Molecular Psychiatry (2011) 16, 252–264

www.nature.com/mp

FEATURE REVIEW

The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research?

G MacQueen[1] and T Frodl[2]

[1]*Department of Psychiatry, University Calgary, Calgary, Canada and* [2]*Department of Psychiatry, Institute of Neuroscience, University Dublin, Trinity College, Dublin, Ireland*

Major depressive disorder (MDD) has until recently been conceptualized as an episodic disorder associated with 'chemical imbalances' but no permanent brain changes. Evidence has emerged in the past decade that MDD is associated with small hippocampal volumes. This paper reviews the clinical and biological correlates of small hippocampal volumes based on literature searches of PubMed and EMBASE and discusses the ways in which these data force a re-conceptualization of MDD. Preclinical data describe the molecular and cellular effects of chronic stress and antidepressant treatment on the hippocampus, providing plausible mechanisms through which MDD might be associated with small hippocampal volumes. Small hippocampal volumes are associated with poor clinical outcome and may be a mechanism through which MDD appears to be a risk factor for Alzheimer's disease. The pathways through which stress may be linked to MDD, the emergence of chronicity or treatment resistance in MDD and the association between MDD and memory problems may be at least partially understood by dissecting the association with depression and changes in the hippocampus. MDD must be re-conceived as a complex illness, associated with persistent morphological brain changes that are detectable before illness onset and which may be modified by clinical and treatment variables.
Molecular Psychiatry (2011) **16,** 252–264; doi:10.1038/mp.2010.80; published online 27 July 2010

Keywords: major depression; hippocampus; neuroplasticity; neuroimaging; genetic; therapy response

Introduction

Lively debates in the pages of psychiatric journals have recently challenged whether there is any evidence that studying biological mechanisms of psychiatric illness has changed clinical practice. We do not wish to wade into the debate. We do suggest that studies focusing on the hippocampus (HC) in major depressive disorder (MDD) enable an integration of basic experimental, neuroimaging and clinical findings into plausible biological models that are influencing the ways in which we conceptualize the nature and course of MDD.

Convergent lines of research implicate the HC in the pathogenesis of MDD. First, MDD is clinically recognized as a highly stress-sensitive illness[1] and the HC is a highly stress-sensitive brain region.[2] Stress, including psychological or psychosocial stress, is associated with structural changes to the HC.[3–5] Conditions of chronic hypercortisolemia, such as Cushing's disease are associated with HC atrophy that is reversible following normalization of cortisol levels,[6] supporting the hypothesis that stress-related changes in the HC are observable in humans as well as other species. Effective antidepressant treatments may ameliorate stress-associated changes in the HC.[7,8]

Second, when the various domains of cognitive function are assessed in patients with depression, their greatest degree of impairment is on memory measures that are heavily dependent on HC function.[9] Poor memory performance is associated with small volumes of HC gray matter in non-clinical samples as well.[10] Furthermore, while there has been a debate about whether mood congruent memory biases are present for implicit material, such biases can be reliably demonstrated in explicit memory tasks, which are heavily dependent upon medial temporal lobe structures, including the HC.[11]

Third, the HC is one of several regions, including the dorsomedial and dorsolateral prefrontal cortex, the anterior cingulate cortex and the amygdala[12] that connectivity studies have identified as components of a network that is dysregulated in MDD.[13] Evidence from neuroimaging, neuropathological and lesion analysis studies further implicates limbic–cortical–striatal–pallidal–thalamic circuits, including prefrontal cortex, amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal and midline

Correspondence: Professor T Frodl, Department of Psychiatry, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland.
E-mail: thomas.frodl@tcd.ie
Received 28 January 2010; revised 16 May 2010; accepted 6 June 2010; published online 27 July 2010

thalamic nuclei and ventral pallidum, in the pathophysiology of mood disorders. These networks normally regulate aspects of emotional behavior and fit therefore well to pathophysiological concepts of mood disorders.[14,15] The hippocampus has a role in these networks with its connections to and from the other brain regions[16] (Figure 1b).

Finally, many structural imaging studies have reported that the HC is small in patients with MDD. A recent meta-analysis of hippocampal volumes in patients with MDD confirmed that patients had hippocampal volumes that were approximately 4–6% smaller than matched control subjects in the left and right HC. The analysis included 1167 patients and 1088 control subjects, across a wide range of ages from pediatric to geriatric populations. Conclusions from this meta-analysis were consistent with the findings of earlier meta-analyses of HC volume in patients with MDD[17,18] (for anatomical location of the HC see Figure 1a). A summary of the evidence of HC involvement in MDD is provided in Figure 1.

Despite consistency in the studies implicating the HC in MDD, questions remain regarding the pathophysiological underpinnings of these findings, the clinical factors that are associated with dysregulation in the HC, the clinical significance of HC changes in MDD and the likelihood that medication can ameliorate HC-related dysfunction in patients with MDD. We review the data relevant to each of these issues.

Materials and methods

A search of the PubMed and EMBASE databases till November 2009 was conducted using the search terms hippocampus/or HC and depression and MRI. An overview of the current literature is provided.

Can hippocampal dysregulation be linked to MDD?

There is credible evidence that the HC is part of a network that, when dysregulated, could contribute to a variety of depressive symptoms.

Hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis and the resulting increase in glucocorticoid levels in the brain are associated with early stage reversible dendritic remodelling in the C1 and C3 pyramidal granule neurons, paralleled by reversible remodelling of synaptic terminal structures. As the HC provides negative modulation to the HPA stress hormone axis through its projections to

