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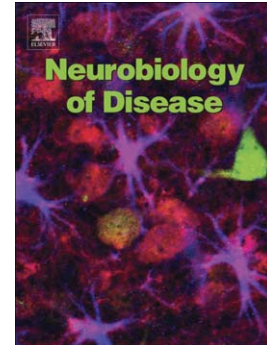
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Thomas Frodl, Veronica O'Keane

PII: S0969-9961(12)00083-6
DOI: doi: [10.1016/j.nbd.2012.03.012](https://doi.org/10.1016/j.nbd.2012.03.012)
Reference: YNBDI 2672

To appear in: *Neurobiology of Disease*

Received date: 29 September 2011
Revised date: 1 February 2012
Accepted date: 1 March 2012



Please cite this article as: Frodl, Thomas, O'Keane, Veronica, How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans, *Neurobiology of Disease* (2012), doi: [10.1016/j.nbd.2012.03.012](https://doi.org/10.1016/j.nbd.2012.03.012)

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**How does the brain deal with cumulative stress? A review with focus on
developmental stress, HPA axis function and hippocampal structure in humans**

Thomas Frodl^{1,2,3,4}, Veronica O'Keane^{1,2,4}

1. Department of Psychiatry, University Dublin, Trinity College
2. Adelaide and Meath Hospital incorporating the National's Children Hospital (AMNCH)
3. St. James's Hospital
4. Trinity College Institute of Neuroscience

Correspondence:

Thomas Frodl
Department of Psychiatry,
University Dublin,
Trinity College,
Ireland
Email: thomas.frodl@tcd.ie,
Phone: 00353-1896-4181
Fax: 00353-1896-1313

Abstract 264 words, manuscript 6500 words

Abstract

There is evidence that excessive stress exposure of the brain, mediated through the neurotoxic effects of cortisol and possibly neuroinflammation, causes damage to brain structure and function: the glucocorticoid cascade hypothesis. Functional changes of hypothalamic-pituitary-adrenal (HPA) axis as well as alterations in brain structures like the hippocampus have been consistently reported in major depression. However, there has not been a lot of emphasis on bringing findings from studies on early childhood stress, HPA axis functioning and hippocampal imaging together. This is the subject for this systematic review of the literature on how developmental stress, specifically childhood maltreatment, may impact on HPA axis function and hippocampal structure. We will also review the literature on the relationship between HPA axis function and hippocampal volume in healthy, depressed and other disease states. There is evidence that prenatal stress and childhood maltreatment is associated with an abnormally developing HPA system, as well as hippocampal volume reduction. Smaller hippocampal volumes are associated with increased cortisol secretion during the day. We conclude that a model integrating childhood maltreatment, cortisol abnormalities and hippocampal volume may need to take other factors into account, such as temperament, genetics or the presence of depression; to provide a cohesive explanation of all the findings. Finally, we have to conclude that the cascade hypothesis, mainly based on preclinical studies, has not been translated enough into humans. While there is evidence that early life maltreatment results in structural hippocampal changes and these are in turn more prominent in subjects with higher continuous cortisol secretion it is less clear which role early life maltreatment plays in HPA axis alteration.

Keywords: Major depressive disorder, cortisol, MRI, hippocampus, childhood maltreatment, dexamethason suppression test, DST, CAR,

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Introduction

Stress is believed to play an important role in the pathogenesis of major depressive disorder (MDD). Currently, there is much debate about the effect of early life adversity and its potential associations with the specific course of illness, long-lasting emotional problems (Carboni et al., 2010; Heim C, 2001; Mann and Currier, 2010), and hippocampal volumetric changes (Chen et al., 2010). Chronic stress can increase rates of depression in susceptible individuals but the detailed pathophysiology underlying this process remains unknown (Tsankova et al., 2006). In the following paragraphs of the “Introduction” section we will describe normal stress responses and the abnormal stress responses commonly found in MDD. This will form a setting to systematically explore the effects of early life stress on the development of the HPA axis system and hippocampal structure. We will then systematically review the studies that examine hypothalamic-pituitary-adrenal (HPA) system responses and simultaneous brain neuroimaging structure and function in MDD, specifically focusing on the effects of early life adversity.

