# Imaging and neurobiological changes in late-life depression

***Depression was previously thought of as a 'functional' illness, without demonstrable pathology, but the advent of sophisticated neuroimaging techniques has changed this perspective. This article reviews the latest structural and functional brain imaging studies, describing the neurobiological changes which underlie this common condition.***

Major depressive disorder is common, with a lifetime prevalence of 10–15% (Andrade et al, 2003; Kessler et al, 2003) and accounts for significant morbidity worldwide. A range of biological, psychological and social factors contribute to its aetiology, but in late life psychosocial and genetic factors are less relevant (Brodaty et al, 1991; Schoevers et al, 2000). While much of the imaging literature has focussed on pre-frontal structures and networks, particularly those with a role in depressive state changes (Ebert and Ebmeier, 1996; Halloran et al, 1999), this article focuses on structural trait changes.

In those developing major depressive disorder for the first time over the age of 60 years ('late-onset depression'), brain abnormalities, cerebrovascular disease and cognitive impairment are common (Alexopoulos et al, 1997). This is in contrast to patients with earlier onset of illness, who even at an advanced age retain relatively more normal executive function (Herrmann et al, 2007), cerebral white matter (Herrmann et al, 2008), and less cerebral atrophy (Sexton et al, 2012b). On the other hand, medial temporal and hippocampal atrophy appears to grow with longer duration of illness and is consequently more pronounced in early onset older patients with depression (Sexton et al, 2012b). The 'natural experiment' of early *vs* late onset depression in older patients thus allows for a dissociation of diverse potential causes of depression.

## Structural brain changes in the hippocampus

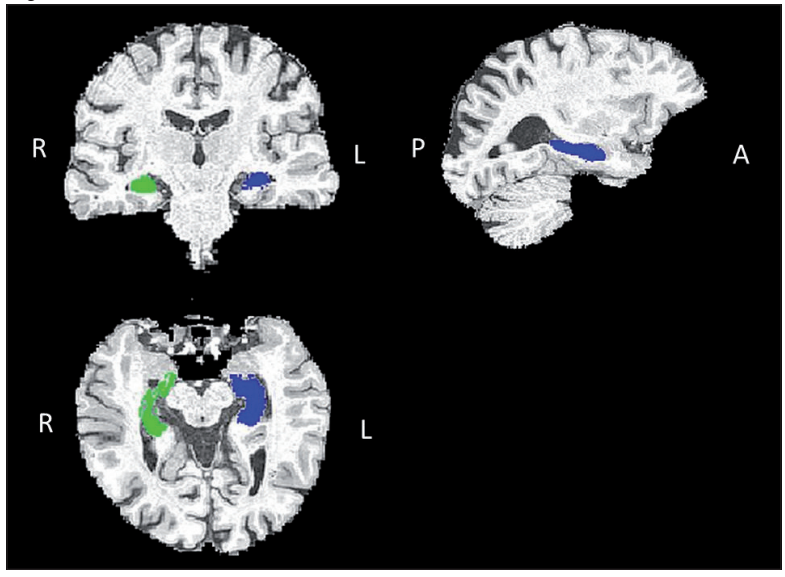
### Comparison with healthy controls

The hippocampus has been identified as a central component in a network that is affected in major depressive disorder (*Figure 1*). Reduction of hippocampal volume and grey matter density is a neurobiological feature of major depressive disorder, and has been consistently reported in patients with major depressive disorder compared with healthy controls. Meta-analyses of volumetric magnetic resonance imaging studies of patients with unipolar depression revealed reductions in bilateral hippocampal volumes (Campbell et al, 2004; Videbech and Ravnkilde, 2004; Koolschijn et al, 2009; McKinnon et al, 2009; Cole et al, 2011; Arnone et al, 2012). The most recent meta-analysis of volumetric magnetic resonance imaging studies reported volume reduction in the left (d = −0.26; 95% confidence interval = −0.39, −0.13) and right (d = −0.27; 95% confidence interval = −0.40, −0.13) hippocampus (Arnone et al, 2012), whereas a meta-analysis of voxel-based morphometry (or voxelwise) studies found reduced hippocampal grey matter density on the right side only (Du et al, 2012).