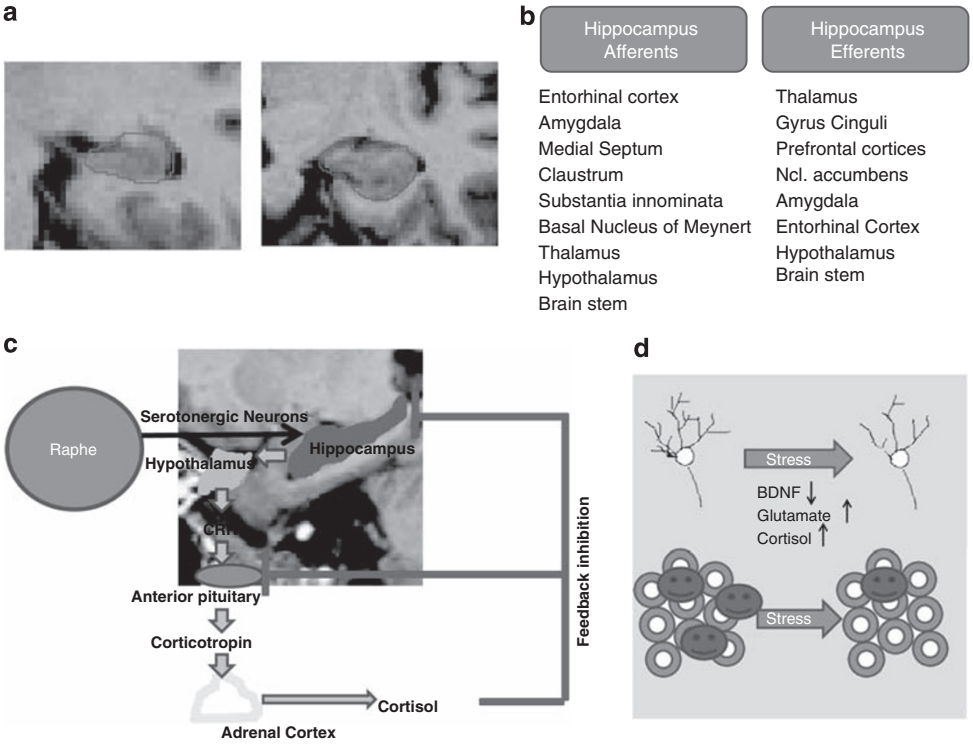

Figure 1 Hippocampal involvement in stress-regulation and depression. (**a**) Evidence that hippocampal dysregulation is involved in MDD derives from studies that show smaller hippocampal volumes in MDD. Depicted are two MRI images that present the hippocampus within the temporal lobe region and how it is traced in a manual region of interest analysis. (**b**) The hippocampus is involved in a neural network of affect regulation and has intensive connections from and to other brain regions[16]. (**c**) Moreover, the hippocampus has a major role in the regulation of the HPA axis, which is involved in stress response and MDD. The serotonergic system, which is involved in the neurobiology of MDD and which is mechanism of action for most of the antidepressants, interacts with the HPA stress axis in the hippocampus. (**d**) Experimental animal studies showed that stress affects hippocampal neurons in a way that dendrites decrease in size, length and numbers (top row) and that neurogenesis is inhibited (bottom row).

the hypothalamus, HC dysfunction may contribute to the sustained dysregulation of the stress response that is commonly observed in MDD (Figure 1c). With extreme or chronic stress, there are volumetric decreases in the HC formation, with an increased vulnerability to metabolic insults and even death of the CA3 region. Prolonged stress and increased levels of glucocorticoids also disrupt HC neurogenesis[19,20] (Figure 1d).

The HC is a key regulator of prefrontal cortical function.[21,22] Disruption of HC function may contribute to the deficits in concentration that are identified among the diagnostic features of MDD as well as to the memory deficits that are common in MDD. Hippocampal afferents are critical regulators of both the nucleus accumbens and the ventral tegmental area.[23] An indirect excitatory projection from HC to ventral tegmental area may be critical for coordinating the firing of ventral tegmental area cells in response to novelty.[24] Anhedonia, another core feature of MDD, might result in part from impaired HC function resulting in reduced dopaminergic tone.[25]

Among the various brain areas implicated in MDD, the HC may have a particular role in the control of 5-Hydroxytryptamine (5-HT) system—HPA axis interactions (Figure 1d). Of particular interest is the negative regulation of 5-HT1A mRNA expression by the co-activation of mineralocorticoide and glucocorticoid receptors. Transcription of the 5-HT1A receptor gene is negatively regulated by corticosteroids in the limbic system. In rodents, adrenalectomy results in a rapid and marked increase of *de novo* 5-HT1A mRNA synthesis, total 5-HT1A mRNA levels and 5-HT1A-binding sites in the HC and the septum and these changes are reversed by treatment with low doses of corticosterone.[26] Finally, the contributions of the HPA axis and the 5-HT system to the respective negative/positive control of granule cell proliferation within the dentate gyrus of the HC are probably of key importance among neurobiological mechanisms associated with MDD (for review see Lanfumey *et al*.[27]).

Clinical and demographic variables influencing hippocampal volumes in MDD

The question on the clinical and demographic variables that influence HC volumes has been addressed in detail in a recent review so that we do not want to extend this section here.[28] The prevalence of MDD is twice as high in women as in men,[29] with this sex differential becoming apparent after girls achieve puberty. Paradoxically, perhaps, in animal models there is evidence that estrogen may protect the hippocampus from both the behavioral and structural changes observed in male animals after exposure to stress. Acute stress has different effects in male and female rats on performance of tasks that involve hippocampal function, such as classical eyeblink conditioning or Y-maze or Morris Water Maze.[30] When animals are chronically stressed, male rats show a decrease in dendritic arborization, whereas females show no dendritic atrophy.[31] Estrogen treatment in OVX rats protects the hippocampus from neuronal loss due to chronic stress exposure.[32] The relations between stress, depression, hippocampus and estrogen levels require further investigation. In clinical studies, small HC volumes in patients compared to control subjects are apparent when study groups are comprised of women only. The average reduction in HC volumes in samples that included women only is 4.5 and 5.7 percent, respectively for the left and right HC, values that are comparable to studies in which men and women were examined as a group.[28]

With respect to clinical variables, small HC volumes in MDD have been linked to high levels of depressive symptoms,[33,34] early age at illness onset,[35–38] non-responsiveness to treatment,[33,39,40] long duration of untreated days of illness,[41] high illness burden,[42–45] positive history of childhood abuse,[46] and high levels of anxiety.[47,48] Significant inconsistencies exist, however, particularly with respect to the relation between clinical variables (for example, age at illness onset, duration of illness, etc.) and reductions in HC volume. For example, numerous studies report no relations between HC volumes and age at onset.[39,41,49–52] Although some studies showed a correlation between small HC volumes and more severe depressive symptomatology,[33,34] the majority of structural studies that have investigated the relations with depression severity have not found a significant correlation between high ratings of depressive symptomatology and smaller HC volumes.[43,49,50,53] When examined in the aggregate, Mc Kinnon and colleagues reported that differences in HC volume were apparent only for patients with an illness duration of at least two and one half years or more than one episode of depression.[28] Some studies examining HC volume in patients with a long history of depression find a correlation with the amount of time spent symptomatically ill, suggesting that successful treatment and symptom reduction may halt a neurodegenerative process.[42,43,54] Another group reported that volume in the left HC showed a marginally significant relation with duration of illness in a group of drug-free patients with MDD.[34] Other studies, however, have not found evidence of an effect of illness duration on HC volume.[35,36,39,49,50,55–61] These negative findings may reflect, in part, small sample sizes,[51,60] the inclusion of patients with bipolar disorder,[35] or samples comprised of primarily young adult patients,[51,57,59] and of patients with a low number of illness episodes.[57]

Biological mechanisms that may contribute to small hippocampal volume in MDD

Genetic influences on hippocampal volumes in MDD

Hippocampal size is highly genetically determined.[62,63] An association between heritability and brain size is supported by twin studies[64] and a wide range of imaging genetic studies.[65] Alternative pheno-

typic markers for genetic association studies that are more closely related to the underlying neurobiology of the disease are increasingly being used for genetic association studies. This partly derives from a need to address problems of clinical heterogeneity in psychiatric disorders, and partly from the need to delineate the functional consequences of identified risk variants at the level of brain structure and function. Imaging genetics facilitates an elucidation of the impact of genes at the level of the brain that can then be extended to the pathophysiology of the disease.