Healthy stress and the HPA axis

How our bodies respond to stressors to a large extent determines our overall health. Physiological function is altered in response to acute stressors but with the ultimate outcome of returning to homeostatic, or baseline, control of these systems (7). This adaptive process is known as allostasis. If the stressor is excessive, or our stress systems are faulty, the strain exerted on our physiological systems by chronic stress prevents a return to a healthy state of homeostasis. The pathophysiological alterations in our stress-sensitive neuroendocrine, cardiovascular, immune and

neural systems brought about by this excessive strain is known as allostatic load (Juster et al., 2010; McEwen, 1998). It is important to note that in order to keep our physiological environment relatively constant that stress responses are necessary to continually adapt to an ever changing environment.

The brain is the main regulatory organ for stress responses. The hypothalamus-pituitary-adrenal (HPA) axis, the major stress system in the body, is a neuroendocrine system involved in the production of the stress hormone cortisol by the adrenal glands. Cortisol is a glucocorticoid, so called because it alters the function of numerous tissues in order to mobilize, or store, energy to meet the demands of the stress challenge (de Kloet et al., 2005). Among the many processes affected by cortisol are glucose and fat metabolism, bone metabolism, cardiovascular responsiveness and immune function. Glucocorticoids also modify brain functions by binding to two nuclear receptors that also function as transcriptional factors: the high-affinity glucocorticoid receptor (GR) in the hippocampus and the low-affinity mineralocorticoid receptor (MR) distributed throughout the brain.

CRH is the main brain peptide involved in the activation of the HPA axis. It is released from the paraventricular nucleus of the hypothalamus in response to many somatic stimuli and to perceived psychological stress. Somatic stimuli, such as hunger (Ott et al., 2011) and inflammation (Straub et al., 2011), consistently cause stimulation of the HPA axis; whereas responses to psychological stress tests, such as social stress or mental arithmetic stress, are inconsistent and have large inter-individual variation, including no cortisol response in some people (Trestman et al., 1991). CRH is

secreted into the portal hypothalamic-hypophyseal neurosecretory system and carried to the corticotropes on the anterior pituitary, bringing about the secretion of ACTH into the peripheral circulation. ACTH, in turn, brings about the secretion of glucocorticoids from the cortex of the adrenal gland. In relation to the HPA axis, cortisol mediates a negative feedback effect both on ACTH secretion from the pituitary and on CRH secretion, through the cortisol receptors in the hypothalamus/hippocampus. In order to appreciate the importance of the HPA axis in health, it is necessary firstly to understand that the communication of the components of this system needs to be finely balanced. Secondly, that as well as the control that CRH, ACTH and cortisol exert on the activation of the HPA axis, these hormones have multiple effects on most body tissues. For the purposes of this review, we will focus on the effects of the stress system on the brain.

Behavioural and cognitive effects of glucocorticoids

The brain effects of glucocorticoids, outside of inhibition of the HPA axis at the hypothalamus, are extensive. Effects of hypercortisolaemia on brain structure and function are difficult to separate from the effects of CRH and/or AVP. Cushing's Syndrome is characterized by hypercortisolaemia and low levels of hypothalamic ACTH secretagogues, and provides a model for understanding the selective effects of high cortisol levels in the brain. Depression occurs in about 60% of patients with Cushing's Syndrome, the majority of whom remit when cortisol levels are normalized (Kelly et al., 1996). Premature cortical atrophy and cognitive impairments also occur in Cushing's (Simmons et al., 2000).

