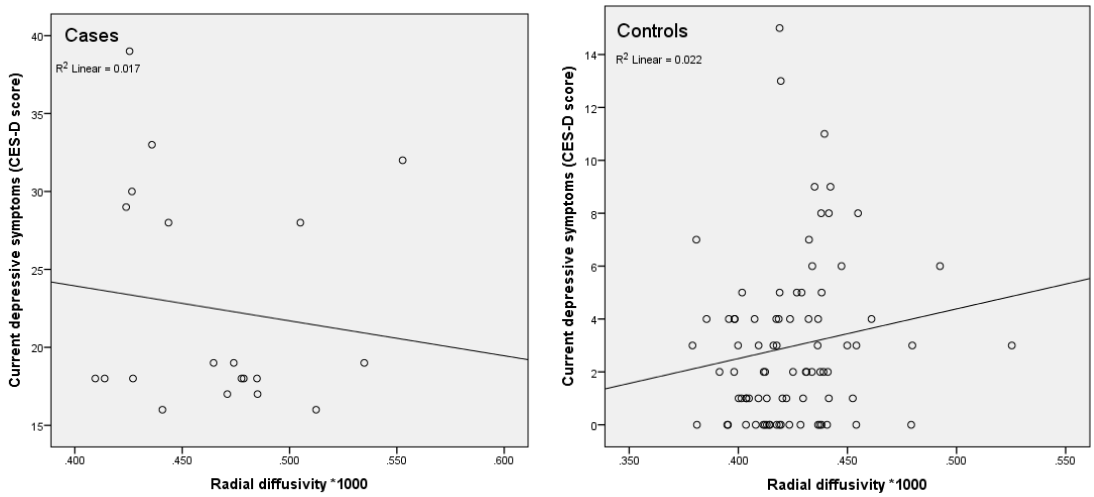


Figure 14. Scatterplot to show the correlation between current depressive symptoms and radial diffusivity in regions of statistically significant difference (p<0.05)



8.3.2 Late-onset depressive symptoms

In Chapter 6 a group of 190 participants was identified who did not have major neurological conditions and had adequate-quality MRI data. From this sample 26 subjects were identified as phase 10 participants with late-onset depressive symptoms identified through elevated CES-D scores over the age of 60 years. All were included as cases. There were 164 potential controls. Participants were excluded from the control group on account of current depressive symptoms (n=15), current use of antidepressant medication (n=6), previous depressive symptoms (n=12), missing previous CES-D data (n=1) and incomplete or poor-quality MRI data (n=6). Further exclusions were made on the basis of age, years of education and TOPF score (n=47) to create a group of controls who were comparable with the cases. In total, there were 87 exclusions; therefore, 77 participants were included in the control group.

Cases had significantly higher current depressive symptoms and use of antidepressant medication, compared to controls. Compared to the group with current depressive symptoms (section 8.3.1), CES-D scores were lower (10.5 ± 7.4, compared to 22.5 ± 7.0) but use of antidepressant medication was similar (13.0% compared to 15.0%). Table 39 shows that there were no significant differences between the case and control groups based on age, sex, education or TOPF score. There were significant differences between groups based on cognitive assessments including the MOCA ($p=0.04$), HVLT for short-term verbal recall ($p<0.001$), and for two measures of executive function (DSFW, $p=0.05$; DSBW, $p=0.03$).

Visual measures

There were no significant group differences between cases and controls using visual or automated measures (Table 40).

Table 39. Participant demographics: late-onset depressive symptoms and controls

	Cases (n=26)		Controls (n=77)		p-value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Demographics					
Sex, *male*	21 (80.8%)	-	67 (87.0%)	-	0.44
Age, *years*		73.3 ± 5.6		71.3 ± 4.6	0.10
Education, *years*		13.8 ± 3.1		13.7 ± 3.1	0.87
TOPF		59.5 ± 11.4		61.3 ± 8.6	0.46
Pre-morbid IQ*		117.3 ± 8.3		118.0 ± 9.7	0.69
Cognitive testing					
MOCA		25.5 ± 3.0		26.9 ± 2.4	0.04
HVLT		21.9 ± 4.0		26.7 ± 5.1	<0.001
TMTB, *secs*		76.1 ± 30.3		67.2 ± 28.0	0.21
DSFW		10.1 ± 2.3		11.1 ± 2.1	0.05
DSBW		8.4 ± 2.2		9.6 ± 2.4	0.03
DC		56.0 ± 14.8		59.6 ± 13.1	0.29
Depressive symptoms					
CES-D		10.5 ± 7.4		3.1 ± 3.0	<0.001
Current antidepressant medication	3 (13.0%)	-	0 (0.0%)		0.002

* Estimated from the Test of Premorbid function (TOPF), education and sex

Table 40. Group differences in MRI measures: late-onset depressive symptoms and controls

	Cases (n=26)		Controls (n=77)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	1 (3.8)	-	1 (1.3)	-	0.17†
1 (mild)	6 (23.1)	-	26 (33.8)	-	
2 (moderate)	13 (50.0)	-	43 (55.8)	-	
3 (severe)	6 (23.1)	-	7 (9.1)	-	
Automated	-	27.6 ± 3.2	-	26.6 ± 2.8	0.11†
Left medial temporal lobe atrophy					
0 (normal)	9 (34.6)	-	18 (23.4)	-	0.25†
1 (slight increase)	8 (30.8)	-	38 (49.4)	-	
2 (mod. increase)	9 (34.6)	-	19 (24.7)	-	
3 (severe increase)	0 (0.0)	-	2 (2.6)	-	
Automated	-	0.23 ± 0.04	-	0.23 ± 0.04	0.64†
Right medial temporal lobe atrophy					
0 (normal)	8 (30.8)	-	16 (20.8)	-	0.21†
1 (slight increase)	10 (38.5)	-	45 (58.4)	-	
2 (mod. increase)	7 (26.9)	-	15 (19.5)	-	
3 (severe increase)	1 (3.8)	-	1 (1.3)	-	
Automated	-	0.24 ± 0.03	-	0.24 ± 0.03	0.84†
Deep white matter hyperintensities (DWM)					
0 (absent)	1 (3.8)	-	1 (1.3)	-	0.09†
1 (punctate foci)	8 (30.8)	-	44 (57.1)	-	
2 (beginning confluence of foci)	15 (57.7)	-	26 (33.8)	-	
3 (large confluent areas)	2 (7.7)	-	6 (7.8)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.28
1 (caps or pencil thin lining)	16 (61.5)	-	42 (54.5)	-	
2 (smooth halo)	10 (38.5)	-	28 (36.4)	-	
3 (irregular and extending to DWM)	0 (0.0)	-	7 (9.1)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	0.49†
1	1 (3.8)	-	1 (1.3)	-	
2	7 (26.9)	-	33 (42.9)	-	
3	9 (34.6)	-	18 (23.4)	-	
4	7 (26.9)	-	16 (20.8)	-	
5	2 (7.7)	-	6 (7.8)	-	
6	0 (0.0)	-	3 (3.9)	-	
Automated	-	0.78 ± 0.8	-	0.52 ± 0.6	0.09†

*p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

Grey matter

For grey matter using VBM, there were no significant group differences between those with late-onset depressive symptoms and controls at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, the patient group showed reduced FA compared to controls in a small number of regions including the splenium of the corpus callosum, left forceps major and the left anterior thalamic radiation (Figure 15).This indicates impaired white matter integrity in these areas in patients compared to controls.

The patient group showed increased MD bilaterally in multiple regions, including the superior longitudinal fasciculus, corticospinal tract, superior corona radiata, anterior thalamic radiation and the body of the corpus callosum. This indicates reduced white matter integrity in the patient group compared to controls. Significant differences in RD were seen bilaterally in the superior corona radiata, anterior corona radiata, the right corticospinal tract and the body of the corpus callosum. Significant differences in AD were seen bilaterally in the superior corona radiata, anterior corona radiata, posterior corona radiata and anterior limb of the internal capsule, and in the right corticospinal tract (Figure 15).

A correlation was performed between CES-D scores in the patient group (n=26) and measures of white matter integrity (FA, MD, RD, AD) to see whether these were significantly associated. There were no significant correlations in FA. For MD, RD and AD there were small clusters representing areas of significant difference, which might explain some (but certainly not all) of the variance between groups. For MD there were small clusters in the left posterior and superior corona radiata, left corticospinal tract, left superior longitudinal fasciculus and the body of the corpus callosum. There were small clusters for RD in the left superior longitudinal fasciculus and for AD in the left superior longitudinal fasciculus and left posterior corona radiata.

The correlation between current depressive symptoms and white matter changes is further illustrated in Figures 16 and 17. These scatterplots show the correlation between late-onset depressive symptoms and significantly different FA and RD values ($p=<0.05$), for cases and controls.

Figure 15. Group differences in white matter: late-onset depressive symptoms

Regions in which there are significant group differences in Fractional Anisotropy (red), Mean Diffusivity, Radial Diffusivity and Axial Diffusivity (blue) at a threshold of $p<0.05$, overlaid on the mean FA skeleton (green). Significant regions are dilated for illustrative purposes.
R=right; L=left; P=posterior; A=anterior

Slice locations:
X 74, Y 136, Z 92 and Z 120

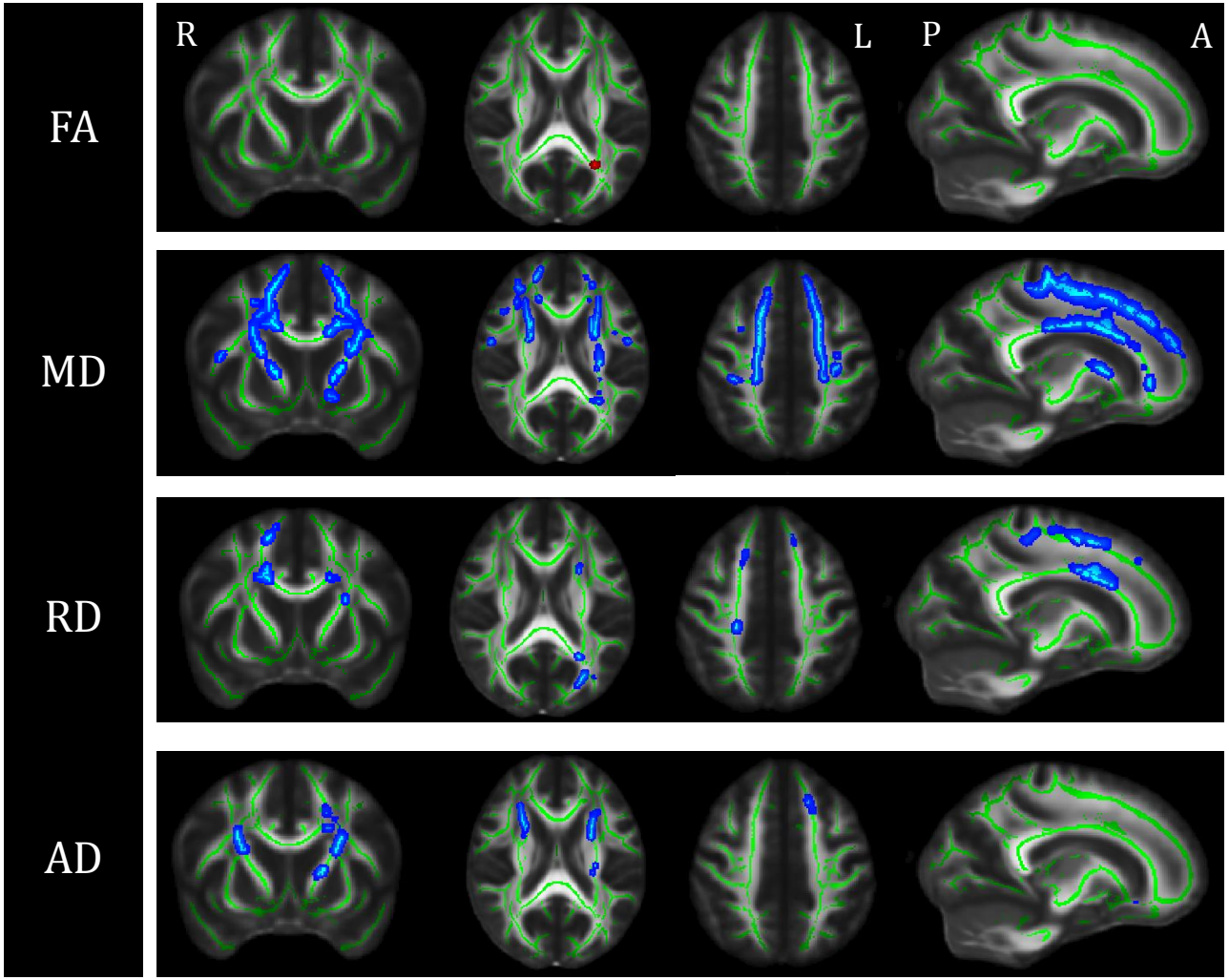


Figure 16. Scatterplot to show the correlation between late-onset depressive symptoms and fractional anisotropy in regions of statistically significant difference (p<0.05)