### Age

In a meta-analysis examining clinical predictors of hippocampal volume in patients with major depression compared with controls, McKinnon et al (2009) divided data into four age categories at the time of scanning: children (≤ 18 years), young adults (18–33 years), middle-

***Figure 1. FIRST image of the hippocampus from a 76-year-old healthy male overlaid on T1-weighted magnetic resonance imaging. Sections in coronal, sagittal and axial orientations; left (blue) and right (green) hippocampus. FIRST = Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Integrated Registration and Segmentation Tool.***

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aged adults (34–64 years) and older adults (≥ 65 years). The authors examined 95% confidence intervals to determine whether the pooled effects were maintained within these sub-groups. The pooled effect remained significant for left and right hippocampi in children and middle-aged participants, and for the right hippocampus only in older adults. The volume reduction observed in patients compared with controls was not significant for the sub-group of young adults or for the left hippocampus in older adults. In contrast to these findings, other meta-analyses of volumetric magnetic resonance imaging studies which compared hippocampal volumes between patients with major depressive disorder and healthy controls found no modulating effect of age on the pooled effect sizes (Videbech and Ravnkilde, 2004; Koolschijn et al, 2009; Cole et al, 2011; Arnone et al, 2012).

## Clinical correlates

In their meta-regression Koolschijn et al (2009) found that symptom scores did not explain any additional variance. McKinnon et al (2009) divided data into two categories based on illness severity: euthymic or mild illness and moderate to severe illness. The authors found no effects of illness severity on hippocampal volume; when examining the 95% confidence intervals they observed differences between patients and controls in both the euthymic/mild and moderate/severe group.

## Number of episodes and duration of illness (age at onset)

Videbech and Ravnkilde (2004) found that the number of depressive episodes was significantly correlated with pooled effect sizes of volume reduction in the right hippocampus, but not in the left. However, a more recent meta-regression by Arnone et al (2012) could not confirm this. In their follow-up analysis McKinnon et al (2009) divided data based on number of episodes: first episode (1 episode), moderate number of episodes (2–4 episodes), and a high number of episodes (≥5 episodes). They found that patients with a moderate or high number of episodes had bilaterally reduced hippocampi, but not those experiencing their first episode.

Similarly, McKinnon et al (2009) divided data based on duration of illness into the following groups: brief (≤2 years), moderate (2–9 years), and chronic (≥10 years). Only patients with brief or chronic illness, but not those with a moderate length of major depressive disorder, showed reduced hippocampi in relation to healthy controls. Volume loss was more pronounced in the right hippocampus among patients with a moderate length of illness than in those with a brief or a chronic duration. Random effect meta-analytical studies that used meta-regression to estimate the effect of illness duration reported no significant results, possibly because of the limited power of studies using pooled effect sizes (Koolschijn et al, 2009; Cole et al, 2011; Arnone et al, 2012).

Finally, McKinnon et al (2009) examined the effect of patient age at illness onset, using the same age groups defined for testing the effect of age on hippocampal volume (children ≤18 years, young adults 18–33 years, middle-aged adults 34–64 years, older adults ≥65 years). They found differences in hippocampal volume among patients with an illness onset in childhood, young adulthood and middle age, but not in older age. It therefore seems likely that hippocampal atrophy is related to the duration of time patients have suffered from depression.

## Effect of medication

It has been suggested that antidepressant medication is neuroprotective and promotes hippocampal cell growth (Duman et al, 2001; Boldrini et al, 2009). Consistent with these reports a meta-analysis of seven independent studies of patients with first episode major depressive disorder found a marginally significant effect related to medication, in which un-medicated patients had volume reductions in the right hippocampus (Cole et al, 2011). However, the comprehensive meta-analysis by Arnone et al (2012), which included all seven studies analysed by Cole et al (2011) except Cole et al (2010), found no evidence that medication contributed to the differences in hippocampal volume between patients and controls.