It is now known that the damaging effects of glucocorticoids on memory and learning are mediated through the hippocampus (Goosens and Sapolsky, 2007), a brain structure situated on the medial aspect of the limbic cortex and very rich in GRs. The hippocampus is both central to learning and memory function and to mediating the cortisol-induced feedback inhibition of the HPA axis. Human studies demonstrate that where cortisol levels are artificially acutely elevated or reduced, below or above average ranges, that impairments in learning and memory occur (Lupien et al., 2002). A similar impairment has been observed with artificial, but chronic, elevation of cortisol levels (Young et al., 1999). Rat work demonstrates that the impairments in cognitive function brought about by excessive exposure of the hippocampus to glucocorticoids result from glucocorticoid-induced changes in synaptic plasticity, reduction in neurogenesis and in some situations, neuronal atrophy and cell death (Goosens and Sapolsky, 2007). The hippocampal damage brought about by excessive exposure to glucocorticoids should cause reduction in the feedback inhibition mediated by cortisol, via the hippocampus, on CRH secretion; resulting in further excessive cortisol secretion, and creating a cascade of hippocampal damage: the “glucocorticoid cascade hypothesis” (Sapolsky et al., 1986). The cascade hypothesis was formulated in 1986 and is now widely thought of as a pathophysiological pathway leading to brain changes associated with severe and enduring stress. At a transcriptional level, glucocorticoids stimulate an increase in excitatory amino acid neurotransmitters such as glutamate with initial reversible remodelling and eventual cell death in the hippocampus (Campbell and Macqueen, 2004). Glucocorticoids also eliminate activity-dependent increases in brain-derived neurotrophic factor (BDNF), a growth factor important in the formation of neural

connections, thus inhibiting dendritic branching in response to stimuli (Campbell and Macqueen, 2004).

This mechanism explains how chronic stress can lead to brain changes that result in dysfunctional central control of the HPA axis, and subsequent depression. It should be noted that in normal senescence a similar process occurs leading to reduced ability of the hippocampus to control the HPA axis and a gradual reduction in cognitive tasks mediated by the hippocampus (Sapolsky et al., 1986). Abnormal HPA axis findings are most likely to occur in older individuals who suffer from depression, probably reflecting the cumulative burden of these two major risk factors (23).

Toxic stress and the HPA axis: findings in depression

Most of our knowledge about the chronic effects of high levels of cortisol and of stress on the brain is inferred from human studies of HPA axis function in MDD. Cortisol is released in a pulsatile ultradian pattern that varies in amplitude under different conditions of stress. Abnormal patterns of cortisol secretion occur in depression, with increased secretion of cortisol and blunting of the normal dip that should occur in the evening, leading to increased 24h production of cortisol (Pariante and Lightman, 2008). Cortisol can be measured in saliva, allowing for easy measurement throughout the day. Cortisol is bound to a protein carrier in the blood whereas salivary cortisol is unbound, or free; representing another advantage of salivary measurement over blood sampling. On the other hand, differences between depressed and healthy control groups are much smaller when measuring saliva, compared to blood (Stetler and Miller, 2011). A test that is being frequently employed to examine abnormal cortisol secretory patterns in depression is the

cortisol response to awakening (CAR). The CAR is unlikely to be a useful clinical tool as it lacks sensitivity and specificity for the detection of depression but is useful for comparing the physiological stress response to awakening in large numbers of individuals with and without depression. A study involving over 1,500 participants in the Netherlands, 701 of whom were depressed, has demonstrated that basal cortisol levels and the CAR tends to be increased in those with depression (Vreeburg et al., 2009). Evening cortisol levels were also measured in this group and were higher in those who were depressed but levels returned to normal with remission of the depression. Diurnal secretion of cortisol probably reflects the feedback mechanisms of cortisol on CRH and other ACTH secretagogues, such as arginine vasopressin. The CAR did not alter with remission of depression. That the increased CAR may be genetically determined is suggested by the finding from this group that unaffected individuals with a parental history of depression have responses similar to affected individuals (Vreeburg et al., 2010). Thus, diurnal secretion of cortisol may be a state marker and likely to be impaired in state depression; whereas the CAR may be a trait marker of a depressive diathesis.