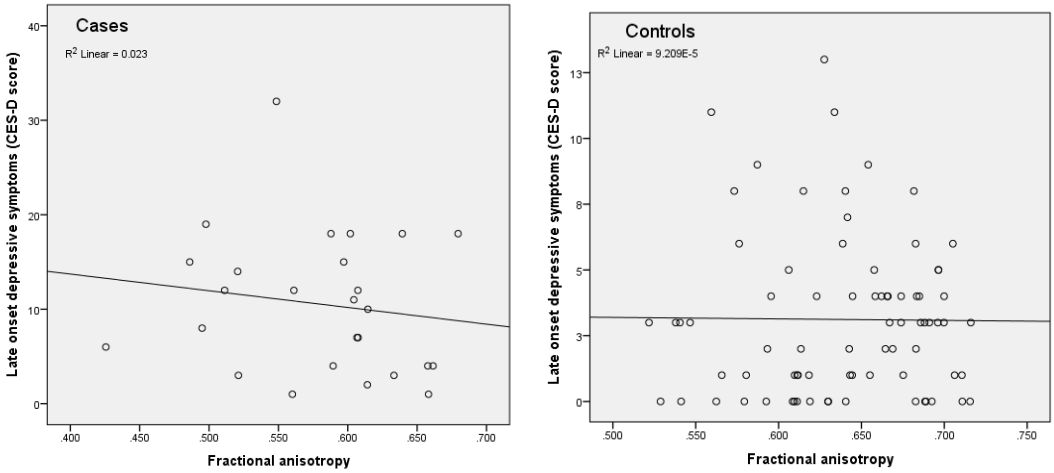
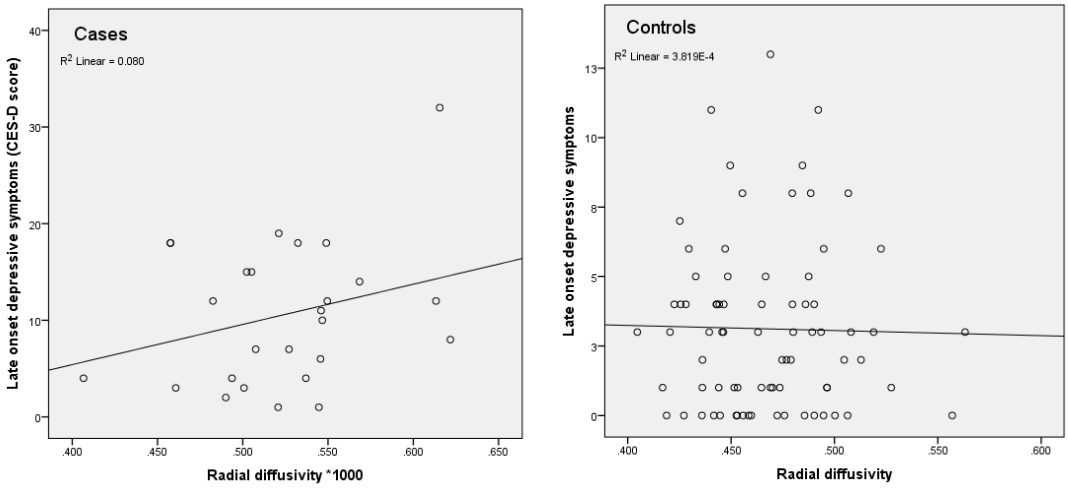


Figure 17. Scatterplot to show the correlation between late-onset depressive symptoms and radial diffusivity in regions of statistically significant difference (p<0.05)



8.3.3 Major depressive disorder

In Chapter 6 a group of 190 participants was identified who did not have major neurological conditions and had adequate-quality MRI data. From this group, 36 subjects were identified as potential cases, with a diagnosis of DSM-IV major depressive disorder according to the SCID. Four cases were excluded due to lack of DTI data, and therefore 32 cases were included. There were 154 potential controls. Participants were excluded from the control group on account of a previous SCID diagnosis of mental illness (n=23), current depressive symptoms (n=7), current use of antidepressant medication (n=2) and incomplete or poor-quality MRI data (n=9). Further exclusions were made to create a group of controls who were comparable with the cases on the basis of mean age and age range, mean years of education and mean TOPF score (n=19). In total, there were 60 exclusions. Therefore 94 participants were included in the control group.

Despite being selected on the basis of previous depressive episodes, cases exhibited significantly increased current depressive symptoms compared with controls, with a similar mean CES-D score to the group with late-onset depressive symptoms (section 8.4.2). Table 41 shows that there were no significant differences between the case and control groups based on age, sex, education or TOPF score. There were no significant differences between the groups based on MOCA or HVLT score, in contrast to the group identified in Chapter 8.3.2 with late-onset depressive symptoms. For tests of executive function, digit coding scores were significantly different between groups, and digit span forward scores approached, but did not reach, significance.

Visual measures

There were no significant group differences between cases and controls using visual or automated measures (Table 42).

Table 41. Participant demographics: major depressive disorder and controls

	Cases (n=32)		Controls (n=94)		p-value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Demographics					
Sex, *male*	25 (78.1%)	-	82 (87.2%)	-	0.21
Age, *years*		68.9 ± 5.7		69.2 ± 5.3	0.83
Education, *years*		14.1 ± 3.7		14.0 ±3.0	0.94
TOPF		63.3 ± 5.6		63.2 ± 4.9	0.95
Pre-morbid IQ*		119.6 ± 8.4		119.5 ± 8.2	0.97
Cognitive testing					
MOCA		26.8 ± 2.7		27.3 ± 2.0	0.38
HVLT		26.9 ± 5.1		27.0 ± 4.8	0.97
TMTB, *secs*		64.1 ± 22.0		60.2 ± 25.2	0.42
DSFW		10.7 ±2.2		11.5 ± 2.3	0.07
DSBW		9.9 ± 2.5		10.7 ± 2.6	0.71
DC		58.6 ± 12.2		64.5 ± 12.8	0.02
Depressive symptoms					
CES-D		10.3 ± 9.1		3.2 ± 3.5	<0.001
Current antidepressant medication	4 (14.3 %)	-	0 (0%)	-	<0.001

*Estimated from the Test of Premorbid function (TOPF), education and sex

Table 42. Group differences in MRI measures: major depressive disorder and controls

	Cases (n=32)		Controls (n=94)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Global atrophy					
0 (absent)	2 (6.3)	-	0 (0.0)	-	0.87†
1 (mild)	15 (46.9)	-	43 (45.7)	-	
2 (moderate)	11 (34.4)	-	45 (47.9)	-	
3 (severe)	4 (12.5)	-	9 (6.4)	-	
Automated	-	25.9 ± 2.9	-	25.9 ± 2.7	0.96†
Left medial temporal lobe atrophy					
0 (normal)	9 (28.1)	-	27 (28.7)	-	0.94†
1 (slight increase)	16 (50.0)	-	44 (46.8)	-	
2 (mod. increase)	6 (18.8)	-	23 (24.5)	-	
3 (severe increase)	1 (3.1)	-	0 (0.0)	-	
Automated	-	0.23 ± 0.04	-	0.24 ± 0.03	0.24†
Right medial temporal lobe atrophy					
0 (normal)	5 (15.6)	-	28 (29.8)	-	0.23†
1 (slight increase)	21 (65.6)	-	47 (50.0)	-	
2 (mod. increase)	5 (15.6)	-	19 (20.2)	-	
3 (severe increase)	1 (3.1)	-	0 (0.0)	-	
Automated	-	0.24 ± 0.04	-	0.24 ± 0.03	0.21†
Deep white matter hyperintensities (DWM)					
0 (absent)	1 (3.1)	-	1 (1.1)	-	0.27†
1 (punctate foci)	21 (65.6)	-	61 (64.9)	-	
2 (beginning confluence of foci)	7 (21.9)	-	29 (30.9)	-	
3 (large confluent areas)	3 (9.4)	-	3 (3.2)	-	
Periventricular white matter hyperintensities (PVWM)					
0 (absent)	0 (0.0)	-	0 (0.0)	-	0.79
1 (caps or pencil thin lining)	19 (59.4)	-	54 (57.4)	-	
2 (smooth halo)	10 (31.3)	-	34 (36.2)	-	
3 (irregular and extending to DWM)	3 (9.4)	-	6 (6.4)	-	
Total white matter hyperintensities (sum of DWM and PVWM)					
0	0 (0.0)	-	0 (0.0)	-	0.64†
1	1 (3.1)	-	1 (1.1)	-	
2	15 (46.9)	-	43 (45.7)	-	
3	9 (28.1)	-	27 (28.7)	-	
4	3 (9.4)	-	16 (17.0)	-	
5	2 (6.3)	-	6 (6.4)	-	
6	2 (6.3)	-	1 (1.1)	-	
Automated	-	0.54 ± 0.72	-	0.44 ± 0.4	0.31†

*p-value from chi-squared test (categorical variables) or analysis of variance (automated variables)
† For chi-squared test, categories with very low frequencies have been combined

Grey matter

For grey matter using VBM, there were no significant group differences between those with major depressive disorder and controls at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, there were no significant differences in FA, MD, RD or AD between those with major depressive disorder and controls using the threshold $p<0.05$ and TFCE.

8.3.4 Long-term exposure to depressive symptoms

In Chapter 6 a group of 190 participants was identified who did not have major neurological conditions and had adequate-quality MRI data. From this group a further 19 subjects were excluded on the basis of poor-quality MRI data or lack of DTI data, resulting in a sample of 171 participants for this analysis. There were therefore 58 exclusions from the total sample (n=229); there were no significant differences between included and excluded participants in terms of age, gender, years of education and pre-morbid cognitive function (Table 43). On cognitive assessment, the only significant difference was in performance on HVLT; performance on other cognitive tests was not significantly different.

The majority of included participants were male, with a mean age of 69.4 years and above-average mean IQ of 118. Mean cognitive test scores were high (26.9 ± 2.5 for MOCA and 26.5 ± 5.1 HVLT). The cross-sectional and cumulative CES-D score was below the cut-off for significant depressive symptoms, although in both cases the range of scores included individuals with significant depressive symptoms (cross-sectional CES-D range=0 - 39; cumulative CES-D range=0 - 31). Over 30% of participants had a history of DSM-IV mood disorder, yet less than 6% of the sample were currently using antidepressant medication.

Table 43. Participant demographics: long-term exposure to depressive symptoms

	Included cases (n=171)		Excluded cases (n=58)		p-value*
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Demographics					
Sex, *male*	139 (81.3%)		50 (86.2%)	-	0.40
Age, *years*		69.4 ± 5.5		68.6 ± 4.7	0.26
Education, *years*		14.1 ± 3.3		14.1 ± 2.7	0.94
TOPF		60.8 ± 9.5		61.7 ± 9.5	0.56
Pre-morbid IQ †		117.9 ± 10.1		118.1 ± 10.1	0.93
Cognitive testing					
MOCA		26.9 ± 2.5		27.2 ± 2.1	0.43
HVLT		26.5 ± 5.1		28.0 ± 4.4	0.03
TMTB, *secs*		66.9 ± 33.4		70.8 ± 36.7	0.48
DSFW		11.0 ± 2.3		10.5 ± 2.2	0.19
DSBW		9.8 ± 2.7		10.0 ± 2.5	0.65
DC		61.4 ± 13.9		61.2 ± 15.2	0.93
Indicator of long-term exposure to depressive symptoms					
CES-D		6.3 ± 7.4		4.8 ± 4.6	0.14
Current antidepressant medication	10.0 (5.8%)		6.0 (10.3%)		0.25
Longitudinal CES-D, *mean*‡		7.4 ± 6.4		6.2 ± 5.0	0.21
History of mental illness	55 (32.2%)		17.0 (29.3%)		0.69
History of mood disorder **	54 (31.6%)		16.0 (27.6%)		0.57

* p-value from analysis of variance (continuous variables), chi-squared (ordinal variables)
† Estimated from the Test of Premorbid Function (TOPF), education and sex
‡ Calculated as mean score across 3 phases (phase 7, phase 9 and Imaging sub-study)
** SCID diagnosis of major depressive disorder, minor depressive disorder or dysthymia

Visual measures

Visual and equivalent automated measures were correlated with CES-D score across the whole sample using Pearson's correlation. For cross-sectional measures there was a weak but significant association with right medial temporal lobe atrophy; this was not replicated using

the equivalent automated measure, or by using longitudinal data (Table 44). Given that no corrections were made for multiple comparisons, this suggests that visual or equivalent automated MRI measures detect very few differences in brain structure.