Elimination of 5-HT from the synaptic cleft is mediated by a single protein, the 5-HT transporter (5-HTT), which determines the size and duration of the serotonergic responses.[66] The promoter region of 5-HTT has a polymorphism that results in allelic variation in functional 5-HTT expression.[67] The long (l) allele is associated with production of more 5-HTT transcript than the short (s) allele and hence more functional 5-HT uptake than the (s) allele.[67] The short (s) allele of the 5-HTT polymorphism is associated with anxiety, depression and aggression-related personality traits in some reports,[66,67] but a recent meta-analysis did not confirm an association between 5′HTT polymorphism and vulnerability to MDD.[68] The importance of variation in 5-HTTLPR to HC volume in patients with MDD has been noted in three published reports that utilized diallelic analysis and two reports using triallelic analysis.[37,69,70]

Brain-derived neurotrophic factor (BDNF) regulates neuronal survival, migration, phenotypic differentiation, axonal and dendritic growth and synapse formation.[71] BDNF is also a key regulator of synaptic plasticity and behavior[72] and may be important for memory acquisition and consolidation.[73] Interestingly, a reduction of BDNF expression—introduced through BDNF knockdown by RNA interference and lentiviral vectors injected into specific subregions of the hippocampus—in the dentate gyrus, but not the region CA3 of the hippocampus, reduces neurogenesis and affects behaviors associated with depression.[74] A single-nucleotide polymorphism in the pro-domain of BDNF converts the 66th amino acid valine into methionine (Val66Met). This Val66Met polymorphism affects dendritic trafficking and synaptic localization of BDNF and impairs its secretion. The Val66Met SNP is associated with deficits in short-term episodic memory.[75] Healthy met-BDNF carriers have relatively small HC volumes;[76,77] an effect of the Met-BDNF allele on HC volume is also apparent in patients with MDD.[55] A recent study in healthy volunteers reported that subjects carrying the Met-BDNF allele have smaller HC volumes when they have more sub-threshold symptoms of depression and a higher extent of neuroticism.[78]

Gray matter volumes in temporal lobe regions including the HC were associated with glycogen synthase kinase-3 polymorphisms in a large sample of depressed patients and healthy controls.[79] The underlying neurobiological background of this finding is unknown; it is interesting, however, that glycogen synthase kinase-3 activity might be associated with therapeutic effects of antidepressants and lithium.[79] Thus, these first genetic imaging studies provide evidence that genetic polymorphisms are relevant for neurobiological mechanisms in MDD, possibly in part through their contribution to HC volumes.

Effects of stress on the hippocampus

The HC is vulnerable to stress, particularly during the early developmental period,[80] but there may be species-specific and time-dependent variation in how stress affects the brain. While separation of monkeys from their siblings or mothers seems not to determine HC volumes,[62,81] chronic stress exposure in rats or tree shrews does result in reduced HC volumes.[82,83] Although transient mild stress may enhance HC function,[84] chronic or severe stress disrupts HC-dependent memory in experimental animals (reviewed in Sapolsky[85]). Extended or high-dose treatment with glucocorticoids has a negative effect on HC-dependent memory in both animal models,[86,87] and humans.[88,89]

Sustained elevations in stress or glucocorticoids impair the HC at the level of morphological neuroplasticity (reviewed in Sapolsky[90]). High levels of glucocorticoids[91] or behavioral stress[92,93] result in atrophy and retraction of the apical dendrites of HC pyramidal cells. A reduction in the amount of neuropil without frank cell loss has also been observed, a finding that appears consistent with observations from post-mortem studies of the HC in patients with MDD.[94]

Glutamatergic excess may also contribute to cell damage and even to cell death.[85,90] Stress-induced increases in extrasynaptic glutamate may perturb the balance between synaptic and extrasynaptic NMDA tone and have a net inhibitory effect on the mechanisms of synaptic plasticity and neuronal growth and survival (reviewed in Pittenger *et al*.[95]).

Signaling pathways implicated in neuroplasticity target, among other downstream targets, genes for growth factors such as BDNF.[96] Acute and chronic stress reduces neurogenesis in the rodent HC (reviewed in Dranovsky and Hen; Duman[19,20]). As neurogenesis may be required for the behavioral response to antidepressants in rodents[8] and impaired neurogenesis may represent a pathophysiological component of MDD,[20] suppressed neurogenesis may represent another way that the effects of stress on mechanisms of neuroplasticity contribute to the development of MDD. The specific functional role and relevance of new neurons in the HC is not firmly established, but a link between neurogenesis and the learning-related functions of the HC is an intriguing possibility.[97] Some computational theories of HC function predict a role for new neurons in HC-dependent learning.[98] Figure 2 describes the putative links between the molecular, cellular and functional levels of analysis in studies of HC pathophysiology in MDD.

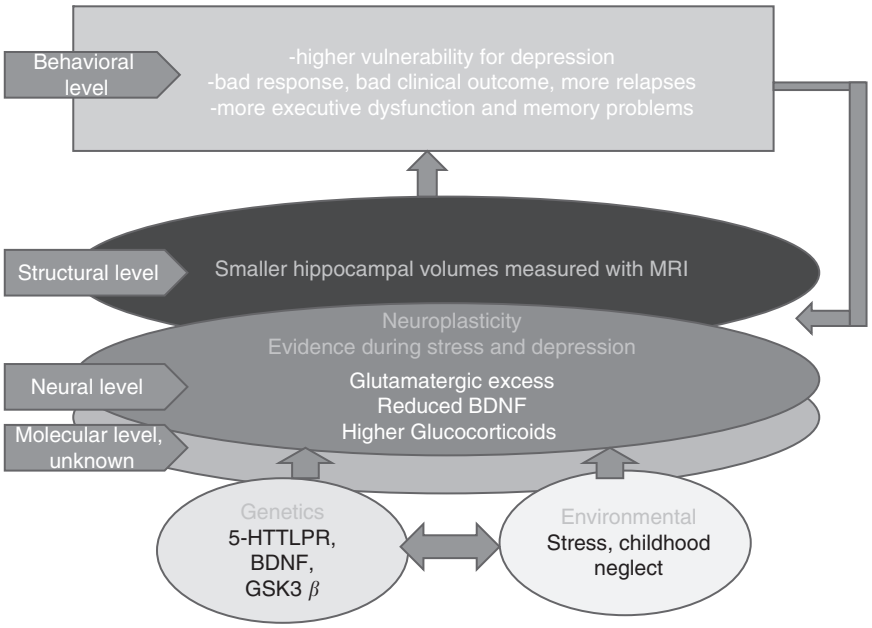

Figure 2 Overview of the factors influencing small HC volumes and the consequence of HC volume changes in MDD: There is evidence that genetic polymorphisms and early life stress may contribute to HC volumes before onset of illness. Repeated episodes of illness may further contribute to loss of HC volume via stress toxicity, reduced neurotrophic factors and excess in glutamatergic neurotransmission on hippocampal neurons. The underlying molecular basis is an ongoing matter of research. Speculatively, the changes in the HC may then contribute to treatment resistance or chronicity and may further increase the vulnerability for the disease. Consistent with this are studies reporting that small HC volumes predict poor short- and long-term responsiveness to treatment and a higher vulnerability. A more chronic course of disease and relapses seem to have further affects on neural connectivity and might result in further structural changes.