The cause of the impaired shut-down of the HPA axis in depression is not known but there is much animal work indicating that negative feedback control on CRH secretion may be impaired because of altered GR function in the hypothalamus (Claes, 2009). Recent human genetic work suggests that specific GR polymorphisms may be associated with a vulnerability to depression (Lahti et al., 2011). The relative resistance of brain glucocorticoid feedback mechanisms is thought to explain the reduced cortisol suppression to dexamethasone found in many patients suffering

from depression (Pariante and Lightman, 2008; Paslakis et al., 2011). As a synthetic GR agonist, dexamethasone should shut down the HPA axis via negative feedback and this should be reflected in lowered cortisol concentrations 12 to 16 hours post-dexamethasone administration. Dexamethasone non-suppression, thought to reflect impaired feedback, has only about 25% specificity for the detection of depression (Schule et al., 2009). Dexamethasone non-suppression is more likely to occur in more familial types of depression and in more severely ill patients (Rush et al., 1996). MRs are also involved in hypothalamic/hippocampal feedback inhibition and altered MR function may occur in more severe forms of depression resistant to first-line treatments (Juruena et al., 2009). MR receptor function is tested by examining cortisol suppression following prednisolone, a MR receptor agonist, administration.

The dexamethasone/CRH (DEX/CRH) test combines the oral administration of dexamethasone with a CRH bolus (usually 100µgm) given usually 16 hours later. The exaggerated cortisol response found in those with depression is thought to reflect the underlying overactivity of the HPA axis when cortisol inhibition is removed (Ising et al., 2007). In a DEX/CRH study comparing (a) healthy individuals with a positive family history for depression versus (b) healthy individuals with no family history and (c) individuals suffering from acute depression, the levels of cortisol was greatest in the depressed group, lowest in the healthy controls, and at an intermediate level in individuals with a positive family history indicating an increased risk for developing this disease (Modell et al., 1998). Consistent with this, the Munich Vulnerability Study, conducted by Holsboer *et al.* in 1995, showed that individuals who do not suffer from a psychiatric condition but have a positive family history for depression

show abnormal results to the DEX/CRH test (Holsboer, 2000). In common with the DST, the DEX/CRH test, although initially promising, has been found to have a sensitivity of only about 26% for the detection of clinical depression (23).

Structural Brain changes in MDD

As mentioned above experimental studies showed that stress or cortisol administration lead to depressive-like states and atrophy of neurons in the hippocampus (Duman, 2002). During therapy there is a reverse of these changes (Santarelli 2003). Studies in humans strengthen the evidence that depression is associated with structural changes. Many structural imaging studies have reported that the hippocampus 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 hippocampus. The analysis included 1167 patients and 1088 control subjects, across a wide range of ages from pediatric to geriatric populations (McKinnon et al., 2009). Conclusions from this meta-analysis were consistent with the findings of earlier meta-analyses of hippocampal volume in patients with MDD (Campbell et al., 2004; Videbech and Ravnkilde, 2004). The above mentioned associations between glucocorticoids and stress and neuronal damage in the hippocampus indicate that the neurotoxic effects of GC on the hippocampus can be visualised in terms of overall volume changes. Evidence from neuroimaging, neuropathological, and lesion analysis studies further implicates limbic-cortical-striatal-pallidal-thalamic circuits, including prefrontal cortex (OMPFC), amygdala,