Table 44. Correlation between MRI measures and depressive symptoms

	Cross-sectional CES-D score (n=171)		**Longitudinal CES-D score (n=171)***	
	Pearson's correlation, *r*	p-value	Pearson's correlation, *r*	p-value
Visual measures				
Global atrophy	0.03	0.66	0.05	0.56
Medial temporal lobe atrophy				
Left	0.02	0.84	0.00	0.97
Right	0.15	0.05	0.10	0.18
White matter hyperintensities				
Total	0.06	0.41	0.00	0.98
Periventricular	0.01	0.95	-0.08	0.32
Deep	0.10	0.18	0.07	0.36
Automated measures				
Global atrophy	0.07	0.35	0.09	0.22
Medial temporal lobe atrophy				
Left	0.05	0.55	-0.01	0.93
Right	-0.01	0.86	-0.03	0.72
White matter hyperintensities	0.13	0.09	0.09	0.23

* Calculated as mean score across 3 phases (phase 7, phase 9 and Imaging sub-study)

Grey matter

For grey matter using VBM, there were no significant correlations with long-term exposure to depressive symptoms at the threshold of $p<0.05$ using TFCE.

White matter

For white matter using TBSS, there were no significant correlations with long-term exposure to depressive symptoms for FA, MD, RD or AD using the threshold of $p<0.05$ and TFCE.

8.4 Summary

There were no significant differences in grey matter between cases and controls using VBM. However, significant differences were identified in white matter using TBSS (Table 45). Analysis of current and late-onset depressive symptoms revealed reduced FA in patient groups, albeit in relatively small areas; there were more widespread increases in MD, RD and AD within the patient groups. These findings indicate reduced white matter integrity in participants with current and late-onset depressive symptoms (both defined using the CES-D score). Frontal-subcortical tracts were particularly affected, including the superior longitudinal fasciculus, corona radiata, anterior thalamic radiation, corticospinal tract and corpus callosum. In general the greatest differences were seen in RD, rather than AD. The fact that many of these changes were seen bilaterally, and that there was overlap between affected regions in both current and late-onset groups, adds further weight to these results. Participants with a history of major depressive disorder had no significant group differences in white matter identified using TBSS. Longitudinal depressive symptoms were not correlated with structural changes using VBM or TBSS.

The most widespread differences were seen in the group with current depressive symptoms identified using CES-D. Interestingly, although the mean CES-D score was similar for the late-onset depression and major depression groups, the former showed significant differences in cognitive function and white matter, whereas the latter did not. This indicates that there may be something specific about the brain structural changes associated with late-onset depressive symptoms, compared to symptoms manifesting at earlier ages.

Visual measures, and their equivalent automated measures, did not reveal statistically significant group differences, or a correlation with depressive symptoms.

Table 45. Summary of statistically significant MRI correlates of depressive symptoms

Depressive symptoms	MRI measure		
	Visual	Grey matter (VBM)	White matter (TBSS)
Current	-	-	Widespread changes in MD, RD, AD: superior longitudinal fasciculus, corona radiata, anterior thalamic radiation, corticospinal tract, corpus callosum
Late-onset	-	-	Widespread changes in MD, RD, AD: superior longitudinal fasciculus, corona radiata, anterior thalamic radiation, corticospinal tract, corpus callosum
Major depressive disorder	-	-	-
Long-term exposure to depressive symptoms	-	-	-

Chapter 9. Common MRI correlates for vascular risk and depression

9.1 Introduction

Chapter 9 reviews previous literature, focussing on structural MRI brain changes associated with vascular risk factors in people with depression. The second part of this chapter summarises the results of MRI analysis from Chapters 7 and 8. By presenting the key MRI findings together, this chapter provides a summary of structural MRI brain correlates related to vascular risk and depression.

9.2 Previous literature using MRI to investigate vascular factors and depression

Blood pressure

A previous study found that older, depressed, hypertensive participants had significantly more white matter hyperintensities compared with normotensive participants with and without depression (162). An increased volume of white matter hyperintensities has been associated with a drop in orthostatic blood pressure in a cross-sectional study of older people with major depressive disorder (329). The white matter changes were thought to be driven by changes within the deep white matter, and the findings suggested that systolic blood pressure had a greater effect than diastolic blood pressure on associated structural brain changes. In a longitudinal study, the Cardiovascular Health Study, increased white matter hyperintensity volumes have also been associated with hypertension and depressive symptoms (measured using the CES-D scale) (330). In a study of older people (mean age 70 ± 6 years) being treated for depressive disorder, there were significant associations between FA and blood pressure throughout the anterior cingulate and in multiple frontostriatal and frontotemporal regions (331), suggesting that hypertension is associated with microstructural white matter abnormalities. However, this study had a relatively small number of participants, did not have a control group, and used less-sophisticated MRI methodology and analysis than that employed in the present study.

Cholesterol

There is a limited literature investigating the associations between cholesterol and atherosclerosis, and depressive symptoms using MRI. In one small cross-sectional study, older adults with depression had poorer endothelial function, increased risk of atherosclerosis, and a greater risk of brain white matter hyperintensities (332). However, increases in white matter hyperintensities in the patient group were not statistically significant. Two longitudinal studies have investigated atherosclerosis and lipid levels, and the association with depressive symptoms. The Rotterdam study, a longitudinal population-based study, found that atherosclerosis did not increase the risk of incident depression in older adults (135). The Esprit study found that the clinical level of depression was associated with higher atherosclerosis risk in women and a lower risk in men (333). Neither of these studies presented MRI data in their papers, although both used MRI in their protocols.

Diabetes

Previous studies have identified grey matter differences in those with diabetes and depression. A study of grey matter volumes in diabetic patients with and without depression showed that both groups had smaller whole-brain volumes compared to controls, with no significant difference between them on neuroimaging measures (196). In a study comparing patients with type 1 diabetes mellitus, with and without depressive symptoms, both groups had reduced pre-frontal grey matter cortical thickness compared to controls (334). A similar study compared patients with type 2 diabetes mellitus, with and without depressive symptoms. Both patient groups showed reduced cortical grey matter thickness in the left anterior cingulate region when compared to controls (197). Additionally, participants with type 2 diabetes and depression showed significant cortical grey matter decreases in bilateral prefrontal areas (197). In a community-dwelling sample, diabetes has been found to be associated with increased brain atrophy (but not with differences in white matter or white matter hyperintensity volumes), independent of either depression or vascular risk factors (195).

In patients with type 2 diabetes and depression, differences in pre-frontal white matter have been demonstrated, with reduced FA and increased RD in the right anterior limb of the internal capsule, compared to controls (335).

Smoking

As previously described in Chapters 2.2 and 2.3, smoking has been linked to increased risk of depressive disorder, and to grey and white matter brain changes. There are few studies investigating the combined effects of smoking and depression on MRI outcomes, partly because many studies control for this variable rather than investigating it specifically. Smoking has been linked to decreased grey matter density in the posterior cingulum, precuneus, right thalamus and frontal cortex, regions associated with incipient Alzheimer's disease that have an overlap with regions affected in late-onset depression (212). Smoking has an important role in the pathophysiology of late-onset major depressive disorder, and is highly correlated with white matter lesion load (117). The location of lesions is important: lesions within the superior longitudinal fasciculus and right frontal projections of the corpus callosum may have a greater association with depressive symptoms than total lesion volume (117).

Framingham Stroke Risk Score

Elevated FSRS has been associated with greater white matter hyperintensities in deep and periventricular regions in middle-aged and older adults with major depressive disorder (336). More specifically, the FSRS has been associated with reduced white matter integrity in patients with depression within the corpus callosum and corticospinal tract (337). This finding is consistent with the hypothesis that raised cardiovascular risk may be a modifiable risk factor for late-onset depression, mediated by observable brain changes.

Coronary heart disease

In a study of over 3000 people with CHD at baseline, persistence of depressive symptoms across two consecutive time points was associated with small basal ganglia lesions and large cerebral cortical white matter lesions (338). These findings suggest that cerebrovascular disease at baseline is related to depressive symptoms over time. A further study of CHD and major depression found that participants with both conditions had decreased grey matter volumes in the bilateral orbitofrontal cortex, bilateral amygdala/parahippocampal gyrus and right insula, compared to controls, supporting the hypothesis that brain regions involved in emotional regulation may be relevant to the relationship between CHD and major depressive disorder (339).

Depressive symptoms, which are common after acute coronary syndrome, are associated with vascular brain changes including reduced FA in the anterior cingulate cortex and increased deep white matter changes (340). However, many of these effects do not remain significant after controlling for cardiovascular morbidity or modifiable cardiac risk factors.

9.3 Common MRI correlates identified for vascular risk and depression

This section describes the common MRI correlates for long-term exposure to vascular risk and depressive disorder, which have been identified through the present study and were presented in Chapters 7 and 8 respectively. These common MRI correlates are summarised in Table 46.

Blood pressure

Using clinical visual measures, mean arterial pressure was significantly associated with bilateral medial temporal lobe atrophy. This finding was not replicated for depressive symptoms. Visual measures did not find increased white matter hyperintensities related to hypertension or depressive symptoms. However, using equivalent automated measures, increased white matter hyperintensities were associated with both mean arterial pressure and current depressive symptoms. There were no common MRI correlates using VBM and TBSS.

Cholesterol

There were no common MRI correlates in relation to cholesterol score and depressive symptoms. The previous literature (135, 332, 333) helps to explain why the present study did not find an association between MRI correlates of mean total cholesterol level and MRI correlates of depression. If there is an effect, it seems likely to be a modest effect that requires large samples in order to have adequate power. The current sample may not be large enough to detect a significant difference, especially if an effect is most likely in women, given that in this sample over 80% of participants are men.

Diabetes

There were no common MRI correlates in relation to mean fasting glucose or type 2 diabetes status and depressive symptoms using visual measures, equivalent automated measures or VBM. However, long-term exposure to high fasting glucose was associated with widespread differences in white matter integrity (reduced FA, increased RD) within frontal-subcortical regions. These changes overlapped with reductions in white matter integrity observed in participants with current and late-onset depressive symptoms. There were no differences in white matter in those with type 2 diabetes, possibly owing to the small sample size.

Smoking

There were no common MRI correlates in relation to smoking status and depressive symptoms. The sample of smokers was small, which is likely to have reduced the power to detect a significant difference.

Framingham Stroke Risk Score

The present study found significant correlations between FSRS and visual MRI measures for global atrophy, medial temporal lobe atrophy and deep white matter hyperintensities, as well as for their automated equivalents. However, these results had minimal overlap with visual MRI correlates of depressive symptoms. There were no common MRI correlates using VBM and TBSS.

Coronary heart disease

There were no common MRI correlates in relation to CHD and depressive symptoms. However, the number of participants with CHD as defined by previous MI and/or current angina was small, and this element of the study was underpowered. Furthermore, CHD was investigated as a cross-sectional variable and did not take into account disease duration or severity.

Table 46. Common MRI correlates for vascular risk and depression

MRI measures	Vascular risk factors						Depressive symptoms			
	BP	Chol	DM	Smoke	FSRS	CHD	Current	Late	Major	Long
Clinical measures										
Global atrophy	-	✓	-	-	✓	-	-	-	✓	-
Medial temporal lobe atrophy										
Left	✓	-	-	✓	✓	-	-	-	-	-
Right	✓	-	-	-	✓	-	-	-	-	✓
White matter hyperintensities										
Total	-	-	-	-	-	-	-	-	-	-
Peri-ventricular	-	-	-	-	-	-	-	-	-	-
Deep white matter	-	-	-	-	✓	-	-	-	-	-
Automated measures										
Global atrophy	✓	-	-	-	✓	-	-	-	-	-
Medial temporal lobe atrophy										
Left	-	-	-	-	✓	-	-	-	-	-
Right	-	-	-	-	✓	-	-	-	-	-
White matter hyperintensities	✓	-	-	-	✓	-	✓	-	-	-
Grey matter (VBM)										
	-	-	-	-	-	-	-	-	-	-
White matter (TBSS)										
Superior longitudinal fasciculus	-	-	✓	-	-	-	✓	✓	-	-
Corona radiata	-	-	✓	-	-	-	✓	✓	-	-
Anterior thalamic radiation	-	-	✓	-	-	-	✓	✓	-	-
Corticospinal tract	-	-	✓	-	-	-	✓	✓	-	-
Corpus callosum	-	-	✓	-	-	-	✓	✓	-	-

Abbreviations

Vascular risk factors: BP=blood pressure; Chol=total cholesterol; DM=diabetes mellitus; Smoke=smoking status; FSRS=Framingham Stroke Risk Score; CHD=coronary heart disease;
Depressive symptoms: Current=current depressive symptoms; Late=late-onset depressive symptoms; Major=major depressive disorder; Long=long-term exposure to depressive symptoms

9.4 Summary

For visual MRI measures there were some associations with vascular risk factors, but few overlapping MRI correlates with depressive symptoms. For equivalent automated measures the findings were similar: neither visual nor automated measures were able to distinguish a pattern of common MRI correlates for vascular risk factors and depressive symptoms. Use of more sophisticated analysis techniques enabled analysis of grey matter using VBM and white matter using TBSS. Neither vascular risk factors nor depressive symptoms showed significant differences in grey matter. For white matter, diabetes (measured as mean fasting glucose), as well as current and late-onset depressive symptoms, showed common MRI changes with reduced white matter integrity in the corpus callosum and frontal-subcortical tracts. For mean fasting glucose the structural changes were largely on the right-hand side, whereas for depressive symptoms the structural changes were largely bilateral. No other vascular risk factors showed significant MRI correlates with depressive symptoms.