The effects of early childhood stress on HC volumes

A recent meta-analysis based on 14 250 participants demonstrated that early adverse life events confer significant risk of subsequent MDD.[68] Youth and adults exposed to early-life adversity appear to have small HC volumes;[99] for an overview on HC volume changes in post traumatic stress disorder see also Bremner *et al.*[100] and Karl *et al.*[101] Although a large population-based study from Australia did not find small HC volumes in subjects exposed to adverse childhood events, this study used voxel-based morphometry to conduct a whole brain analysis and the necessary corrections for multiple comparisons can decrease the probability of detecting changes in small structures like the HC.[102]

Vythilingam *et al.*[46] reported 18% smaller left HC volumes in patients with early life trauma and MDD compared to non-abused patients with MDD who did not differ from healthy controls (see Table 1). Moreover, patients with MDD and childhood emotional neglect had smaller HC volumes compared to patients with MDD without emotional neglect. The small volumes were more pronounced in the left HC and in men.[103] In contrast, however, HC volumes did not correlate significantly with early life events in a sample of women with remitted unipolar MDD.[104] A potential explanation for the discrepancy in reports might be that standard correlational analyses of a continuous measure of early adversity might not show significant results if the underlying association between adversity and HC volumes, for example, is not described by a linear function. Comparing group differences between participants with and without abuse/neglect might then be an advantage for detecting relations that are best described by a non-linear function. Furthermore, gender effects have not been assessed in the majority of studies investigating the association between stress and HC volumes (although see Frodl *et al.*[103]), so that further investigation is necessary to understand whether there are gender-specific effects in the impact that stress has on the HC.

In summary, there is evidence from studies of healthy subjects, patients with PTSD and patients with MDD that early childhood stress is associated with small HC volumes. Whether variables such as the type of stress, the developmental period during which a child experiences the stress or the chronicity and intensity of the stress can determine HC structure and function later in life needs further investigation.

Stress × gene interactions on HC volumes

Early life stress and variations in the serotonin transporter promotor polymorphism 5-HTTLPR may interact to predict development of MDD.[105] An increased risk of depression was detected in maltreated children homozygous for the *S*-allele.[106] In a recent study, patients carrying the s-allele had

Table 1 Human studies investigating the effect of acute or early life stress on hippocampal volumes based on PubMed and Embase research till 5/2010 with the terms stress, hippocampus, MRI, excluded are studies, who already are included in meta-analysis on PTSD

	Subjects/patients	*Method*	*Gender effect*	*Result*
Frodl *et al.*[103]	43 patients with MDD, 44 healthy controls	1.5 Tesla, manual tracing of whole hippocampus	More pronounced in male patients	Left hippocampal white matter was smaller in patients, who had emotional childhood neglect, compared to those without neglect. In male patients also the right hemisphere was significantly smaller when they had emotional child neglect
Lenze *et al.*[104]	31 women with remitted unipolar depression, 24 healthy controls	1.5 Tesla manual tracing of whole hippocampus	Only females	Childhood adversity was associated with a history of recurrent depression and with earlier age of depression onset, whereby childhood adversity and hippocampal volume were not correlated
Vythilingam *et al.*[46]	32 women with current unipolar depressive disorder, 21 with a history of prepubertal sexual/physical abuse, 11 without and 14 healthy female controls	1.5 Tesla MRI, manual tracing of hippocampal volume	Only females	The depressed subjects with childhood abuse had an 18% smaller mean left hippocampal volume than the non-abused depressed subjects and a 15% smaller mean left hippocampal volume than the healthy subjects. Right hippocampal volume was similar across the three groups
Gatt *et al.*[10]	89 healthy subjects	1.5 Tesla, manual tracing of prefrontal cortex (lateral and medial portions), hippocampus and amygdala	Gender used as factor in the analysis	In addition, significant BDNF–early life events interactions indicated that BDNF Met carriers exposed to greater early life events have smaller hippocampal and amygdala volumes
Ganzel *et al.*[147]	17 healthy adults who were 9/11-exposed, 17 healthy controls	MRI field not indicated, Voxel-based morphometry	No gender differences assessed	Lower gray matter volume in amygdala, hippocampus, insula, anterior cingulate, and medial prefrontal cortex in exposed adults compared to controls. Nonlinear (first-order quadratic) association between total number of traumas in lifetime and amygdala gray matter volume and function in the whole group
Szesko *et al.*[148]	21 healthy volunteers	1.5 Tesla, manual tracing of anterior and posterior hippocampus, Association between hippocampal volume	No gender differences assessed	Greater psychological stress as measured with Derogatis Stress Profile was negatively correlated significantly and more strongly with anterior than posterior hippocampal volume
Cohen *et al.*[102]	265 healthy volunteers	1.5 Tesla, voxel-based morphometry-based assessments of volumes for hippocampus, amygdala, anterior cingulate cortex (ACC), caudate	No gender differences assessed	Participants with greater than two adverse childhood events had smaller ACC and caudate nuclei than those without adverse childhood events. A significant association between total adverse childhood events and volumes for these structures was observed

smaller HC volumes when they had a history of emotional neglect compared to patients who had only one risk factor (environmental or genetic). Childhood stress further predicted HC alterations independent of genotype.[107] Meta-analytic approaches suggest, however, that *5-HTTLPR* may not further increase the risk for MDD in subjects who experience critical life events.[68]

In a recent study of 89 participants, significant interactions between BDNF genotype and early life stress were apparent in HC and amygdala volumes, heart rate and working memory. The investigators used structural equation modeling to investigate the pathways through which BDNF genotype and early life stress interact to produce effects on brain structure, body arousal, emotional stability, which in turn predict alterations in symptoms and cognition. Structural equation modeling suggested that the combination of Met carrier status of the BDNF polymorphism and exposure to early life stress predicted reduced HC volumes, associated lateral prefrontal cortex volumes and, in turn, higher depression.[10] The gene × environmental interaction seems to be particularly relevant in patients with MDD. The relevance of small HC volumes as a risk factor for MDD has now been documented by both longitudinal studies and studies of subjects at high-risk for MDD as reported in the following section.

The clinical relevance of small hippocampal volumes in MDD

Alterations of hippocampal volumes in high-risk subjects

A period of high risk for MDD begins in the early teens, and risk continues to rise in a linear fashion throughout adolescence, with lifetime rates estimated to range from 15 to 25% by late adolescence.[108,109]

In a recent study, small HC volumes were apparent before the manifestation of clinical symptoms of MDD in at-risk adolescents, particularly in those who experienced high levels of adversity during childhood. Both early-life adversity and smaller HC volume were associated with a higher probability of depressive episodes during prospective follow-up.[110] Moreover, 23 daughters of mothers with a history of MDD had reduced HC volumes compared to 32 daughters of mothers with no history of psychopathology, indicating again that neuroanatomic anomalies associated with depression may precede the onset of a depressive episode and influence the development and course of this disorder. In another recent study, adults at-risk for MDD had HC volumes that were not significantly different from those already affected with MDD, suggesting that small volumes may precede the onset of MDD and might render subjects more vulnerable to MDD.[111] Early life adversity appears to contribute to both small HC volumes and increased risk of MDD; whether changes in HC volumes represent a biological mechanism through which early life adversity is transduced into risk of MDD remains to be confirmed.