## Functional correlates of hippocampal atrophy

Major depressive disorder is associated with hippocampal dysregulation (Frodl et al, 2008; MacQueen and Frodl, 2011) so that hippocampal atrophy may serve as a clinical biomarker for diagnosis and prognosis of depression (Cole et al, 2010; Nouretdinov et al, 2011). The hippocampus has a major role in hypothalamo–pituitary–adrenal axis regulation, which is involved in stress response and major depressive disorder (*Figure 2*). Sustained dysregulation of the stress response, which is a common feature of major depressive disorder, may be the result of hippocampal dysfunction. Extreme or chronic stress results in volumetric decreases in the hippocampus as well as increased levels of glucocorticoids, which disrupt hippocampal neurogenesis. The hippocampus is also a key regulator of the prefrontal region, and a disruption in its function could contribute to the memory and concentration problems that are among the key diagnostic features of major depressive disorder (Hasler et al, 2004; Squire, 2004). Depression is associated with an increased risk of dementia, which may occur parallel to recurrent episodes with progressing hippocampal atrophy (Ownby et al, 2006; Caraci et al, 2010; Saczynski et al, 2010; Costafreda et al, 2011).

A crucial implication of this research is the need to advance our understanding of early risk factors (such as adverse life events) and early interventions that could reduce or prevent relapse. Halligan et al (2007) provided some of the first evidence that hypothalamo–pituitary–

adrenal axis hyperactivity mediates the link between early negative life experiences and later psychiatric disorders. They found that adolescents whose mothers suffered from postnatal depression had higher early-morning glucocorticoid levels and an increased risk of depression by the age of 16 years (Evans and English, 2002; Vythilingam et al, 2002; Lupien et al, 2009).

Despite this, some authors (O'Brien et al, 2004) argue against cortisol toxicity, and small hippocampal volumes have been found before the manifestation of depressive symptoms in adolescents who experienced adversity during childhood (Rao et al, 2010). This led to the hypothesis that there could be an interaction between early-life adversity and genetics, which caused hippocampal volume reductions and an increased risk of major depressive disorder (Vythilingam et al, 2002; Charney and Manji, 2004; Burke et al, 2005; Amico et al, 2011). In their review, MacQueen and Frodl (2011) proposed a model that elegantly links the molecular, cellular and functional levels of hippocampal pathophysiology in depression (*Figure 3*). Future studies are needed to confirm the neurobiological mechanisms through which early life adversity translates into a risk for depression.

### Late-onset depression

Lloyd et al (2004), in comparing early and late-onset depression, found that age at onset was negatively correlated with hippocampal volume, but lifetime duration of depression was not. Sexton et al (2012b) reported a direct correlation of global brain volume with age at onset in a sample of elderly depressed patients. After controlling for brain size, hippocampal volume was inversely correlated with age at onset, suggesting that longer duration of illness was associated with greater hippocampal atrophy. In contrast, later onset appeared to be associated with non-specific brain atrophy, consistent with evidence of generalized brain changes.

## Structural brain changes in white matter

Structural changes in white matter, e.g. white matter hyperintensities, are a well-replicated finding in late-life depression, reflecting underlying ischaemic changes (Thomas et al, 2002). White matter hyperintensities appear as bright lesions on T2-weighted magnetic resonance imaging scans and can be found adjacent to the ventricles, or within deep white matter. Neuroimaging studies (computed tomography and magnetic resonance imaging) have demonstrated that white matter hyperintensities are more common, and more severe, in those with late-life depression (Herrmann et al, 2008). There is evidence that deep white matter hyperintensities have a stronger association with late-life depression than periventricular changes (Krishnan et al, 2006). Deep white matter hyperintensities have particular clinical significance, and in people with depression they are associated with reduced cognitive function, and reduced quality of life (Kang et al, 2012). There is some evidence that white matter abnormalities are more pronounced when depressive symptoms are more severe (Cole et al, 2012). Longitudinal follow-up from a multicentre trial has demonstrated that the progression of white matter changes is significantly associated with incident depression, supporting the hypothesis that these changes have a causal effect in the pathogenesis of late-life depression (Firbank et al, 2012). The progression of white matter hyperintensities also appears to predict a poor course of depression, and may reflect underlying worsening of vascular disease (Taylor et al, 2013).