Chapter 10. Study of vascular risk and depression

10.1 Introduction

Chapter 10 explores whether long-term exposure to vascular risk factors and vascular disease are associated with the development of depressive disorder (defined according to DSM-IV criteria) and depressive symptoms (defined as a CES-D score of ≥16). To this end, this chapter combines prospective data on long-term exposure to vascular risk acquired since 1985, with clinical measures related to depression acquired during phase 1 of the Whitehall Imaging sub-study in Oxford.

The aim of this chapter is to use an epidemiological approach to investigate whether lifetime vascular risk factors (blood pressure, cholesterol, diabetes, smoking, Framingham Stroke Risk Score) and vascular disease (coronary heart disease) lead to increased risk of depressive disorder and depressive symptoms. The hypothesis is that elevated vascular risk factors and the presence of vascular disease are associated with increased prevalence of depressive disorder and depressive symptoms, in line with the vascular depression hypothesis (24).

10.2 Methods

Long-term exposure to vascular risk factors was calculated based on prospective data collected from 1985 to 2009 (i.e. from the Whitehall II Study phases 1, 3, 5 and 9). Continuous measures were used wherever possible, as these provided greater power for statistical modelling. Mean arterial pressure, total cholesterol (baseline and mean), fasting glucose (baseline, mean and follow-up) and FSRS were calculated at each phase, and the overall mean calculated. Additionally, dichotomised ordinal variables were used to investigate the presence of type 2 diabetes and smoking status. Coronary heart disease was defined cross-sectionally on the basis of the presence or absence of angina and/or previous myocardial infarction, as recorded in the participants' self-reported medical histories using the Whitehall Imaging sub-study questionnaire (see appendix 1).

Outcome measures were based on SCID diagnosis of major depressive disorder, defined as none, minor depressive disorder or major depressive disorder. Significant depressive symptoms were also defined using the CES-D score. The distribution of CES-D scores was skewed towards scores at the lower end of this range. Therefore, scores were dichotomised to

reflect CES-D caseness: no significant depressive symptoms (CES-D <16) and significant depressive symptoms (CES-D ≥16).

Statistical analysis used SAS software version 9.2 (SAS Institute, Cary, NC, USA). To study the longitudinal association a model was computed based on each continuous vascular risk factor, with depressive disorder or symptoms as the dependent variable. For analysis of ordinal variables, logistic regression was used. All analyses were adjusted for age and sex. Reported p-values are 2-tailed; p-values ≤0.05 were considered to indicate statistical significance.

10.3 Results

190 participants were included in this analysis (the same sample as described in Chapter 6). A DSM-IV diagnosis of minor depression was documented in 19 (10.0%) participants; a diagnosis of major depression was documented in 36 (18.9%) participants. Current depressive symptoms as defined by CES-D score were present in 21 (11.1%) participants.

10.3.1 Blood pressure

Table 47 shows that mean arterial pressure was not associated with depressive disorder (p=0.47) or depressive symptoms (p=0.80).

Table 47. Mean arterial pressure 1985-2009 and depressive symptoms in 2012-2013

	SCID diagnosis				**CES-D depressive symptoms**		
	n	None	Minor	Major	n	None	Present
Mean arterial pressure, *mm Hg*	187	90.1	88.1	90.9	190	90.1	90.5
p-value*		0.47				0.80	

* Test of heterogeneity

10.3.2 Cholesterol

Table 48 shows that mean total cholesterol across all phases and mean baseline total cholesterol were not associated with depressive disorder (p=0.15 and p=0.71 respectively) or depressive symptoms (p=0.59 and p=0.89 respectively).

Table 48. Mean cholesterol level 1985-2009 and depressive symptoms in 2012-2013

	SCID diagnosis				**CES-D depressive symptoms**		
	n	None	Minor	Major	n	None	Present
Mean total cholesterol, *mmol/L*	187	5.73	6.10	5.71	190	5.77	5.67
p-value*		0.15				0.59	
Baseline total cholesterol, *mmol/L*	186	5.72	5.91	5.76	189	5.75	5.72
p-value*		0.71				0.89	

10.3.3 Diabetes

Table 49 shows that mean fasting glucose across all phases, baseline fasting glucose and follow-up fasting glucose were not significantly associated with depressive disorder (p=0.81, p=0.52, p=0.98 respectively) or depressive symptoms (p=0.07, p=0.30, p=0.18 respectively). The model for mean fasting glucose and CES-D depressive symptoms was the only measure that approached, though still did not reach, significance.

It was not possible to compute a model to investigate the frequency of type 2 diabetes and depressive symptoms on account of small group sizes, and therefore lack of power. This is illustrated in Table 50: no participants with diabetes had minor depressive disorder, only five had major depressive disorder and only two had significant depressive symptoms as measured by CES-D.

Table 49. Mean fasting glucose levels 1985-2009 and depressive symptoms in 2012-2013

	SCID diagnosis				CES-D depressive symptoms		
	n	None	Minor	Major	n	None	Present
Mean fasting glucose, *mmol/L*	165	5.17	5.13	5.13	164	5.18	5.02
p-value*		0.81				0.07	
Baseline fasting glucose, *mmol/L*	158	5.21	5.10	5.27	148	5.20	5.07
p-value*		0.52				0.30	
Follow-up fasting glucose, *mmol/L*	154	5.17	5.15	5.15	145	5.17	4.99
p-value*		0.98				0.18	

Table 50. Proportion of participants with depressive symptoms amongst diabetic cases and controls

	SCID diagnosis			CES-D depressive symptoms	
	None	Minor	Major	None	Present
Diabetic cases, *% (n)*	70.6 (12)	0.0 (0)	29.4 (5)	88.2 (15)	11.8 (2)
Controls, *% (n)*	71.0 (115)	11.1 (18)	17.9 (29)	90.3 (149)	9.7 (16)

10.3.4 Smoking

It was not possible to compute a model to investigate smoking status (at baseline or follow-up) with depressive disorder or depressive symptoms on account of the low frequency of participants who were smokers, and who had depressive symptoms (Table 51).

Table 51. Proportion of participants with depressive symptoms amongst smokers and non-smokers

	SCID diagnosis			**CES-D depressive symptoms**	
	None	Minor	Major	None	Present
Smoking status at baseline					
Smoker, *% (n)*	73.7 (14)	10.5 (2)	15.8 (3)	89.5 (17)	10.5 (2)
Non-smoker, *% (n)*	70.2 (118)	10.1 (17)	19.6 (33)	88.9 (152)	11.1 (19)
Smoking status at follow-up					
Smoker, *% (n)*	86.7 (13)	0.0 (0)	13.3 (2)	100 (15)	0.0 (0)
Non-smoker, *% (n)*	69.5 (116)	10.8 (18)	19.8 (33)	88.2 (150)	11.8 (20)

10.3.5 Framingham Stroke Risk Score

Table 52 shows that Framingham Stroke Risk Score was not associated with depressive disorder (p=0.14) or depressive symptoms (p=0.11).

Table 52. Mean Framingham Stroke Risk Score 1985-2009 and depressive symptoms in 2012-2013

	SCID diagnosis				CES-D depressive symptoms		
	n	None	Minor	Major	n	None	Present
FSRS, *% risk per 10 yr*	185	2.22	1.49	2.03	188	2.16	1.57
p-value*		0.14				0.11	

* Test of heterogeneity

10.3.6 Coronary heart disease

It was not possible to compute a model to investigate CHD and depressive disorder or depressive symptoms because of the low frequency of participants with a history of angina and/or MI. This is illustrated in Table 53: only one case had minor depressive disorder, three had major depressive disorder, and one had depressive symptoms.

Table 53. Proportion of participants with depressive symptoms amongst participants with a history of coronary heart disease and controls

	SCID diagnosis			CES-D depressive symptoms	
	None	Minor	Major	None	Present
CHD case, *% (n)*	63.6 (7)	9.1 (1)	27.3 (3)	90.9 (10)	9.1 (1)
No history of CHD, *% (n)*	71.0 (125)	10.2 (18)	18.8 (33)	88.8 (159)	11.2 (20)

10.4 Summary

Long-term exposure to vascular risk factors (blood pressure, cholesterol, fasting glucose and FSRS) is not associated with the development of depressive disorder or depressive symptoms in this cohort. It was not possible to compute models for type 2 diabetes, smoking or coronary heart disease, due to small group sizes. Replication of these analyses with a greater number of participants would provide increased power to detect any small, but significant associations between vascular risk factors and depressive disorder. This will be possible when the Whitehall Imaging sub-study is completed in 2016. The present analyses indicate that there are no major associations between longitudinal vascular risk factors and development of depression.

Chapter 11. Discussion

11.1 Introduction

The vascular depression hypothesis proposes that cardiovascular disease and risk factors predispose to and precipitate depressive disorder. However, several studies have shed doubt on the strength or frequency of this association. In this thesis the combination of epidemiological and neuroimaging techniques has provided a powerful method for investigating the vascular depression hypothesis further. This thesis has used MRI to investigate the association of vascular risk factors with brain structure, and the association of depressive symptoms and depressive disorder with brain structure. The aim has been to identify common structural changes in both conditions, in order to gain a better understanding of the anatomical mechanisms by which these conditions may be associated. This final chapter summarises the main results and critically appraises the findings, considering how the results help to explain the underlying mechanisms linking vascular risk factors and depression, and the clinical implications.

11.2 Synopsis of main results

This thesis is based on a study of a sample of 229 participants from the Whitehall II Study, UCL, who were recruited for the Whitehall Imaging sub-study, University of Oxford. The sub-study extended the scope of investigation with respect to the original Whitehall II analyses, through use of detailed clinical and neuropsychological assessment as well as multi-modal magnetic resonance brain imaging. Over 80% of participants were male, with a mean age of 69.2 ± 5.3 years, and above-average pre-morbid IQ. Individuals who had experienced a stroke or TIA were not included in the study sample. While participants were generally not cognitively impaired, the range of cognitive abilities included those with a level of impairment that could indicate clinically significant cognitive impairment (mean MOCA 27.0 ± 2.4; range 17.0 – 30.0). Depressive symptoms were common in this sample: one-third of participants had a lifetime diagnosis of DSM-IV mood disorder, 10% met criteria for significant current depressive symptoms defined by the CES-D scale, and 7% currently used antidepressant medication. Vascular risk factors were highly prevalent: 55% of participants had hypertension, 54% had dyslipidaemia and 10% had diabetes. Less than 6% of participants were current smokers.

The brain MRI analysis used visual measures, which were shown to be reliable, and comparable to equivalent automated techniques, **confirming hypotheses one and two**. These findings suggest that visual measures deserve wider usage by clinicians to quantify structural brain changes in older adults and to bridge the gap between sophisticated computerised methods and clinical practice. Here, the use of visual MRI measures throughout the thesis has helped to maintain a clinical focus, integrating the methods used by clinicians for reporting MRI scans with the more complex analysis techniques used in research settings to analyse group data. In addition to these visual MRI measures, this thesis has employed more-sophisticated MRI analysis techniques using FSL tools to investigate grey matter (using VBM) and white matter (using TBSS).

The focus of this thesis has been to investigate brain MRI correlates of depression and vascular risk. The study of MRI correlates of long-term exposure to vascular risk has focussed on blood pressure, cholesterol, diabetes, smoking and, Framingham Stroke Risk Score. This has utilised data collected through the Whitehall II Study (1985 – 2009), combined with MRI measures. The cross-sectional association between coronary heart disease (measured at the time of the MRI scan) and structural brain changes was also investigated. **Contrary to hypothesis three**, there proved to be minimal changes in grey matter using visual measures, and none using VBM. As hypothesised, white matter brain changes were more pronounced than grey matter changes. However, in contrast to predictions, significant white matter changes were only found for the mean fasting glucose variable and not for the other vascular risk factors. Using TBSS to investigate structural changes in white matter, long-term exposure to high fasting glucose proved to be associated with reduced white matter integrity in frontal-subcortical tracts (corona radiata, right corticospinal tract, right superior longitudinal fasciculus, and the splenium and body of the corpus callosum), with reduced FA and increased RD. These changes suggest reduced myelin integrity (341, 342). This demyelination has previously been suggested as secondary to cerebrovascular changes (27).