Associations between clinical response and hippocampal volume

There are a number of studies reporting associations between HC volume and probability of achieving and sustaining a clinical remission (Table 2). In one such study of patients with geriatric depression, patients with right HC volumes in the lowest quartile of the sample were less likely to achieve remission compared to those with HC volumes in the highest quartile.[40] Another study reported that women who responded to 8 weeks of fluoxetine had larger right HC volumes than non-responders.[33] More recently a study reported that small HC volumes predicted

Table 2 Shown are studies that investigated the effect of hippocampal volumes on treatment response or therapy outcome in patients with MDD based on PubMed and Embase research till 11/2009

	Number of patients	*Outcome assessed*	*Gender effect*	*Result*
Vakili *et al.*[33]	38	Response after 8 weeks of fluoxetine	Effect apparent only in women	Association apparent in right HC
MacQueen *et al.*[112]	46	Remission after 8 weeks of AD treatment	Not apparent	Association apparent bilaterally
Hsieh *et al.*[40]	60 elderly only	Remission after 12 weeks of AD treatment	Not apparent	Association stronger in right HC
Frodl *et al.*[39]	30	In remission at 1 year	Not reported	Association stronger in right HC
Kronmuller *et al.*[114]	57	Sustained recovery for 2 years	Effect apparent in men	Association apparent bilaterally
Frodl *et al.*[113]	30	Remission for 3 years	Not reported	Association apparent bilaterally

Indicated is the number of patients enrolled in the study, the outcome variables assessed and the results as well as whether gender effects were reported. All studies found an association between hippocampal volumes and clinical outcome, one of the six studies only in women and one only in men.

low rates of remission even in patients with no past treatment history, suggesting that the association between HC volumes and short-term clinical response was not simply a function of past treatment responsiveness.[112] Frodl *et al*. reported that depressed patients who were not remitted from an episode of depression 1 year after discharge had smaller left and right HC volumes at baseline scan.[39] The association between smaller HC volumes and poor clinical outcome was detectable after a 3-year follow-up.[113] Kronmuller *et al*.[114] also found associations between HC volumes and 2-year outcome, although the associations between large HC volume and good outcome were restricted to men.

The relations between small HC volumes and response to treatment suggest that the association between illness duration and HC volumes may arise from the effect that small HC volumes have on outcome. That is, there may be an iterative relation between HC volume and illness burden, with small HC volumes contributing to poor clinical outcome, which in turn may put further stress on the HC leading to structural changes that increase the likelihood of a poor clinical response. Whether such relations contribute to the development of illness chronicity remains to be determined.

Associations between cognitive function and hippocampal volume

Cognitive impairment is a core feature of MDD.[115] An effect size analysis of cognitive functioning in 726 patients with MDD conducted using meta-analytic principles found that depression had the largest effect on recollection memory.[9] Recollection memory tasks are highly dependent on the HC in addition to some frontal regions.[116] Hippocampal volumes are correlated with verbal learning and memory performance in various neuropsychiatric conditions. Vermetten *et al*.[117] reported that antidepressant treatment reversed HC volume reduction in patients with PTSD; declarative memory also improved in the treated group. Hippocampal volumes are also correlated with executive functioning in patients with MDD[49,118] and emotional memory in middle-aged healthy women.[119]

There is an epidemiological association between MDD and Alzheimer's disease[120] and this association does not seem to be restricted to late onset depression that is a prodrome to the clinical symptoms of Alzheimer's disease.[121] Rather, meta-analyses suggest that MDD may be a risk factor for Alzheimer's disease.[121] Stress-related brain changes, decreases in neurogenesis and programmed neurodegeneration may contribute to this association[122] as may inflammatory processes that are characteristic of MDD.[123] Moreover, both MDD and the APOE ε4 allele are risk factors for dementia, suggesting that the association between the APOE ε4 allele and small HC volumes[124] may provide a further mechanism for understanding the links between late onset depression and dementia.

Evidence that treatment for MDD may have an impact on hippocampal volumes

As data has emerged to suggest that a long history of illness is associated with small HC volumes, questions have also been raised concerning the potential role of treatments in minimizing or ameliorating the apparent decline in HC volume.

Experimental studies show that antidepressants, for example, SSRIs, clomipramine or tianeptine, suppress stress toxic effects on the HC, increase hippocampal neurogenesis and synaptic plasticity.[3,8,125–127] Although the effect of antidepressants on neurogenesis seems to be important for some depressive-like models, there seem to also be neurogenesis-independent mechanisms of antidepressant action.[128] Some results reduce the importance of neurogenesis for antidepressant response even more; when neurogenesis was blocked antidepressants retained their therapeutic efficacy perhaps by re-establishment of neuronal plasticity, like dendritic remodeling and synaptic contacts, in the hippocampus and prefrontal cortex.[129] Recent research demonstrated in a mice model with high versus low 5HT1a-autoreceptor availabilities a role for the 5HT1a-autoreceptor, because 5-HT1a-autoreceptor-modulated intrinsic raphe firing rates are directly related to resilience under stress and to the response to antidepressant treatment.[130] However, since tianeptine was shown not to act on the serotonergic system,[131] other non-serotonergic mechanisms seem to be relevant too. For example, neurotrophic factors and the glutamatergic system need to be mentioned here; by enhancing neurotrophic factor signaling, environmental factors such as exercise and chemicals such as antidepressants may optimize glutamatergic signaling and protect against neurological and psychiatric disorders.[132]

An important mechanism for neurogenesis is indeed physical exercise, for example, wheel running in rodents resulted in enhanced hippocampal neurogenesis,[133] improved synaptic plasticity[134,135] and increased spine density.[136] Activity in experimental animal studies increased angiogenesis, accompanied by increased insulin-like growth factor[137] and vascular endothelial growth factor[138] and also enhanced the serum levels of the BDNF.[139] In addition, activity stimulates the glutamatergic system with effects on NMDA receptors in the HC.[135] Interestingly, exercise increased the blood flow in the gyrus dendatus of the HC in mice and also in healthy subjects, who took part in a 12-week aerobic programme with a frequency of 4 times a week.[140] These factors have an important role in hippocampal neurogenesis and might imply that the positive effect of exercise in depression might be due to the stimulating neuroplastic effects.

Given the complexity of longitudinal studies in which treatment is controlled over long periods of time, it is not surprising that there are few studies that have examined the question of whether individual

treatment modalities exert an effect on HC volume over time.

Increases in HC volume following treatment with the antidepressants sertraline and paroxetine[117,141] have been reported in patients with PTSD. In MDD, the results are less clear, with some studies failing to find an association between antidepressant therapy and HC volume.[142] One study, however, found a trend toward higher HC volumes in patients who had declines in cortisol levels with pharmacotherapy,[143] but see Vythilingam *et al.*[142] (for a contradictory pattern of findings). Right HC volumes increased in patients who took their antidepressants over the full 3-year time interval, however, the study was not designed to investigate medication effects distinct from illness effects during the naturalistic 3-year follow-up.[113] These studies were all carried out in relatively small samples so that slight effects might not have been detected. In addition, the difficulty to design a study with an adequate comparison group not receiving the antidepressant treatment under observation, limits research in this area.