ventromedial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum, in the pathophysiology of mood disorders (Miller et al., 2010). In line with the glucocorticoid cascade theory are some longitudinal imaging studies. In a longitudinal study on 30 patients with MDD and 30 healthy controls we could demonstrate that a negative clinical outcome with more relapses and a chronic course during a 3 year follow-up was associated with hippocampal, amygdala, anterior cingulate cortex, and dorsomedial prefrontal cortex volume decline (FRODL et al., 2008). In a long-term follow-up study it was evaluated whether any possible difference in hippocampal volume and brain structure between depressed in-patients and healthy controls at inclusion disappeared over a 11 year period when the patients were in remission. At baseline, patients had smaller volumes in right and left superior and middle temporal gyri, medulla and body of the right hippocampus. At follow-up, there were no significant local brain differences between patients and controls. In a group of 19 patients and 19 controls who were investigated at baseline and follow-up no significant hippocampal volume differences were detected (Ahdidan et al., 2011). While the cross-sectional parts of the study are well powered, for the longitudinal part of the study a larger sample would have been desirable, since a sample of 19 seems not to have enough power to detect small changes in brain structure. Moreover, during successful treatment brain structures like the left inferior-frontal cortex, right fusiform gyrus, and right cerebellum might increase in size (Lai and Hsu, 2011). On the other hand smaller hippocampal volumes were also found to be predictive for a bad clinical outcome in 1 and 3 year follow-up studies and also for response to a course of antidepressant therapy (Frodl et al., 2004; MacQueen and Frodl, 2011). Therefore a predisposition

to depression might be associated with smaller hippocampal volumes and these might further decline during the course of a chronic depression.

While we know that stress-related disorders like depression go ahead with structural brain changes and with alterations of the HPA axis, the link between stress-HPA axis changes and brain structural alterations in humans is less clear. Experimental studies as mentioned above have shown that stress and chronic cortisol administration lead to neuronal changes, however, this never has been translated into humans. To set the basis for such a translation we will here provide a systematic review of the literature on how early life stress is associated with changes in the stress hormone system, the hippocampus and how the stress hormone system is associated with the structural changes in the hippocampus and other brain regions. We extend the literature search to all studies in humans investigating the association between HPA axis functioning and brain structure in order to obtain general findings that can be applied to depression.

Material and Methods

PubMed, Science Direct and Scopus were searched from databases until October 2011. The search was confined to English language articles. Selected articles, as a criterion for inclusion, had to describe an original study. Neuroimaging studies were excluded when they did not use MRI techniques for structural imaging or did not investigate humans. Likewise only human studies were utilized for the HPA axis studies, except when putative mechanisms or pathways were being explored. Review of databases PubMed and Embase found 27 results that could be included

for the keywords prenatal depression/early childhood adversity/maltreatment and HPA axis/cortisol in children/adolescents, 7 of these were included into the systematic review. 32 articles showed up for the keywords childhood maltreatment and hippocampus, and 17 (12 adult populations, 5 children) of these were of an adequate standard to be included in the review. The other 15 articles did not investigate effects of childhood maltreatment on the hippocampal structure using MRI in humans, but in animals. For keywords MRI, cortisol and hippocampus we obtained 87 results. Twenty of these fitted the criteria in that they investigated the association between cortisol measures and hippocampal volumes. Other brain region findings are also described in the table.

Effects of early life maltreatment on the HPA axis

Studies in humans (Table 1) show an association between childhood maltreatment and HPA axis dysfunction. Infants, aged 12-20 months (n=366), experiencing the consequences of social disadvantage and family adversity have higher CAR compared to infants not exposed to social or familial adversity (Saridjan et al., 2010). In keeping with this, early life adversity was found to be associated with higher levels of awakening cortisol compared to women who reported no adverse early life experiences (Gonzalez et al., 2009). Twenty women reporting childhood physical abuse displayed a significantly blunted cortisol response to the Trier Social Stress Test (TSST) compared with 90 subjects without childhood adversity even after controlling for age, estrogen use and other forms of maltreatment (Carpenter et al., 2011). With respect to daily cortisol secretion, maltreated subjects exhibited significantly lower cortisol and ACTH baseline-to-peak deltas. In particular, emotional

neglect and sexual abuse strongly predicted maximal cortisol release (Carpenter et al., 2007). School-aged maltreated children (n = 265) showed a decreased diurnal cortisol secretion compared to non-maltreated (n = 288) children (Cicchetti et al., 2010). Severe maltreatment in 14 patients with anxiety disorder was associated with lower daily cortisol secretion compared with 40 non-maltreated patients. However, in the group of subjects without anxiety disorder no significant difference was found between having a history and no history of maltreatment (van der Vegt et al., 2010). Parental loss in childhood or prolonged parental separation has been found to be associated with increased cortisol response to the DEX/CRH challenge (Tyrka et al., 2008).