The study of MRI correlates of depressive symptoms and depressive disorder considered the association with current depressive symptoms, late-onset depressive symptoms and longitudinal depressive symptoms (presence of major depressive disorder, and persistent depressive symptoms identified using the CES-D). **In contrast to hypothesis four**, there proved to be no statistically significant association with structural differences in grey matter, and white matter changes were prominent only in those with current and late-onset depressive

symptoms, not in the group with persistent depressive symptoms. Current depressive symptoms were associated with increased volume of white matter hyperintensities. Current and late-onset depressive symptoms were associated with reduced white matter integrity in widespread regions, particularly in frontal-subcortical tracts (corticospinal tract, superior longitudinal fasciculus, anterior thalamic radiation, right corona radiata and body of the corpus callosum) where there was reduced FA and increased RD and AD. Again, these changes suggest reduced myelin integrity, which could be linked to cerebrovascular changes (27).There prove to have been no statistically significant associations between MRI correlates and longitudinal measures of depressive symptoms.

As predicted in hypothesis five, the results show overlap in the structural brain changes associated with exposure to long-term vascular risk factors and to depressive symptoms. However, this was only true for long-term exposure to mean fasting glucose, and current and late-onset depressive symptoms. For these variables there was a reduction in white matter integrity in fontal-subcortical tracts.

The study of vascular risk and depression adopted an epidemiological approach to investigate whether long-term exposure to vascular risk factors is associated with the development of depressive disorder and depressive symptoms. **In contrast to hypothesis six**, neither elevated blood pressure, high total cholesterol, high mean fasting glucose nor high FSRS were shown to be associated with increased risk of major depressive disorder (identified using SCID) or depressive symptoms (identified as CES-D ≥16). There were insufficient numbers of participants to investigate the association with type 2 diabetes, smoking, or CHD.

11.3 Comparison with previous studies

MRI correlates of vascular risk

Previously published literature has found an association between hypertension, and altered grey matter structures, reduced whole-brain volumes and hippocampal atrophy (152, 154, 155); however, this is not a universal finding (152, 156). The present study has found that clinical measures of medial temporal lobe atrophy and automated measures of global atrophy show a weak association with mean arterial pressure. This was not replicated using VBM, implying that these results represent a small effect at best. They tend to support previous negative findings that have not found an association between hypertension and global or

regional brain atrophy. However, it is possible that using a larger sample these results may be better replicated across clinical and automated measures. Previously published literature has suggested an association between hypertension and increased white matter hyperintensities (159, 177), and also with reduced white matter integrity (164, 166). While automated measures of white matter hyperintensities showed a significant association, no significant changes in white matter integrity were identified using TBSS, at the conventional threshold of $p<0.05$. Again, it seems that any association between hypertension and MRI structural changes represents a small effect at best. In this study mean arterial pressure has been used as a measure of longitudinal hypertension. It may be that a greater effect would be evident if systolic (329) or diastolic blood pressures were investigated separately.

Studies on cholesterol and associations with structural brain changes are not consistent. The present study supports those studies that found no association between dyslipidaemia and reduced grey (174, 175) and white matter volumes (177). The fact that familial hypercholesterolaemia has been associated with white matter brain changes (180, 181) suggests that individuals with severe dyslipidaemia may develop structural brain changes. However, this group is not well represented in a population-based sample such as the one used in the present study.

Literature focussing on type 2 diabetes and elevated fasting glucose tends to support an association with global and regional atrophy. In the present study there were no significant correlations between long-term exposure to elevated fasting glucose and grey matter changes using either visual measures or VBM. This is in contrast to previous studies (62, 192, 194) in which grey matter changes, particularly hippocampal atrophy, were noted at an early stage of disease. For white matter, while there were no significant associations using visual and equivalent automated measures, with TBSS there were widespread differences in white matter integrity related to mean fasting glucose levels. This is consistent with previous studies that have found changes in the posterior corona radiata (62) and decreased FA in bilateral frontal white matter, mainly caused by an increase in RD (343). In this sample there proved to be no association between type 2 diabetes and structural brain changes. It seems most likely that the small numbers of subjects with type 2 diabetes ($n=12$) meant that the present study lacked power to detect a difference. However, given the positive findings for mean fasting glucose levels, with greater numbers of diabetic participants, case-control analysis would be expected

to replicate the detected reductions in white matter integrity, in relation to mean fasting glucose levels.

Smoking has been reported to be associated with significant grey (204, 209, 210) and white matter brain changes, particularly within the corpus callosum (217, 218). The present study did not replicate these findings, but was limited by the small number of cases (n=14). Given that this is a largely health-conscious cohort subject to regular physical health assessments, it is possible that the smokers may be well aware of their adverse cardiovascular risk profile and may use other strategies (e.g. medication, diet, exercise) to ameliorate the adverse effects of smoking.

The Framingham Stroke Risk Score has been associated with reduced total grey matter volume and thickness (344), increased volume of white matter hyperintensities, and changes to white matter microstructure (337, 345). The results of the present study are in line with these earlier studies. Visual and equivalent automated measures show weak correlations with structural brain changes. Visual correlations did not remain significant following adjustment for age, which may explain the discrepancy with other MRI measures (VBM and TBSS) which were adjusted for the effects of age.

In patients with cardiovascular disease (coronary heart disease or stroke), reductions in regional grey matter volume have been reported (346, 347), a finding that contrasts with those of the present study. However, these changes may have been mitigated by exercise training (346). Indeed, the fact that such changes can be reversed by exercise suggests they are modifiable. Therefore, in the present study of stroke-free participants, where there may also have been a significant time delay between a previous MI and the MRI scan, the negative findings are not unexpected, particularly since while patients with CHD do show reductions in grey matter volume and increases in white matter hyperintensity volume, the changes are less pronounced than in those with established cerebrovascular disease (348). In terms of white matter changes, several studies have identified an association between CHD and increased white matter hyperintensity volume, but few have investigated this using TBSS (349).

MRI correlates of depression

Individual studies and meta-analyses have identified reduced grey matter volumes in depression, particularly in late-life depression (36, 230, 231). The present study found no

significant group differences for depressive symptoms or depressive disorder in grey matter structures, in contrast to these previous studies. Although many studies have found changes in grey matter volume, shape and cortical thickness, the present study's results are in keeping with some previous studies of late-life depression, which also found no significant group differences in grey matter (16, 350-355).

The finding of increased white matter hyperintensities is well replicated in studies of late-life depression (237, 238, 356); deep white matter changes are particularly common in depression (39). The present study found significantly increased white matter hyperintensities, using automated measures, in the group with current depressive symptoms. There was no association between clinical measures and late-onset depressive symptoms or longitudinal depressive symptoms. Some previous studies have shown no significant group differences in white matter hyperintensity volume (16), and it may be that lesion location is more relevant to depression than lesion volume (329). In one study of participants with depressive symptoms but not clinical depression, scores on the Geriatric Depression Scale were not significantly correlated with white matter hyperintensities, but were significantly correlated with DTI measures of MD and FA (245), similar to the results obtained in this study. The association between longitudinal data on depression and white matter hyperintensities is less consistent, and provides a context for the lack of association with longitudinal diagnosis of depression and depressive symptoms in this study (239, 240, 243).

Studies of late-life depression consistently support an association with reduced white matter integrity within the limbic system, frontal cortex and the thalamus (16, 246-248). The results for the current and late-onset depressive symptom groups are consistent with these previous findings of reduced white matter integrity within frontal-subcortical regions, driven by radial, rather than axial diffusivity (16). Of particular interest in the present study, which defines depressive symptoms using the CES-D scale, is that the underlying neurobiological changes in white matter are similar to those identified in patient studies when a clinical diagnosis of major depressive disorder has been made (16). This finding is of particular pertinence to the design of epidemiological studies investigating depression, and suggests that use of CES-D caseness as a proxy marker of depressive symptoms is not only a time-efficient way of gathering data, but is also capable of identifying depressive symptoms severe enough to be associated with structural brain changes. Depressive symptoms defined using the CES-D scale

are also associated with functional impairment, on a spectrum of changes seen in people with a diagnosis of major depressive disorder (44, 45).

For longitudinal depressive symptoms, it seems curious that there were no significant group differences in white matter when groups were distinguished using DSM-IV criteria for major depressive disorder, identified using the SCID interview. Previous studies defining cases according to these criteria have found significant group differences (16, 246). One reason might be that white matter changes are more frequent amongst those with current or late-onset symptoms (24, 29, 240), and would therefore be less pronounced in the two longitudinal groups where the age at onset of depressive symptoms was more frequently below, rather than above, the age of 60. Markers of vascular brain disease (i.e. white matter changes) have been previously associated with depression cross-sectionally, but not longitudinally (244), a finding which mirrors the results of the present study, with its longer follow-up period. The previous study's authors suggest that one reason for the lack of association may be that vascular disease and risk factors might cause depression, rather than vice versa. However, evaluation of vascular risk trajectories in the present study suggest that this hypothesis is unlikely.

Vascular risk and depression

The vascular depression hypothesis developed in response to findings that cardiovascular diseases (e.g. stroke and myocardial infarction) were associated with depressive disorder (24, 113, 114). Although there is good evidence for an association with cardiovascular disease, evidence for an association with vascular risk factors is less clear. One previous meta-analysis found significant variation in individual studies, and showed that hypertension, dyslipidaemia and the FSRS were not associated with a statistically significant increased risk of depression (74). While individual studies were largely cross-sectional in nature, these results are consistent with the present study, which did not find an association between major depressive disorder or depressive symptoms and long-term exposure to vascular risk factors (mean arterial blood pressure, mean total cholesterol, and FSRS).

The same meta-analysis found that smoking, diabetes, cardiovascular disease and stroke were associated with increased risk of depression (74). While some studies have suggested a causal association between depression and diabetes, meta-analyses show a modestly sized bi-directional association between depression and type 2 diabetes (357). Unfortunately, the

present study lacked power to investigate smoking, diabetes and stroke. However, there was no association with mean fasting glucose despite an association between this variable and reduced white matter integrity. This is an interesting finding, given that patients with increased mean fasting glucose are known to develop distinct cardio-metabolic risks before a diagnosis of type 2 diabetes is made (358).

Therefore, even if these vascular risk factors do have an effect on brain structure (e.g. FSRS and white matter (337)), they may not necessarily be associated with the development of depressive symptoms. It is possible that the association between these vascular risk factors and depressive symptoms is not causal, or alternatively that there are structural or functional resilience factors preventing development of depression. Importantly, there may be a role for psychological and social factors, which could increase risk of depression in those who develop cardiovascular disease and elevated vascular risk factors. A previous study within the Whitehall II Cohort assessed vascular risk using the Framingham cardiovascular, coronary heart disease, and stroke risk scores. While clinically diagnosed CHD and stroke were associated with an increased risk for depressive symptoms, for participants without manifest vascular disease, none of the risk scores predicted new-onset depressive symptoms in those aged ≥65 years (115).

Other considerations include the effect of publication bias, although one meta-analysis did not find evidence of publication bias except for the association between diabetes and late-life depression (74). A further issue is whether the measures used in the present study are sufficiently accurate. For example, would systolic blood pressure have been a better measure than mean arterial pressure, or would LDL cholesterol levels have been a better measure than total cholesterol? While these alternative measures could have been used, the measures used in the present study were obtained accurately, using prospective data, and are also consistent with measures used in previous cross-sectional and longitudinal analyses (117, 330, 333, 337, 338).

Taken together, results of the present study and several previous studies appear to suggest that there is no strong association between vascular risk factors and major depressive disorder or depressive symptoms. It is still possible that there is a small effect, and the most promising candidate risk factors are diabetes, mean fasting glucose and smoking status, all of which could

be explored with greater power in 2016 when the Whitehall Imaging sub-study has recruited a larger number of participants.

11.4 Underlying mechanisms

The results of the present study suggest that long-term exposure to vascular risk factors has a limited association with structural brain changes, since an association was only shown for mean fasting glucose. This suggests that vascular risk factors are themselves unlikely to have a causal role, mediated through structural brain changes, in the development of late-life depressive symptoms. This study confirmed that current and late-onset depressive symptoms are also associated with reduced white matter integrity (reduced FA and increased RD), without associated changes in grey matter. Reductions in white matter integrity were identified in similar anatomical locations for these variables (mean fasting glucose, current depressive symptoms and late-onset depressive symptoms). This suggests that vascular risk factors and depression could affect common anatomical substrates, but in view of the lack of evidence from other vascular risk factors, and from longitudinal depressive symptoms, this is by no means certain. Further doubt is placed on the vascular depression hypothesis given that the epidemiological approach used here showed that lifetime vascular risk factors did not lead to increased risk of depressive disorder or depressive symptoms.

Based on the results of the present study, the evidence for an association between vascular risk factors and depressive disorder or depressive symptoms is weak. If such an association does exist, previous studies have hypothesised that it may be mediated by cerebral microvascular damage (359), platelet dysfunction, blood pressure variability, unhealthy lifestyle choices, or elevated cortisol levels in the brain (leading to glucocorticoid-mediated neurotoxicity) (244). Another theory is that focal vascular damage and white matter lesions may contribute to the development of late-life depression by disrupting functional connectivity in regions related to mood and cognition (27, 360). Alternatively, other relevant mechanisms have been proposed as potential links between cognitive impairment and depression: vascular disease, glucocorticoid levels, hippocampal atrophy, beta-amyloid deposition, inflammatory changes and deficits of neurotrophic factors (361).