A recent review concluded that the inclusion of bipolar patients treated with psychotropic medications in structural imaging studies was associated with either null findings or a reduction in volume loss in key regions associated with the pathophysiological mechanisms of the disorder, including the HC.[144] There is evidence that lithium is associated with increases in HC volume with both short- and long-term treatment in patients with bipolar disorder.[145,146] Studies examining the impact of other medications or treatment modalities on HC volumes are lacking across diagnostic categories.

Summary

MDD has until recently been viewed as a 'chemical imbalance' that was not associated with permanent structural brain changes. Meta-analyses of structural imaging studies of the HC now suggest, however, that patients with MDD have small HC volumes compared to healthy subjects. Although the factors associated with small HC volumes are not fully described, there is evidence that genetic polymorphisms and early life stress may contribute to HC volumes before onset of illness. Furthermore, subjects at risk for MDD have reduced HC volumes before the clinical onset of illness. Repeated episodes of illness may further contribute to loss of HC volume, and speculatively, the changes in the HC may then contribute to treatment resistance or chronicity. Consistent with this are studies reporting that small HC volumes predict poor short- and long-term responsiveness to treatment (overview in Figure 2).

Pre-clinical and clinical studies of the HC and related structures have provided a plausible biological model for how stress may interact with genetic vulnerability to increase the risk of MDD. We now know that detecting evidence of HC disruption, as measured by small HC volumes on MRI, can allow us to identify people who are at risk of illness and patients who are at risk for treatment non-response and relapse. Clinicians should begin to consider the possibility that imaging technology, possibly also in combination to genetic data (genetic variants, family history) could be used, not for diagnosis, which may be of uncertain utility, but for matching patients with treatment intensity. If imaging can reliably identify people who are likely to require more than first line treatment to recover, then scanning might become cost effective as it is well recognized that less than 50% of patients have an adequate response to first treatment. Identifying subgroups of patients with specific morphological markers may also facilitate the development of treatment strategies that target neuroplastic processes. With few revolutionary treatment strategies on the horizon, and the cost of MDD continuing to rise across the world, it may be time to contemplate the possibility that imaging data could contribute to clinical care by matching patients to the most appropriate level of intervention.

Conflict of interest

Professor G MacQueen and Professor T Frodl reported no biomedical financial interests or potential conflicts of interest with publishing this article.

Acknowledgments

Professor Frodl received funding for a Stokes Professorship from Science Foundation Ireland, SFI.

References

1 Kessler RC. The effects of stressful life events on depression. *Annu Rev Psychol* 1997; **48**: 191–214.
2 Thomas RM, Hotsenpiller G, Peterson DA. Acute psychosocial stress reduces cell survival in adult hippocampal neurogenesis without altering proliferation. *J Neurosci* 2007; **27**: 2734–2743.
3 Malberg JE, Duman RS. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology* 2003; **28**: 1562–1571.
4 Pham K, Nacher J, Hof PR, McEwen BS. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur J Neurosci* 2003; **17**: 879–886.
5 Vermetten E, Bremner JD. Circuits and systems in stress. I. Preclinical studies. *Depress Anxiety* 2002; **15**: 126–147.
6 Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biol Psychiatry* 1999; **46**: 1595–1602.
7 Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* 2001; **25**: 836–844.
8 Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S *et al.* Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003; **301**: 805–809.
9 Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol Behav Neurol* 1998; **11**: 111–119.
10 Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR *et al.* Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry* 2009; **14**: 681–695.

11 Colombel F. [Memory bias and depression: a critical commentary]. *Encephale* 2007; **33**(3 Part 1): 242–248.
12 Frodl T, Koutsouleris N, Bottlender R, Born C, Jager M, Morgenthaler M *et al.* Reduced gray matter brain volumes are associated with variants of the serotonin transporter gene in major depression. *Mol Psychiatry* 2008; **13**: 1093–1101.
13 Frodl T, Bokde AL, Scheuerecker J, Lisiecka D, Schoepf V, Hampel H *et al.* Functional connectivity bias of the orbitofrontal cortex in drug-free patients with major depression. *Biol Psychiatry* 2010; **67**: 161–167.
14 Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008; **213**: 93–118.
15 Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 2003; **460**: 425–449.
16 Miller EJ, Saint Marie LR, Breier MR, Swerdlow NR. Pathways from the ventral hippocampus and caudal amygdala to forebrain regions that regulate sensorimotor gating in the rat. *Neuroscience* 2010; **165**: 601–611.
17 Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry* 2004; **161**: 598–607.
18 Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* 2004; **161**: 1957–1966.
19 Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry* 2006; **59**: 1136–1143.
20 Duman RS. Depression: a case of neuronal life and death? *Biol Psychiatry* 2004; **56**: 140–145.
21 Jay TM, Burette F, Laroche S. NMDA receptor-dependent long-term potentiation in the hippocampal afferent fibre system to the prefrontal cortex in the rat. *Eur J Neurosci* 1995; **7**: 247–250.
22 Gurden H, Takita M, Jay TM. Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses *in vivo*. *J Neurosci* 2000; **20**: RC106.
23 Floresco SB, Todd CL, Grace AA. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J Neurosci* 2001; **21**: 4915–4922.
24 Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 2005; **46**: 703–713.
25 Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 2006; **16**: 239–249.
26 Mendelson SD, McEwen BS. Autoradiographic analyses of the effects of adrenalectomy and corticosterone on 5-HT1A and 5-HT1B receptors in the dorsal hippocampus and cortex of the rat. *Neuroendocrinology* 1992; **55**: 444–450.
27 Lanfumey L, Mongeau R, Cohen-Salmon C, Hamon M. Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders. *Neurosci Biobehav Rev* 2008; **32**: 1174–1184.
28 McKinnon MC, Yucel K, Nazarov A, MacQueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J Psychiatry Neurosci* 2009; **34**: 41–54.
29 Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG *et al.* Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996; **276**: 293–299.
30 Shors TJ, Leuner B. Estrogen-mediated effects on depression and memory formation in females. *J Affect Disord* 2003; **74**: 85–96.
31 Galea LA, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabhar FS. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* 1997; **81**: 689–697.
32 Takuma K, Matsuo A, Himeno Y, Hoshina Y, Ohno Y, Funatsu Y *et al.* 17beta-estradiol attenuates hippocampal neuronal loss and cognitive dysfunction induced by chronic restraint stress in ovariectomized rats. *Neuroscience* 2007; **146**: 60–68.
33 Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM *et al.* Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. *Biol Psychiatry* 2000; **47**: 1087–1090.
34 Saylam C, Ucerler H, Kitis O, Ozand E, Gonul AS. Reduced hippocampal volume in drug-free depressed patients. *Surg Radiol Anat* 2006; **28**: 82–87.
35 Hickie I, Naismith S, Ward PB, Turner K, Scott E, Mitchell P *et al.* Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br J Psychiatry* 2005; **186**: 197–202.
36 Lloyd AJ, Ferrier IN, Barber R, Gholkar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. *Br J Psychiatry* 2004; **184**: 488–495.
37 Taylor WD, Steffens DC, Payne ME, MacFall JR, Marchuk DA, Svenson IK *et al.* Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late-life depression. *Arch Gen Psychiatry* 2005; **62**: 537–544.
38 Janssen J, Hulshoff Pol HE, de Leeuw FE, Schnack HG, Lampe IK, Kok RM *et al.* Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. *J Neurol Neurosurg Psychiatry* 2007; **78**: 638–640.
39 Frodl T, Meisenzahl EM, Zetzsche T, Hohne T, Banac S, Schorr C *et al.* Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. *J Clin Psychiatry* 2004; **65**: 492–499.
40 Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry* 2002; **17**: 519–525.
41 Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry* 2003; **160**: 1516–1518.
42 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999; **19**: 5034–5043.
43 MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT *et al.* Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci USA* 2003; **100**: 1387–1392.
44 Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; **93**: 3908–3913.
45 MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. *BMC Med* 2004; **2**: 2.
46 Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R *et al.* Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002; **159**: 2072–2080.
47 Rusch BD, Abercrombie HC, Oakes TR, Schaefer SM, Davidson RJ. Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. *Biol Psychiatry* 2001; **50**: 960–964.
48 MacMillan S, Szeszko PR, Moore GJ, Madden R, Lorch E, Ivey J *et al.* Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *J Child Adolesc Psychopharmacol* 2003; **13**: 65–73.
49 Frodl T, Schaub A, Banac S, Charypar M, Jager M, Kummler P *et al.* Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *J Psychiatry Neurosci* 2006; **31**: 316–323.
50 Frodl T, Meisenzahl EM, Zetzsche T, Born C, Groll C, Jager M *et al.* Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry* 2002; **159**: 1112–1118.
51 Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL *et al.* Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Mol Psychiatry* 2007; **12**: 360–366.
52 Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 2004; **29**: 952–959.