***Figure 2. The serotonergic system interacts with the hypothalamic–pituitary–adrenal axis through the hippocampus; negative feedback via cortisol effects on hippocampus and pituitary gland.***

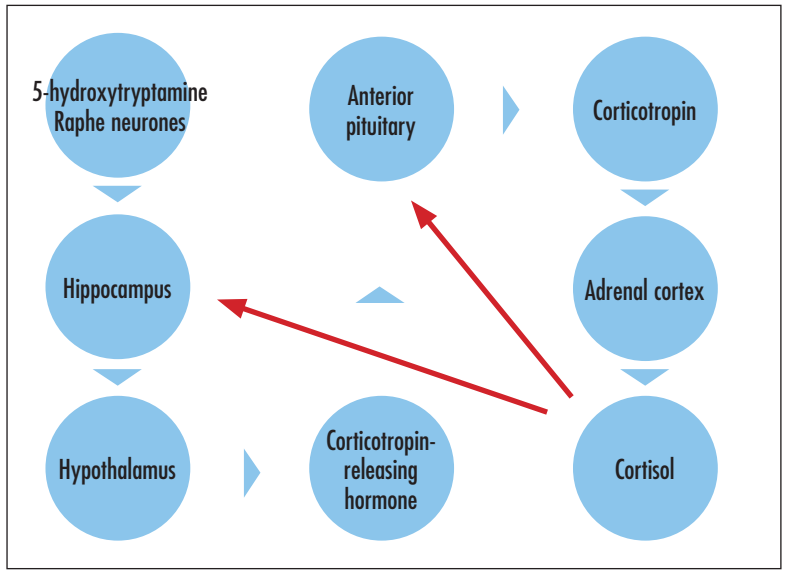
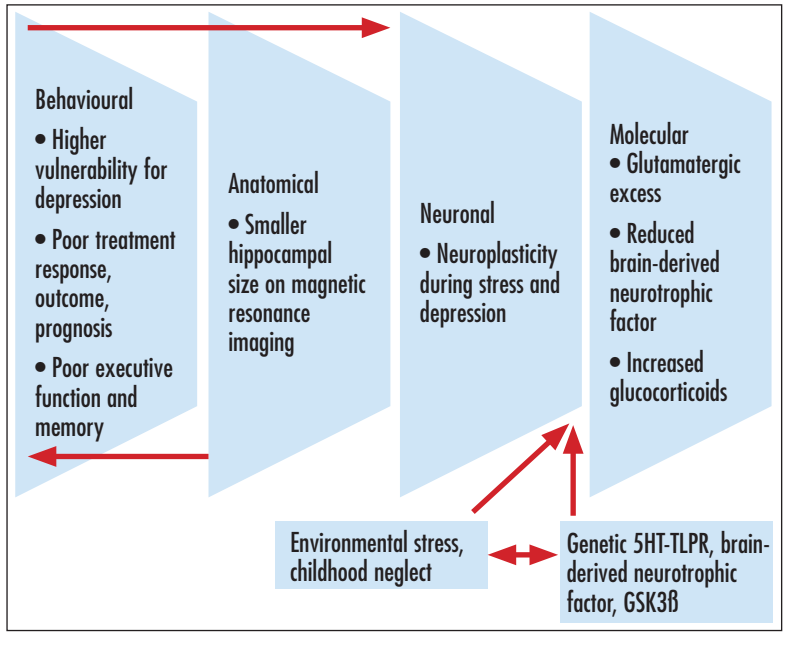



***Figure 3. Effects and results of small hippocampus volumes in major depressive disorder. Adapted from MacQueen and Frodl (2011). 5HT-TLPR = 5-hydroxytryptamine-transporter-linked polymorphic region; GSK3B = glycogen synthase kinase-3 beta.***