Where there is reduced white matter integrity (due to either depression or vascular risk factors), functional connectivity may show reduced coherence in the default mode network (362). However, some individuals may have biological functional changes in the brain capable

of compensating for structural brain changes, thereby increasing resilience to the effects of vascular risk factors and depression. Successful ageing involves synaptogenesis and neurogenesis, and some individuals (e.g those with high pre-morbid IQ or education level) may be able to increase frontal activation with age – a marker of an adaptive brain in which capacity for plasticity and reorganisation is maintained (362). Hypoperfusion may also affect cognition and mood regulation, without demonstrable effects on brain structure: functional resilience may be impaired by reduced cerebral blood flow, or influenced by orthostatic changes and blood pressure variability (27).

Studies of vascular risk and depression that control for the presence of chronic illness show an attenuated effect size (74). It therefore seems possible that in addition to brain-related factors, personality and psychological factors (e.g. high tolerance of stress) and social factors (e.g. varied social network, financial stability) may provide alternative coping strategies. Psychosocial factors may make an important contribution to resilience, but may also represent additional risk factors for the development of depressive disorder. It is possible that such psychosocial factors could also contribute to an effect on structural brain measures.

There is still the issue that late-onset depression is associated with organic brain disease (29, 240), a high prevalence of cognitive impairment, including executive deficits (24, 34, 338), and overall a reduced contribution from psychological and social risk factors (10, 21). Yet, if there is an effect mediating these factors, the contribution from vascular risk factors towards development of depression is likely to be small. Consistent with previous studies that show an association between brain changes and late-life depression, but a weak or absent link between vascular risk factors and late-life depression (127, 239, 244, 363), the main findings of this thesis confirm that participants with late-onset depressive symptoms have structural brain changes in white matter that do not have a robust link with previous vascular risk factors.

This casts doubt on the theory that there is a direct, causal relationship between vascular risk factors and depression. However, vascular risk may still be relevant to the aetiology of late-life depression with other factors potentially contributing to, or mediating this relationship. For example, depression and depressive symptoms could themselves drive vascular damage, leading to white matter structural changes (235, 237, 332, 359). An alternative explanation for the weak association between vascular risk factors and depression is that that the mechanisms are mediated by processes that are more difficult to measure, for example blood pressure

variability, or orthostatic blood pressure changes (329, 364-367). Genetic factors, though hypothesised to be less important, may still have a role in the aetiology of late-life depression, with polymorphisms in brain-derived neurotrophic factor, serotonin transporter genes, and the hypothalamic pituitary adrenal axis potentially influencing vulnerability to depression (368). A further interesting hypothesis is that polymorphisms in genes related to the renin-angiotensin system (and therefore controlling blood pressure variability) may contribute to the development of depression and structural brain changes: this explanation is in agreement with the vascular depression hypothesis (27, 369-372).

It has also been proposed that raised inflammatory markers might themselves lead to depressive disorder. This theory is not incompatible with the vascular depression hypothesis, since raised inflammatory markers may mediate the interaction between vascular risk factors and depression. This seems plausible, since ageing and disease-related states are pro-inflammatory, and inflammation can exacerbate atherosclerosis, CHD and stroke (27, 373). Ageing results in increased peripheral immune responses, impaired communication between peripheral and central nervous systems, and a shift of the central nervous system towards a pro-inflammatory state, hypothesised to lead to changes in the function of brain networks relevant to late-life depression (33). In cross-sectional and longitudinal meta-analyses, raised inflammatory markers, particularly C-reactive protein and interleukin-6, are associated with development of depressive disorder and depressive symptoms (30-32, 374). The hypothesis that inflammation and inflammatory disorders might lead to depression could explain why depression is more common in those with chronic illnesses, such as arthritis (375, 376).

Inflammation not only causes mood changes, but also has an effect on brain structure and function. One study showed that in response to an inflammatory stimulus, participants developed increased activity in the subgenual anterior cingulate cortex, a region previously implicated in depressive disorder (377). Microstructural white matter changes are affected in the early stages of cognitive impairment (378), suggesting shared mechanisms with depression. Increased levels of pro-inflammatory cytokines could act by reducing plasticity and neurogenesis, thus providing a common mechanism which could predispose to both depression and dementia (378). Greater understanding of the effects of inflammatory pathways on mood regulation and the development of depression may provide an important translational approach to increasing treatment-response to current antidepressant therapies, and to introducing strategies for prevention of depressive disorder (379).

Late-life depression is a heterogeneous disorder, and it is unlikely that a single mechanistic theory will explain the link between brain structure and clinical phenotype. There is evidence from clinical and neuroimaging studies for an association between major cardiovascular disease (e.g. stroke and myocardial infarction) and depression, but in keeping with some previous studies, this thesis casts doubt on the importance of individual vascular risk factors to the aetiology of depression. When considered in the light of previous literature, vascular risk factors seem likely to have only a small effect, relevant to only some individuals. Most importantly, the lack of substantial findings in this field should prompt future research to explore alternative theories and mechanisms.

11.5 Strengths and limitations

The key strengths of this study relate to the combination of epidemiological and imaging methodologies. The Whitehall II Cohort provides access to prospective, longitudinal data collected five times over a 25-year period. The particular advantage of this unique data set is the possibility it gives of identifying mid-life antecedents to late-life depressive symptoms and structural brain changes. The MRI acquisition techniques using a 3 Tesla scanner and a multi-modal sequence, and the use of FSL analysis techniques, place the imaging methodology at the forefront of research.

Access to the Whitehall II Cohort has provided the possibility of selecting a large sample for MRI imaging. The Whitehall Imaging sub-study aims to recruit 800 participants over a four year period 2012 – 2016. A limitation of the present study is that it only included data from the first phase of this study (n=229). While this yielded a large amount of MRI data, in excess of the sample sizes frequently used to investigate late-life depression (36, 246), it follows that there was reduced power to investigate some variables (e.g. smoking and diabetes). It also meant that it was not possible to further sub-divide groups (e.g. to consider hypertensive and depressed participants, compared to hypertensive and euthymic participants). It has been recognised that the average statistical power of studies in the neurosciences, and neuroimaging in particular, is low, leading to a low probability of finding true effects, overestimates of effect size and low reproducibility of results (380, 381). While the numbers used in this study increase the power compared to many smaller studies, a further advantage of the present study is the opportunity to replicate analyses using a much larger sample on completion of the Whitehall Imaging sub-study.

Further analysis with a larger number of participants would present certain advantages. However, it is important to emphasize the advantages of the detailed analysis performed in this thesis, based on the first 229 participants. The hypotheses investigated in this thesis have provided a valuable opportunity to test and evaluate the study protocol and data-collection systems at a stage when modifications to the protocol are still possible, and before a much larger set of data is acquired. Second, the present study has been important in determining future hypotheses worthy of investigation, and therefore the direction of future analysis. The work presented in this thesis therefore represents an important learning phase in the Whitehall Imaging sub-study, based on the first phase of data collection, as well as providing meaningful results in its own right.

Within the Whitehall II Cohort, the majority of participants were men (67 % at baseline), reflecting the sex distribution in the workforce at the time of recruitment. A limitation of the sample used for the present study is that the proportion of men is even higher (>80%), limiting the generalisation of the findings. Whitehall participants were originally recruited as part of an occupational cohort, from all grades of the civil service; however, the present study has a greater proportion of participants with higher socio-economic status. Despite the breadth of employment grades and social class, the sample remains of above-average intelligence (mean IQ 118 ± 10). Continuing participation in the Whitehall II Study and the associated regular physical health checks mean that this is in general a health-conscious cohort, with, for example, a lower percentage of smokers compared to the national population (Table 3).

The ability to measure long-term exposure to vascular risk factors is a strength of this study. Since analysis for this thesis was begun, the Whitehall II Cohort has completed data collection for phase 11 (2012-2013); however, at the time of writing this data was not available for analysis, and vascular risk factors are therefore calculated from data collected between phases 1 and 9 only. On completion of the Whitehall Imaging sub-study in 2016, longitudinal data will be available from phase 11 and possibly phase 12 as well (2014-2016). The availability of additional data relating to vascular risk, and a reduction in the intervals between data-collection phases will further increase the analysis possibilities.

In the present study, two main measures were used to define depressive symptoms: major depressive disorder using DSM-IV criteria (following a SCID interview), and the presence of

depressive symptoms as defined by CES-D caseness (≥16). This provided both a clinical diagnosis, and one based on a self-administered questionnaire. A key finding in this thesis is that current CES-D caseness is associated with similar changes in white matter integrity compared to those expected in people with clinically diagnosed depression. Use of the CES-D as a longitudinal measure is likely to be more problematic, for two reasons. Firstly, participants may have had significant depressive symptoms before the first phase of data collection; and secondly, the CES-D only asks about depressive symptoms in the week prior to data collection, meaning that there are long intervals that are not accounted for, during which participants could have had depressive symptoms. Conversely, an individual with a recent adverse event may have an uncharacteristically elevated score. These limitations of the CES-D mean that it is important to combine this measure with records of current antidepressant medication use to help identify or exclude those with significant depressive symptoms, or those who are currently euthymic but have had significant depressive symptoms previously.

Previous literature suggests that structural brain abnormalities are more common in those developing depression in later life, typically over the age of 60. Late-onset depressive symptoms as defined using CES-D were used to investigate this, but owing to low numbers of people with major depressive disorder that developed for the first time at age ≥60 (n=8), further analysis relating to this variable could not be undertaken. This would be an interesting analysis to undertake in the larger sample, particularly in view of the widespread white matter differences that were identified in the group with late-onset depressive symptoms.

The analysis of vascular risk factors for depression (Chapter 10) used the same sample as that used elsewhere in this thesis. The purpose of doing so was to ensure that associations with major depressive disorder could be investigated; this data was only available for Whitehall Imaging sub-study participants who had had a more detailed clinical interview. There would have been greater power to investigate the association between long-term exposure to vascular risk factors and depressive symptoms if these were only defined using CES-D. However, the negative results identified in the present study were consistent with previous results from analysis of Whitehall data (115), suggesting that increasing the power would be unlikely to alter the results.

11.6 Clinical implications

These findings indicate that patients with single vascular risk factors are unlikely to have increased risk of depressive disorder; however, clinicians should be aware that people presenting with hyperglycaemia (raised fasting glucose or HBA1c) may be at increased risk of depressive disorder. This is a particularly important finding for clinicians working within primary care services who may be able to modify risk factors with the aim of preventing depression. Consistent with previous literature (115), the data presented in this thesis suggests that public health measures to improve vascular risk status will influence the incidence of late-life depressive symptoms via reduced rates of manifest vascular disease, rather than by a direct effect on individual vascular risk factors. For psychiatrists who are likely to treat patients with a clinical diagnosis of depression, the results emphasise earlier findings that even mild depressive symptoms can have an adverse effect on brain structure, which may reduce the efficacy of antidepressant treatment (27).

In this study, use of visual methods of MRI analysis rarely proved able to distinguish effectively between participant groups. This evidence fails to support the utility of these visual measures in clinicians' evaluation of MRI scans in depressive disorder. They may, however, be used to detect changes associated with cognitive impairment, particularly global and hippocampal atrophy (as described in Chapter 6).

11.7 Future directions

The present study has focused on MRI correlates of depression and vascular risk factors to interrogate the vascular depression hypothesis in detail. Several unanswered questions remain, and the results obtained suggest opportunities for further analysis and research.

The most obvious future direction for this research is to replicate the current analyses using a larger sample once the Whitehall Imaging sub-study has recruited 800 participants, a recruitment target that is anticipated to be complete in 2016. This would be particularly interesting in terms of identifying the MRI correlates of smoking and type 2 diabetes, as well as providing further scope to consider the MRI correlates of late-onset major depressive disorder. A larger sample size would make it possible to investigate the MRI correlates of depression plus another vascular risk factor (e.g. by comparing those with depression and hypertension, to those with depression and normotension, to euthymic individuals with hypertension, and to

controls without depression or hypertension). It would be sensible to undertake such a sub-group analysis for vascular risk factors such as mean fasting glucose, where the current results suggest there is more likely to be a positive association.

A further way of investigating brain structure in the context of the vascular depression hypothesis would be to identify a sub-group of individuals with severe white matter changes (e.g. Fazekas score ≥4), and then return to the clinical and neuropsychological data to identify any associations with increased depressive symptoms or cognitive impairment. Selecting such a subgroup would enable investigation of risk factors that significantly affect structural brain changes. Based on the current results, factors other than depressive symptoms would be expected to contribute to these changes.

This thesis has focused on structural brain changes associated with vascular risk and depression. There are still unanswered questions about how these risks affect brain function and neural circuitry (382-384). Data acquired through the Whitehall Imaging sub-study include sequences relating to resting-state functional connectivity (385), which would be interesting to analyse, with the hypothesis that there would be increased connectivity within the default-mode network, and reduced connectivity within the executive control and affective networks.