53 Caetano SC, Hatch JP, Brambilla P, Sassi RB, Nicoletti M, Mallinger AG *et al.* Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Res* 2004; **132**: 141–147.
54 Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry* 1998; **172**: 527–532.
55 Frodl T, Schule C, Schmitt G, Born C, Baghai T, Zill P *et al.* Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry* 2007; **64**: 410–416.
56 Janssen J, Hulshoff Pol HE, Lampe IK, Schnack HG, de Leeuw FE, Kahn RS *et al.* Hippocampal changes and white matter lesions in early-onset depression. *Biol Psychiatry* 2004; **56**: 825–831.
57 Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI *et al.* High-dimensional mapping of the hippocampus in depression. *Am J Psychiatry* 2003; **160**: 83–89.
58 O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry* 2004; **161**: 2081–2090.
59 Lange C, Irle E. Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. *Psychol Med* 2004; **34**: 1059–1064.
60 Xia J, Chen J, Zhou Y, Zhang J, Yang B, Xia L *et al.* Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression. *J Huazhong Univ Sci Technolog Med Sci* 2004; **24**: 500–502, 506.
61 MacMaster FP, Mirza Y, Szeszko PR, Kmiecik LE, Easter PC, Taormina SP *et al.* Amygdala and hippocampal volumes in familial early onset major depressive disorder. *Biol Psychiatry* 2008; **63**: 385–390.
62 Lyons DM, Yang C, Sawyer-Glover AM, Moseley ME, Schatzberg AF. Early life stress and inherited variation in monkey hippocampal volumes. *Arch Gen Psychiatry* 2001; **58**: 1145–1151.
63 Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP *et al.* Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002; **5**: 1242–1247.
64 Bartley AJ, Jones DW, Weinberger DR. Genetic variability of human brain size and cortical gyral patterns. *Brain* 1997; **120**(Part 2): 257–269.
65 Frodl T, Moller HJ, Meisenzahl E. Neuroimaging genetics: new perspectives in research on major depression? *Acta Psychiatr Scand* 2008; **118**: 363–372.
66 Lesch KP, Mossner R. Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? *Biol Psychiatry* 1998; **44**: 179–192.
67 Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S *et al.* Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; **274**: 1527–1531.
68 Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J *et al.* Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA* 2009; **301**: 2462–2471.
69 Frodl T, Meisenzahl EM, Zill P, Baghai T, Rujescu D, Leinsinger G *et al.* Reduced hippocampal volumes associated with the long variant of the serotonin transporter polymorphism in major depression. *Arch Gen Psychiatry* 2004; **61**: 177–183.
70 Frodl T, Zill P, Baghai T, Schule C, Rupprecht R, Zetzsche T *et al.* Reduced hippocampal volumes associated with the long variant of the tri- and diallelic serotonin transporter polymorphism in major depression. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 1003–1007.
71 Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci* 2001; **24**: 677–736.
72 Lu B. Pro-region of neurotrophins: role in synaptic modulation. *Neuron* 2003; **39**: 735–738.
73 Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learn Mem* 2002; **9**: 224–237.
74 Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Mol Psychiatry* 2010; **15**: 80–92.
75 Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A *et al.* The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; **112**: 257–269.
76 Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biol Psychiatry* 2006; **59**: 812–815.
77 Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE *et al.* The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci* 2004; **24**: 10099–10102.
78 Joffe RT, Gatt JM, Kemp AH, Grieve S, Dobson-Stone C, Kuan SA *et al.* Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: Implications for depressive illness. *Hum Brain Mapp* 2009; **30**: 1246–1256.
79 Inkster B, Nichols TE, Saemann PG, Auer DP, Holsboer F, Muglia P *et al.* Association of GSK3beta polymorphisms with brain structural changes in major depressive disorder. *Arch Gen Psychiatry* 2009; **66**: 721–728.
80 Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* 2003; **27**: 33–44.
81 Spinelli S, Chefer S, Suomi SJ, Higley JD, Barr CS, Stein E. Early-life stress induces long-term morphologic changes in primate brain. *Arch Gen Psychiatry* 2009; **66**: 658–665.
82 Lee T, Jarome T, Li SJ, Kim JJ, Helmstetter FJ. Chronic stress selectively reduces hippocampal volume in rats: a longitudinal magnetic resonance imaging study. *Neuroreport* 2009; **20**: 1554–1558.
83 Ohl F, Michaelis T, Vollmann-Honsdorf GK, Kirschbaum C, Fuchs E. Effect of chronic psychosocial stress and long-term cortisol treatment on hippocampus-mediated memory and hippocampal volume: a pilot-study in tree shrews. *Psychoneuroendocrinology* 2000; **25**: 357–363.
84 Luine V, Martinez C, Villegas M, Magarinos AM, McEwen BS. Restraint stress reversibly enhances spatial memory performance. *Physiol Behav* 1996; **59**: 27–32.
85 Sapolsky RM. Stress and plasticity in the limbic system. *Neurochem Res* 2003; **28**: 1735–1742.
86 de Quervain DJ, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature* 1998; **394**: 787–790.
87 Bodnoff SR, Humphreys AG, Lehman JC, Diamond DM, Rose GM, Meaney MJ. Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *J Neurosci* 1995; **15**(Part 1): 61–69.
88 Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K *et al.* Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry* 1999; **56**: 527–533.
89 de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci* 2000; **3**: 313–314.
90 Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000; **57**: 925–935.
91 Woolley CS, Gould E, McEwen BS. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res* 1990; **531**: 225–231.
92 Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res* 1992; **588**: 341–345.
93 Magarinos AM, McEwen BS, Flugge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippo-