----insert Table 1 about here-----

A significant interaction has been reported between childhood maltreatment and genetic variation of the corticotropin-releasing hormone receptor (*CRHR1*). For participants without a history of moderate to severe maltreatment, cortisol response to the DEX/CRH test did not vary according to genotypes. A genotype variation, however, was associated with a specific DEX/CRH response in subjects with childhood maltreatment (54). Another study has reported that variations in the *CRHR1* gene may mediate a pathway between childhood abuse only for specific types of abuse (physical) or for one gender only (men) (Heim et al., 2009). This may indicate that HPA axis activation could represent a pathway of interactions of high risk genes and gender with stress (Tyrka et al., 2009).

Effects of early life maltreatment on the hippocampus and related structures**Structural MRI in adult samples**

Over the last 2 decades studies have analyzed the effects that childhood maltreatment and traumatization have on the hippocampus (Table 2). In 1997 Bremner and colleagues showed that adult survivors of severe childhood abuse had a 12% smaller left hippocampus volume compared to comparison subjects (Bremner et al., 1997). In keeping with this women who reported having been sexually abused in childhood were found to have significantly reduced left-sided hippocampal volume compared to the non-victimized women (Stein et al., 1997). Smaller left hippocampal volumes in subjects with childhood maltreatment were later replicated by a further study in patients with MDD (Vythilingam et al., 2002). We found that patients with MDD and a history of emotional neglect during childhood had reduced left hippocampal white matter compared to those without a history of emotional neglect, but no significant differences were detected in the whole hippocampus (Frodl et al., 2010). An effect of childhood adversity on hippocampal structure was also shown in 35 healthy controls and 22 unaffected first-degree relatives of patients with MDD. Moreover, in 30 patients with depression this association between early life adversity and hippocampal volumes was modulated by parental history of depression (Rao et al., 2010). The finding that childhood maltreatment was associated with smaller hippocampal head volumes also in 20 unaffected 1st degree relatives of patients with MDD is very interesting (Carballedo, 2011). There is an anterior-posterior gradient in the proportional volume of each subfield in the head, body and tail of the hippocampus. Higher proportions of the CA1-3 and subiculum

are found in the hippocampal head, whereas the hippocampal body includes the greatest proportion of the dentate gyrus (DG) (Malykhin et al., 2010). The subfields CA1-3 were found to be altered by experimental stress in animal studies (Sapolsky, 2001) explaining why early stress affected the hippocampal head more than other parts of the hippocampus in family-risk subjects.

Subjects with severe childhood maltreatment, who developed PTSD, showed smaller hippocampal volumes (Weniger et al., 2008). All these above mentioned studies had sample sizes of 17-21 cases versus 17-21 controls. In a large study on healthy men and women (N=265) a trend for smaller hippocampal volumes, and significantly smaller anterior cingulate cortex and caudate volume, was reported in adults with at least 2 adverse child events compared to those without adverse child events (Cohen et al., 2006a).

However, there are also 2 manual tracing studies that have not found effects of childhood maltreatment on the hippocampal volume. Hippocampal volume differences were not seen in 27 survivors of the Nazi Holocaust with and without PTSD, and who were children during the Holocaust, although memory deficits were present, compared to healthy controls (Golier et al., 2005). No significant differences in hippocampal volumes were also found in women with pre-pubertal abuse, who developed later PTSD (N=17), those with abuse, who did not develop PTSD (N=17), and healthy controls (N=17) (Pederson et al., 2004). Interestingly the mean age when the trauma occurred was 13.3 years of age for the group that developed PTSD and 10.5 years for the group that did not develop PTSD in the study of Holocaust

survivors (Golier et al., 2005). Thus, the time when trauma, abuse or neglect affects the individual seems to be important in terms of whether it also affects hippocampal development negatively. Studies investigating early childhood maltreatment thus could show reductions whereas those with later traumas did not find differences in hippocampal volumes.