The ongoing nature of the Whitehall II cohort study, and the quality of the MRI methods employed within the Whitehall Imaging sub-study mean that there are several possibilities for participant follow-up:

1. Identification of individuals with more severe white matter changes, with the hypothesis that this group will be more likely to develop depressive symptoms and cognitive impairment compared to those with minimal structural changes.
2. Follow-up of individuals with significant depressive symptoms or major depressive disorder, with the hypothesis that these individuals will have increased rates of cognitive impairment (386, 387).
3. Identification of common risk factors for depression and dementia, with the hypothesis that these might include: cardiovascular disease, inflammatory changes and glucocorticoid levels (361).

11.8 Conclusions

The results of the present study suggest that long-term exposure to vascular risk factors is not significantly associated with changes in grey matter structure, but that individual risk factors may be associated with changes in white matter integrity. In this study, mean fasting glucose measured repeatedly over time was associated with reduced white matter integrity in frontal and subcortical regions. This study found no association between major depressive disorder or depressive symptoms and changes in grey matter structure. However, current and late-onset depressive symptoms were associated with reduced white matter integrity in frontal and subcortical regions, which overlapped with the regions affected by mean fasting glucose. The present study also demonstrates that lifetime vascular risk factors are not a major driver for increased risk of late-life depressive disorder or depressive symptoms.

An additional focus of this thesis was to consider two methodological elements. Visual measures of MRI analysis were shown to be replicable and reliable in relation to equivalent automated measures. However, they were not useful in distinguishing mood-related structural brain changes. The analysis of MRI correlates of depressive symptoms using CES-D showed that this non-clinical approach to defining symptoms identified a group of individuals with similar underlying neurobiological changes to those expected in individuals with a clinical diagnosis of major depressive disorder. Therefore the use of the CES-D scale in epidemiological studies of depression appears to be a reasonable way of defining symptoms when financial and time constraints preclude use of the gold-standard method of psychiatric interview.

In summary, this thesis does not support the hypothesis that vascular risk factors have a key role in the aetiology of depressive disorder. This implies that to understand the aetiology of late-life depression more fully, and to develop effective treatment strategies, research needs to advance beyond the vascular depression hypothesis, to explore alternative mechanisms such as the effects of inflammation.

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Appendix 1. Questionnaire for the Whitehall Imaging sub-study

1. ID:	Date:

Questionnaire

ID:

Date of Birth:

To be completed after:

DD/MM/YYYY

Date of completion:

DD/MM/YYYY

2. ID:	Date:

Thank you for volunteering to participate in our research and agreeing to complete this questionnaire.

Many questions in this questionnaire are about a specific period, for example the last **week** or the last **month**, so it is important that you read each question carefully. Please try to answer ALL questions. You might also find some of the questions familiar to those at your most recent Whitehall II assessment. This is because your answers could have changed since then.

There are five sections to this questionnaire:

A. Activity

B. Sleep

C. Health and Medical History

D. Mood and Life Events

E. Background

You do not have to complete this questionnaire in one go, but please complete it between:

_____

DD/MM/YYYY – DD/MM/YYYY

Alternatively, one of our researchers can complete the questionnaire with you during your visit to the FMRIB Centre. If you have any questions about any of the items contained within this questionnaire, please do not hesitate to contact us on **whitehall@psych.ox.ac.uk** or **01865 223786** (or 07765 351025 on the day of your testing).

The answers to these questionnaires will be kept strictly confidential and will be stored anonymously. All the information you provide will be used for research purposes only.

Thank you again for your participation, this research is simply not possible without you.

3. ID:	Date:

Section A: Activity

The next questions concern activities that you may have done in the past four weeks.

If you DID the activity in the past four weeks:

Step 1: Tick the YES box

Step 2: Think about how many TIMES a week you usually did it, and write your response in the space provided

Step 3: Tick how many TOTAL HOURS in a typical week you did the activity

Here is an example of how Mrs Jones would answer question 1, which asks 'did you visit with friends or family?' Mrs Jones usually visits her friends Maria and Olga twice a week. She usually spends one hour on Monday with Maria and two hours on Wednesday with Olga. Therefore the total hours a week that she visits with friends is 3 hours a week.

	Yes	No	How many TIMES a week	How many TOTAL hours a week did you usually do it?					
				Less than 1 hour	1 - 2.5 hours	3 - 4.5 hours	5 - 6.5 hours	7 - 8.5 hours	9 or more hours
1.	✓	O	2	O	O	✓	O	O	O

If you DID NOT do the activity

Tick the NO box and move to the next question.

4. ID:	Date:

In a typical week during the **past four weeks**, did you:

	Yes	No	How many TIMES a week	How many TOTAL hours a week did you usually do it?					
				Less than 1 hour	1 - 2.5 hours	3 - 4.5 hours	5 - 6.5 hours	7 - 8.5 hours	9 or more hours
1. Visit with friends or family (other than those you live with)?	O	O		O	O	O	O	O	O
2. Go to a community or day centre?	O	O		O	O	O	O	O	O
3. Do volunteer work?	O	O		O	O	O	O	O	O
4. Attend church or take part in church activities?	O	O		O	O	O	O	O	O
5. Attend other club or group meetings?	O	O		O	O	O	O	O	O
6. Use a computer?	O	O		O	O	O	O	O	O
7. Dance (such as square, folk, line, ballroom)? Do not count aerobic dance here.	O	O		O	O	O	O	O	O
8. Do woodworking, needlework, drawing, or other arts or crafts?	O	O		O	O	O	O	O	O
9. Play golf, carrying or pulling your equipment? Count walking time only.	O	O		O	O	O	O	O	O
10. Play golf, riding a cart? Count walking time only.	O	O		O	O	O	O	O	O
11. Attend a concert, movie, lecture or sport event?	O	O		O	O	O	O	O	O
12. Play cards, bingo, or board games with other people?	O	O		O	O	O	O	O	O
13. Play snooker, pool or billiards?	O	O		O	O	O	O	O	O
14. Play singles tennis? Do not count doubles.	O	O		O	O	O	O	O	O
15. Play doubles tennis? Do not count singles.	O	O		O	O	O	O	O	O
16. Skate (ice, roller, in-line)?	O	O		O	O	O	O	O	O
17. Play a musical instrument?	O	O		O	O	O	O	O	O
18. Read?	O	O		O	O	O	O	O	O
19. Do heavy work around the house (such as washing windows, cleaning gutters)?	O	O		O	O	O	O	O	O
20. Do light work around the house (such as sweeping or vacuuming)?	O	O		O	O	O	O	O	O
21. Do heavy gardening (such as spading, raking)?	O	O		O	O	O	O	O	O
22. Do light gardening (such as watering plants)?	O	O		O	O	O	O	O	O
23. Work on your car, truck, lawn mower, or other machinery?	O	O		O	O	O	O	O	O

5. ID:	Date:

	Yes	No	How many TIMES a week	How many TOTAL hours a week did you usually do it?					
				Less than 1 hour	1 - 2.5 hours	3 - 4.5 hours	5 - 6.5 hours	7 - 8.5 hours	9 or more hours
24. Jog or run? Include use of a treadmill.	O	O		O	O	O	O	O	O
25. Walk uphill or hike uphill? Count only uphill part. Include use of a treadmill.	O	O		O	O	O	O	O	O
26. Walk fast or briskly for exercise? Do not count walking leisurely or uphill. Include use of a treadmill.	O	O		O	O	O	O	O	O
27. Walk to do errands (such as to/from a shop or to take children to school)? Count walk time only.	O	O		O	O	O	O	O	O
28. Walk leisurely for exercise or pleasure?	O	O		O	O	O	O	O	O
29. Ride a bicycle or stationary cycle?	O	O		O	O	O	O	O	O
30. Do other aerobic machines such as rowing, or step machines? Do not count treadmill or stationary cycle.	O	O		O	O	O	O	O	O
31. Do water exercises? Do not count other swimming	O	O		O	O	O	O	O	O
32. Swim moderately or fast?	O	O		O	O	O	O	O	O
33. Swim gently?	O	O		O	O	O	O	O	O
34. Do stretching or flexibility exercises? Do not count yoga or Tai-chi.	O	O		O	O	O	O	O	O
35. Do yoga or Tai-chi?	O	O		O	O	O	O	O	O
36. Do aerobics or aerobic dancing?	O	O		O	O	O	O	O	O
37. Do moderate to heavy strength training (such as hand-held weights of more than 5lbs, weight machines, or push-ups)?	O	O		O	O	O	O	O	O
38. Do light strength training (such as hand-held weights of 5 lbs or less or elastic bands)?	O	O		O	O	O	O	O	O
39. Do general conditioning exercises, such as light calisthenics or chair exercises? Do not count strength training	O	O		O	O	O	O	O	O
40. Play basketball, football, or squash? Do not count time on sidelines	O	O		O	O	O	O	O	O
41. Do other types of physical activity not previously mentioned? Please specify:	O	O		O	O	O	O	O	O

6. ID:	Date:

Please read each statement about exercise and tick one box per statement.

	Strongly Disagree						Strongly Agree
	1	2	3	4	5	6	7
I exercise because I like to rather than because I feel I have to	O	O	O	O	O	O	O
Exercising is not something I would necessarily choose to do, rather it is something that I feel I ought to do	O	O	O	O	O	O	O
Having to exercise is a bit of a bind but it has to be done	O	O	O	O	O	O	O

Thinking about the days of the past four weeks,

On average, how much time did you spend sitting down watching TV (including DVDs and videos)?

On each weekday: _____ Hours _____ Minutes

On each weekend day: _____ Hours _____ Minutes

On average, how much time did you spend sitting down doing any other activity? For example reading, studying, drawing, using a computer, playing video games, driving or sitting in a car, travelling by public transport.

On each weekday: _____ Hours _____ Minutes

On each weekend day: _____ Hours _____ Minutes

Thinking about the days of the past week,

On average, for how long did you walk outside your home / workplace?

On each weekday _____ Hours _____ Minutes

On each weekend day _____ Hours _____ Minutes

On average, for how long did you cycle?

On each weekday _____ Hours _____ Minutes

On each weekend day _____ Hours _____ Minutes

7. ID:	Date:

Section B: Sleep

The following questions relate to your usual sleep habits during the **past month only**. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

During the **past month**, when have you usually gone to bed at night?

Usual bed time: _____

During the **past month**, how long (in minutes) has it usually taken you to fall asleep each night?

Number of minutes:_____

During the **past month**, when have you usually got up in the morning?

Usual getting up time:_____

During the **past month**, how many hours of actual sleep did you get at night? (This may be different from the number of hours spent in bed.)

Hours of sleep per night:_____

During the **past month**, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) Cannot get to sleep within 30 minutes	O	O	O	O
(b) Wake up in the middle of the night or early morning	O	O	O	O
(c) Have to get up to use the bathroom	O	O	O	O
(d) Cannot breathe comfortably	O	O	O	O
(e) Cough or snore loudly	O	O	O	O
(f) Feel too cold	O	O	O	O
(g) Feel too hot	O	O	O	O
(h) Had bad dreams	O	O	O	O
(j) Have pain	O	O	O	O
(j) Other reason(s); please describe:	O	O	O	O

During the **past month**, how would you rate your sleep quality overall?

- O Very good
- O Fairly good
- O Fairly bad
- O Very bad

S. ID:	Date:

During the **past month**, how often have you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Taken medicine (prescribed or 'over the counter') to help you sleep?	O	O	O	O
Had trouble staying awake while driving, eating meals or engaging in social activity?	O	O	O	O

During the **past month**, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

- O No problem at all
- O Only a slight problem
- O Somewhat of a problem
- O A very big problem

Do you have a bed partner or roommate?

- O No bed partner or roommate
- O Partner / roommate in other room
- O Partner in same room, but not same bed
- O Partner in same bed

If you have a roommate or bed partner, ask him/her how often in the **past month** you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Loud snoring	O	O	O	O
Long pauses between breaths while asleep	O	O	O	O
Legs twitching or jerking while you sleep	O	O	O	O
Episodes of disorientation or confusion during sleep	O	O	O	O
Other restlessness while you sleep; please describe:	O	O	O	O

9. ID:	Date:

How often in the past month did you...

	Not at all	1-3 days	4-7 days	8-14 days	15-20 days	21-31 days
(a) Have trouble falling asleep?	O	O	O	O	O	O
(b) Wake up several times per night?	O	O	O	O	O	O
(c) Have trouble staying asleep (including waking far too early)?	O	O	O	O	O	O
(d) Wake up after your usual amount of sleep feeling tired and worn out?	O	O	O	O	O	O
(e) Have disturbed or restless sleep?	O	O	O	O	O	O

During a typical week during the past month,

Have you dozed or taken a nap anytime during the day or before you go to bed?

- O Yes
- O No

If yes, did this happen:

- O About once a week or less
- O Two or three times per week
- O Once every day
- O Two or more times per day

On average, how long is each nap?