campal CA3 pyramidal neurons in subordinate tree shrews. *J Neurosci* 1996; **16**: 3534–3540.
94 Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY *et al.* Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiatry* 2004; **56**: 640–650.
95 Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. *CNS Neurol Disord Drug Targets* 2007; **6**: 101–115.
96 Newton SS, Duman RS. Regulation of neurogenesis and angiogenesis in depression. *Curr Neurovasc Res* 2004; **1**: 261–267.
97 Leuner B, Gould E, Shors TJ. Is there a link between adult neurogenesis and learning? *Hippocampus* 2006; **16**: 216–224.
98 Becker S, Macqueen G, Wojtowicz JM. Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: Effects of interference, stress and depression. *Brain Res* 2009; **1299**: 45–54.
99 Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* 2008; **18**: 729–736.
100 Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res* 2008; **167**: 171–186.
101 Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev* 2006; **30**: 1004–1031.
102 Cohen RA, Grieve S, Hoth KF, Paul RH, Sweet L, Tate D *et al.* Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* 2006; **59**: 975–982.
103 Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *J Psychiatr Res* 2010 (in press).
104 Lenze SN, Xiong C, Sheline YI. Childhood adversity predicts earlier onset of major depression but not reduced hippocampal volume. *Psychiatry Res* 2008; **162**: 39–49.
105 Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003; **301**: 386–389.
106 Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S *et al.* Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biol Psychiatry* 2006; **59**: 673–680.
107 Frodl T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M *et al.* Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology* 2010; **35**: 1383–1390.
108 Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *J Abnorm Psychol* 1998; **107**: 128–140.
109 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593–602.
110 Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry* 2010; **67**: 357–364.
111 Amico F, Meisenzahl E, Koutsouleris N, Moeller H-J, Reiser M, Frodl T. Structural MRI correlates for vulnerability and resilience to major depression? *J Psychiatry Neurosci* 2010 (in press).
112 MacQueen GM, Yucel K, Taylor VH, Macdonald K, Joffe R. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biol Psychiatry* 2008; **64**: 880–883.
113 Frodl T, Jager M, Smajstrlova I, Born C, Bottlender R, Palladino T *et al.* Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci* 2008; **33**: 423–430.
114 Kronmuller KT, Pantel J, Kohler S, Victor D, Giesel F, Magnotta VA *et al.* Hippocampal volume and 2-year outcome in depression. *Br J Psychiatry* 2008; **192**: 472–473.
115 Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 2004; **29**: 1765–1781.
116 Squire LR. Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem* 2004; **82**: 171–177.
117 Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 2003; **54**: 693–702.
118 Vasic N, Walter H, Hose A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord* 2008; **109**: 107–116.
119 Matsuoka Y, Nagamine M, Mori E, Imoto S, Kim Y, Uchitomi Y. Left hippocampal volume inversely correlates with enhanced emotional memory in healthy middle-aged women. *J Neuropsychiatry Clin Neurosci* 2007; **19**: 335–338.
120 Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *Eur J Pharmacol* 2010; **626**: 64–71.
121 Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006; **63**: 530–538.
122 Sotiropoulos I, Cerqueira JJ, Catania C, Takashima A, Sousa N, Almeida OF. Stress and glucocorticoid footprints in the brain-the path from depression to Alzheimer's disease. *Neurosci Biobehav Rev* 2008; **32**: 1161–1173.
123 Leonard BE. Inflammation, depression and dementia: are they connected? *Neurochem Res* 2007; **32**: 1749–1756.
124 Kim DH, Payne ME, Levy RM, MacFall JR, Steffens DC. APOE genotype and hippocampal volume change in geriatric depression. *Biol Psychiatry* 2002; **51**: 426–429.
125 Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. *Mol Psychiatry* 2000; **5**: 578–593.
126 Magarinos AM, Deslandes A, McEwen BS. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *Eur J Pharmacol* 1999; **371**: 113–122.
127 van der Hart MG, Czeh B, de Biurrun G, Michaelis T, Watanabe T, Natt O *et al.* Substance P receptor antagonist and clomipramine prevent stress-induced alterations in cerebral metabolites, cytogenesis in the dentate gyrus and hippocampal volume. *Mol Psychiatry* 2002; **7**: 933–941.
128 David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I *et al.* Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron* 2009; **62**: 479–493.
129 Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA *et al.* The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Mol Psychiatry* 2009; **14**: 764–773, 739.
130 Richardson-Jones JW, Craige CP, Guiard BP, Stephen A, Metzger KL, Kung HF *et al.* 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. *Neuron* 2010; **65**: 40–52.
131 Kato G, Weitsch AF. Neurochemical profile of tianeptine, a new antidepressant drug. *Clin Neuropharmacol* 1988; **11**(Suppl 2): S43–S50.
132 Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. *Ann NY Acad Sci* 2008; **1144**: 97–112.
133 van Praag H. Neurogenesis and exercise: past and future directions. *Neuromolecular Med* 2008; **10**: 128–140.
134 van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* 1999; **96**: 13427–13431.
135 Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats *in vivo*. *Neuroscience* 2004; **124**: 71–79.

136 Stranahan AM, Khalil D, Gould E. Running induces widespread structural alterations in the hippocampus and entorhinal cortex. *Hippocampus* 2007; **17**: 1017–1022.
137 Carro E, Nunez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci* 2000; **20**: 2926–2933.
138 Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ *et al.* VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 2003; **18**: 2803–2812.
139 Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007; **30**: 464–472.
140 Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM *et al.* An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 2007; **104**: 5638–5643.
141 Bremner JD, Vermetten E. Neuroanatomical changes associated with pharmacotherapy in posttraumatic stress disorder. *Ann NY Acad Sci* 2004; **1032**: 154–157.
142 Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson ER, Snow J *et al.* Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol Psychiatry* 2004; **56**: 101–112.
143 Colla M, Kronenberg G, Deuschle M, Meichel K, Hagen T, Bohrer M *et al.* Hippocampal volume reduction and HPA-system activity in major depression. *J Psychiatr Res* 2007; **41**: 553–560.
144 Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 2008; **165**: 313–320.
145 Yucel K, McKinnon MC, Taylor VH, Macdonald K, Alda M, Young LT *et al.* Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. *Psychopharmacology (Berl)* 2007; **195**: 357–367.
146 Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT *et al.* Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology* 2008; **33**: 361–367.
147 Ganzel BL, Kim P, Glover GH, Temple E. Resilience after 9/11: multimodal neuroimaging evidence for stress-related change in the healthy adult brain. *Neuroimage* 2008; **40**: 788–795.
148 Szeszko PR, Betensky JD, Mentschel C, Gunduz-Bruce H, Lencz T, Ashtari M *et al.* Increased stress and smaller anterior hippocampal volume. *Neuroreport* 2006; **17**: 1825–1828.