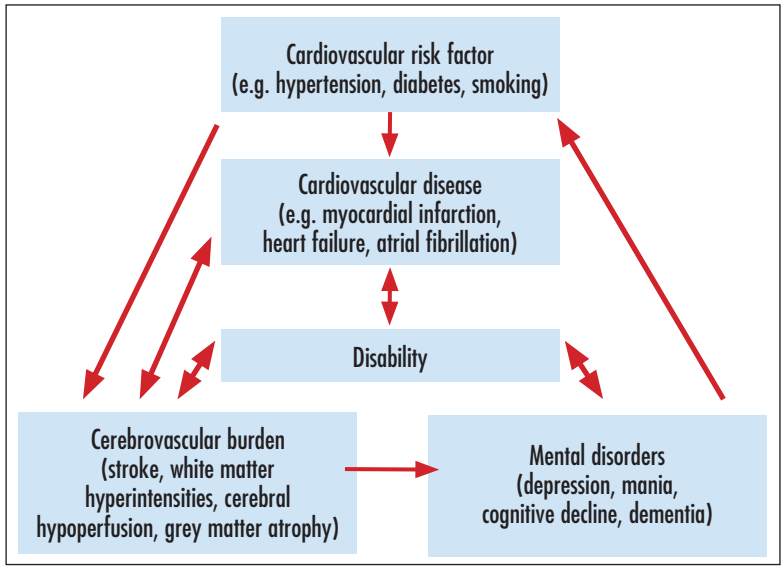
Depression is not only associated with increased white matter hyperintensities, but also with changes in the direction and integrity of white matter tracts. The latter has been investigated using diffusion tensor imaging, a magnetic resonance imaging technique. This has been used in case-control studies of depressive disorders with results consistently demonstrating reduced white matter integrity (lower anisotropy) in frontal and temporal regions and tracts, particularly in late-life depression (Sexton et al, 2009, 2012a; Liao et al, 2013). This supports the hypothesis that white matter abnormalities in frontal-subcortical and limbic networks play a key role in late-life depression (Sexton et al, 2012a).

## Vascular disease and depression

The 'vascular depression hypothesis' proposes that cerebrovascular disease can predispose, precipitate or perpetuate depression (Alexopoulos et al, 1997). The relationship between cardiovascular disease and depression is complex (*Figure 4*), but there is a range of clinical, imaging and neuropathological evidence to support this theory.

Clinical studies make it increasingly clear that there is a bi-directional relationship between cardiovascular diseases, including myocardial infarction and stroke, and depression (Kendler et al, 2009; Greenstein et al, 2010; O'Donnell et al, 2010; Hajjar et al, 2011), with depression more common in those with cardiovascular disease, and cardiovascular disease more likely in those with depression. A recent meta-analysis which focussed specifically on cardiovascular risk factors for depression, concluded that diabetes (odds ratio=1.5, 95% confidence interval = 1.3–1.8), cardiovascular disease (odds ratio=1.8, 95% confidence interval = 1.5–2.0), stroke (odds ratio= 2.1, 95% confidence interval = 1.6–2.8) and a vascular risk factor composite score (odds ratio=1.5, 95% confidence interval = 1.3–1.8) all significantly increased the risk of depression (Valkanova and Ebmeier, 2013). However, other vascular risk factors including dyslipidaemia, hypertension, smoking and Framingham Stroke Risk Score did not significantly increase the risk of depression (Valkanova and Ebmeier, 2013).

***Figure 4. Vascular risk and disease, disability and depression in old age. Adapted from de Toledo Ferraz Alves (2010).***




Deep white matter lesions, more common in late-life depression, are caused by cerebral ischaemia (Thomas et al, 2002). If vascular risk factors do contribute to an increased risk of depression, the effects are most likely to be mediated through the effects on white matter. For example, persistent depressive symptoms are common after acute coronary syndrome, and are associated with greater deep white matter changes and reduced white matter integrity (Rapp et al, 2010). A case-control study of patients with late-life depression and age-matched controls found that an elevated Framingham Stroke Risk Score was associated with reduced white matter integrity within the corpus callosum and corticospinal tracts of the patient group (Allan et al, 2012). This suggests that even if vascular risk factors do not lead directly to depression, they may have subtle effects on white matter structure, and this reduced white matter integrity can be a predisposing factor in those who are otherwise vulnerable.