- O 15 mins or less
- O 30 mins
- O 1 hour
- O 1.5 hours
- O 2 hours or more

10. ID:	Date:

Section C: Health and Medical History

In the following sections, several questions ask about the age at which you were diagnosed with a medical condition, the age at which it was resolved, etc. We realise it may be difficult to accurately remember your age in all cases. So, in those cases in which you are unsure, we ask for you to provide a 'best guess'.

In general would you say your health is:

- O Excellent
- O Very good
- O Good
- O Fair
- O Poor

Do you smoke cigarettes?

- O Yes
- O No
- O Occasional smoker

In a **typical day**, how many cigarettes do you smoke per day?

Number of cigarettes: _____

Thinking about the last four weeks ...

Have you had an alcoholic drink?

- O Yes
- O No

In a **typical week**, please detail what alcoholic drinks you have ...

Small glass red/white/rose wine (125ml, ABV 12%)	
Standard glass red/white/rose wine (175ml, ABV 12%)	
Large glass red/white/rose wine (250ml, ABV 12%),	
Pint of lower-strength lager/beer/cider (ABV 3.6%),	
Pint of higher-strength lager/beer/cider (ABV 5.2%)	
Bottle of lager/beer/cider (ABV 5%):	
Can of lager/beer/cider (440ml, ABV 5%)	
Alcopop (275ml, ABV 5.5)	
Single small shot of spirits (gin, rum, vodka, whisky; 25ml, ABV 40%)	
Other, please specify:	
Other, please specify:	

11. ID:	Date:

Have there been any changes to your health since your last visit at the Whitehall II Clinic?

O Yes
O No

If yes, please detail the changes you have been experiencing:

1.		
2.		
3.		
4.		
5.		

Are you **currently** taking any medicines, tablets, tonics or pills? You may want to check your medicine bottles, pill box or prescription sheet for the exact name. This includes injections and patches as well as any over-the-counter medications, herbal remedies or homeopathy tablets you may have been taking regularly or on occasion.

O Yes
O No

If yes, please list below:

	Medicine	Dose	How often do you take it?	Did a doctor prescribe it?		Please specify the reason for taking this medicine
				Yes	No	
1.				O	O	
2.				O	O	
3.				O	O	
4.				O	O	
5.				O	O	
6.				O	O	
7.				O	O	
8.				O	O	

12. ID:	Date:

Do you have any longstanding illnesses, diseases or medical conditions for which you have received treatment (seen a doctor or a nurse or taken a medication) in the **last 12 months?** Longstanding means anything that has troubled you over a period of time or that is likely to affect you over a period of time.

- O Yes
- O No

If yes, please list below:

	Condition	Age when first diagnosed	Comments
1.			
2.			
3.			
4.			
5.			
6.			

Have you **ever** been admitted to hospital (including as a day case, but excluding outpatient appointments)? This includes surgical procedures or hospitalisations as a child.

- O Yes
- O No

If yes, please specify the reason for hospitalisation(s) and the year:

	Reason for hospitalisation	Age
1.		
2.		
3.		
4.		
5.		
6.		

13. ID:	Date:

Have you **ever** been told by a doctor that you have, or have had, any type of heart problem, suspected or confirmed?

	Yes	No	Age when first diagnosed	Do you currently receive treatment or experience symptoms?			Comments
				Yes	No	Age when resolved	
Angina	O	O		O	O		
Atrial fibrillation	O	O		O	O		
Atrial septal defect / hole in the heart	O	O		O	O		
Cardiac asthma	O	O		O	O		
Congenital heart disease	O	O		O	O		
Coronary insufficiency	O	O		O	O		
Irregular heartbeat	O	O		O	O		
Heart attack (myocardial infarct/coronary thrombosis)	O	O		O	O		
Left ventricular hypertrophy	O	O		O	O		
Valve disease / heart murmur	O	O		O	O		
Other (please specify)	O	O		O	O		

Have you **ever** been told by a doctor that you have, or have had, any type of respiratory condition?

	Yes	No	Age when first diagnosed	Do you currently receive treatment or experience symptoms?			Comments
				Yes	No	Age when resolved	
Asthma	O	O		O	O		
Bronchitis	O	O		O	O		
Emphysema	O	O		O	O		
Other (please specify)	O	O		O	O		

Have you **ever** been told by a doctor that you have, or have had, any type of bone or joint disease?

	Yes	No	Age when first diagnosed	Do you currently receive treatment or experience symptoms?			Comments
				Yes	No	Age when resolved	
Arthritis (osteoarthritis)	O	O		O	O		
Arthritis (rheumatoid)	O	O		O	O		
Gout	O	O		O	O		
Osteoporosis	O	O		O	O		
Other (please specify)	O	O		O	O		

14. ID:	Date:

Have you **ever** been told by a doctor that you have, or have had, any other illness?

	Yes	No	Age when first diagnosed	Do you currently receive treatment or experience symptoms?			Comments
				Yes	No	Age when resolved	
Cancer (please specify)	O	O		O	O		
Diabetes	O	O		O	O		
High blood pressure (hypertension)	O	O		O	O		
High cholesterol	O	O		O	O		
Intermittent claudication (pain in your leg when you walk)	O	O		O	O		
Kidney (renal) disease	O	O		O	O		
Liver disease (e.g. jaundice, hepatitis)	O	O		O	O		
Other (please specify)	O	O		O	O		
Other (please specify)	O	O		O	O		

Have you **ever** been told by a doctor that you have, or have had, any type of neurological or psychiatric illness?

	Yes	No	Age when first diagnosed	Do you currently receive treatment or experience symptoms?			Comments
				Yes	No	Age when resolved	
Anxiety or stress	O	O		O	O		
Dysphasia	O	O		O	O		
Memory problems (e.g. Alzheimer's disease, dementia, mild cognitive impairment)	O	O		O	O		
Mood disorder (e.g. depression or bipolar disorder / manic depression)	O	O		O	O		
Movement disorder (e.g. Parkinson's disease)	O	O		O	O		
Multiple sclerosis	O	O		O	O		
Schizophrenia	O	O		O	O		
Seizure disorder (e.g. epilepsy, blackouts)	O	O		O	O		
Sleep disorder (e.g. insomnia)	O	O		O	O		
Stroke or transient ischemic attack (TIA / mini-stroke)	O	O		O	O		
Substance-related disorder (e.g drugs or alcohol)	O	O		O	O		
Other (please specify)	O	O		O	O		
Other (please specify)	O	O		O	O		

15. ID:	Date:

Are you allergic to anything?

- O Yes
- O No

If yes, please detail below:

The following questions relate to recreational drug use (that is, use unprescribed by a doctor). If you have used any of the substances listed below in the stated time period, even if only one time, please tick yes.

	Have you ever used this drug?		Do you currently use this drug?		Age when last used	Comments
	Yes	No	Yes	No		
Cannabis (marijuana, hashish, etc)	O	O	O	O		
Hallucinogens (ecstasy, LSD, magic mushrooms, etc)	O	O	O	O		
Inhalants (glue, aerosols, poppers, etc)	O	O	O	O		
Opioids (heroin, methadone, etc)	O	O	O	O		
Sedatives (valium, diazepam, etc)	O	O	O	O		
Stimulants (amphetamines, cocaine, speed, etc)	O	O	O	O		
Other, please specify	O	O	O	O		
Other, please specify	O	O	O	O		

16. ID:	Date:

Section D: Mood and Life Events - CESD

The sentences that follow concern your feelings and behaviour over the past **week.** Please read the statements carefully and tick one box for each statement that best describes how often you felt this way during the past **week.**

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
I was bothered by things that usually don't bother me.	O	O	O	O
I did not feel like eating; my appetite was poor.	O	O	O	O
I felt that I could not shake off the blues even with help from my family and friends.	O	O	O	O
I felt that I was just as good as other people.	O	O	O	O
I had trouble keeping my mind on what I was doing.	O	O	O	O
I felt depressed.	O	O	O	O
I felt that everything I did was an effort.	O	O	O	O
I felt hopeful about the future.	O	O	O	O
I thought my life had been a failure.	O	O	O	O
I felt fearful.	O	O	O	O
My sleep was restless.	O	O	O	O
I was happy.	O	O	O	O
I talked less than usual.	O	O	O	O
I felt lonely.	O	O	O	O
People were unfriendly.	O	O	O	O
I enjoyed life.	O	O	O	O
I had crying spells.	O	O	O	O
I felt sad.	O	O	O	O
I felt that people disliked me.	O	O	O	O
I could not get "going".	O	O	O	O

In the **past month,** have you had any problems in concentrating on what you are doing?

O Yes
O No

In the **past month,** have you noticed any problems forgetting things?

O Yes
O No

17. ID:	Date:

Has there ever been a period of time when you were not your usual self and ...

	Yes	No
...you felt so good or hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	O	O
...you were so irritable that you shouted at people or started fights or arguments?	O	O
...you felt much more self-confident than usual?	O	O
...you got much less sleep than usual and found that you didn't really miss it?	O	O
...you were much more talkative or spoke much faster than usual?	O	O
...your thoughts raced through your head or you couldn't slow your mind down?	O	O
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	O	O
...you had much more energy than usual?	O	O
...you were much more active or did many more things than usual?	O	O
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	O	O
...you were much more interested in sex than usual?	O	O
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	O	O
...spending money got you or your family into trouble?	O	O

If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

- O Yes
- O No

How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights?

- O No problem
- O Minor problem
- O Moderate problem
- O Serious problem

Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?

- O Yes
- O No

Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?

- O Yes
- O No

18. ID:	Date:

For the following items, please be as honest and accurate as you can throughout. Try not to let your response to one statement influence your responses to other statements. There are no 'correct' or 'incorrect' answers. Answer according to your own feelings, rather than how you think 'most people' would answer.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
In uncertain times, I usually expect the best.	O	O	O	O	O
It's easy for me to relax.	O	O	O	O	O
If something can go wrong for me, it will.	O	O	O	O	O
I'm always optimistic about my future.	O	O	O	O	O
I enjoy my friends a lot.	O	O	O	O	O
It's important for me to keep busy.	O	O	O	O	O
I hardly ever expect things to go my way.	O	O	O	O	O
I don't get upset too easily.	O	O	O	O	O
I rarely count on good things happening to me.	O	O	O	O	O
Overall, I expect more good things to happen to me than bad.	O	O	O	O	O

The following is a list of things that can happen to people. Try to remember if any of these things happened to you and when they happened.

	Yes	No	If yes, what age were you when they occurred?
Personal serious illness, injury or operation.	O	O	
Death of a close relative or friend.	O	O	
Serious illness, injury or operation of a close relative or friend.	O	O	
Major financial difficulty.	O	O	
Divorce, separation or break up of a personal intimate relationship.	O	O	
Other marital or family problem.	O	O	
Robbery, mugging or similar criminal event.	O	O	

19. ID:	Date:

Section E: Background

What is your marital status?

- O Married
- O Co-habiting
- O Single (never married)
- O Widowed
- O Divorced
- O Separated

Is English your first language?

- O Yes
- O No

What is your highest level of qualifications?

- O No qualifications
- O O levels or equivalent
- O A levels or equivalent
- O College certificate
- O Professional qualifications (for example teaching, nursing, accountancy)
- O University degree
- O Post-graduate / masters / PhD

At what age did you start primary school?

At what age did you (first) leave full-time education?

How many years of full-time education did you complete later in life?

How many years of part-time education have you completed? Include any part-time education that was leading to or led to a qualification (e.g. day release schemes).

Since leaving full-time education, what has been your main occupation?

20. ID:	Date:

Are you currently in paid employment (including self-employment or employment after retirement)?

- O Yes
- O No, retired
- O No, unemployed seeking work

If you are currently in employment, what is the title of your main paid job?

How many hours do you work in a normal week, including work brought home?

21. ID:	Date:

Most people are either right-handed or left-handed. However, there are different 'degrees' of handedness. Some people use one hand for jobs that require skill and the other hand for jobs that involve reaching. For each item please indicate your hand preference by ticking the answer that describes you best.

	Always left	Usually left	No preference	Usually right	Always right
To write a letter legibly.	O	O	O	O	O
To throw a ball to hit a target.	O	O	O	O	O
To play a game requiring the use of a racquet.	O	O	O	O	O
At the top of a broom to sweep dust from the floor.	O	O	O	O	O
At the top of a shovel to move sand.	O	O	O	O	O
To hold a match when striking it.	O	O	O	O	O
To hold scissors to cut paper.	O	O	O	O	O
To hold thread to guide through the eye of a needle.	O	O	O	O	O
To deal playing cards.	O	O	O	O	O
To hammer a nail into wood.	O	O	O	O	O
To hold a toothbrush while cleaning teeth.	O	O	O	O	O
To unscrew the lid of a jar.	O	O	O	O	O

Are either of your parents left-handed?

- O Yes; which one: _____
- O No

How many siblings of each sex do you have?

- O Male: _____
- O Female: _____

How many of each sex are left-handed?

- O Male: _____
- O Female: _____

22. ID:	Date:

Please use the space below to write any further comments:

23. ID:	Date:

Thank you for completing this questionnaire!