While vascular diseases and risk factors do not always lead to depression, there is a great deal of evidence that these conditions can disrupt brain circuitry, affecting the development and course of depressive disorder. In a recent review Taylor et al (2013) propose two hypotheses to explain these mechanisms: first, a 'disconnection hypothesis' where regional vascular damage leads to altered neural connectivity and subsequent clinical symptoms and, second, an 'inflammatory and hypoperfusion' hypothesis, where vascular changes mediated by inflammatory markers (Valkanova et al, 2013) cause altered brain function and subsequent depression.

## Depression and cognitive impairment

Late-life depression is associated with cognitive impairment, with reductions in processing speed and executive function, compared to controls and those with early onset depression (Herrmann et al, 2007). These deficits contribute to altered cognitive function in other domains, and are related to total white matter hyperintensity volume (Vasudev et al, 2012), as well as to reduced white matter integrity in frontal tracts (Sexton et al, 2012c).

Late-life depression and cognitive impairment both show similarities in structural brain changes, such as hippocampal atrophy (O'Brien et al, 2004; McKinnon et al, 2009), in addition to sharing cerebrovascular risk factors. It is not a surprise therefore, that depression is a risk factor for dementia (Ownby et al, 2006; Diniz et al, 2013), and dementia a risk factor for depression (Korczyn and Halperin, 2009). Depressive symptoms are not only asso-

ciated with greater atrophy in grey-matter structures associated with memory, but also with increased risk of cognitive decline, and higher rates of conversion to Alzheimer's disease and vascular dementia (Lee et al, 2012; Diniz et al, 2013; Verdelho et al, 2013). Patients with mild cognitive impairment and depression are particularly at risk of progression to Alzheimer's disease (Lee et al, 2012), and it seems likely that depression acts as an additional marker of subtle, underlying organic dysfunction (Verdelho et al, 2013).

## Conclusions

It is clear from the above that major depressive disorder is not just a functional psychiatric disorder, characterized by abnormally activated frontal lobe brain networks (Mayberg et al, 1994; Ebert and Ebmeier, 1996), but that it is also associated with structural white and grey matter changes. While stress-related mechanisms associated with abnormal hypothalamo–pituitary activity may be responsible for some hippocampal changes and possibly for episodic memory failure (Shah et al, 1998), more global white and grey matter abnormalities with effects predominantly in frontal networks, will be mediated by vascular and possibly inflammatory mechanisms that are responsible for the close link of major depressive disorder with cardiovascular disease, diabetes and dementia. There is thus evidence for mechanisms that lead to a reduction of hippocampal volume with overall duration of illness, whether a result of lack of neurogenesis (Kheirbek and Hen, 2013) or the adverse effects of raised corticosteroid levels (Sapolsky, 2000).

On the other hand, more widespread cerebrovascular brain changes in older patients with recent onset suggest that such changes contribute to their vulnerability to develop depression and also cognitive changes. Such intricate multiple risk factors will only be unravelled by large-scale longitudinal epidemiological imaging studies that are currently under way.

In the meantime, doctors managing depression should pay close attention to optimizing physical health, to minimize the increased risk from cardiovascular and inflammatory conditions. Physicians treating these conditions should be alert to the high prevalence of depressive disorder and the adverse impact on physical and mental health if it is undetected or untreated. **BJHM**

*Conflict of interest: none.*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### KEY POINTS

- Depression is common and associated with significant morbidity and mortality.
- Structural brain changes, in white matter and grey matter (e.g. the hippocampus), are a prominent feature.
- Cerebrovascular disease and risk factors are important in the aetiology of late life depression.
- Shared risk factors for dementia and depression may explain the overlap in these conditions.

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