Studies that used voxel-based morphometry (VBM) to analyze brain structural differences between subjects with childhood maltreatment, compared to those without maltreatment, did not report differences between these groups in relation to the hippocampus, but did report differences in the orbitofrontal cortex (OFC) and anterior cortex cinguli (ACC). A large study in 568 healthy subjects found smaller volumes in the ACC and OFC for those subjects measured with 1.5 Tesla MRI, but this finding could not be confirmed in the group measured with 3 Tesla MRI (Gerritsen et al., 2011). Eighty four patients with depression and/or anxiety, who reported childhood emotional maltreatment, had smaller volumes in the left dorsomedial prefrontal cortex compared to 97 patients with depression or anxiety disorder without childhood maltreatment (van Harmelen et al., 2010). Analysis methods like VBM have the advantage for the investigation of all kind of cortical brain regions, as this is more difficult and because of the lack of clear anatomic boundaries and, for some cortical regions, impossible with manual tracing methods. However, subcortical regions like the hippocampus or the amygdala seem to be more difficult to analyze with automatic VBM methods and thus the two existing VBM studies in large samples provide strong evidence for the effect of early life adversity on brain development.

Thus 8 studies in adult samples using manual hippocampal tracing point towards an effect of childhood maltreatment on hippocampal volumes, whereas two studies with traumatization at later ages and prepubertal age did not find such an association. The two existing VBM studies did not find changes in the hippocampus associated with childhood maltreatment, which likely has methodological reasons associated with the above mentioned anatomy of the hippocampus, but reported frontal brain regions to be affected by childhood maltreatment.

----insert Table 2 here-----

Structural MRI in children

Data in child populations are more inconsistent. While obviously no pre-post childhood trauma studies exist, one longitudinal MRI study in 15 children with childhood maltreatment reported that the presence of early life maltreatment was related to a decrease of hippocampal volumes over time. This study did not have a comparison group of non-maltreated individuals, so that no conclusion can be drawn about whether children with childhood maltreatment are more vulnerable for hippocampal changes over time (Carrion et al., 2007). De Bellis did not find significant differences in hippocampal volumes between 9 children with early life adversity compared to those without (N=9) and no differences in hippocampal volume changes over at least two years of follow-up (De Bellis et al., 2001). These two studies included a small number of patients, so that these findings should not be over interpreted. Recently, De Bellis did not find the hippocampal volume to be

related to PTSD symptoms in children, whereas other variables, like socioeconomic status, general maltreatment and sexual abuse were predictive for PTSD symptoms (De Bellis et al., 2010). No change in hippocampal volumes were detected in a study comparing 17 children exposed to continuous maternal depressive symptomatology since birth compared to 21 control children not exposed to maternal depressive symptomatology (Lupien et al., 2011). In this study, however, the amygdala was larger in children exposed to maternal depression (Lupien et al., 2011). Interestingly, Tupler et al. found larger hippocampal volumes in 61 children with a history of childhood abuse and related PTSD compared to 122 healthy children (Tupler and De Bellis, 2006).

Thus, while the studies in children are rare and none of these shows an association between childhood maltreatment and smaller hippocampal volumes, studies in adults show evidence for decreased hippocampal and also prefrontal volumes, when they have experienced childhood maltreatment. This might support the longitudinal study in children, unfortunately conducted without a comparison group, showing some evidence that history of early life maltreatment renders the hippocampus more sensitive with the result of volume decline over time (Carrion et al., 2007).

Diffusion Tensor Imaging

Magnetic resonance diffusion tensor imaging (DTI) is a novel neuroimaging technique that can evaluate both the orientation and the diffusion characteristics of white matter tracts *in vivo* (Sexton et al., 2009). Recently, we reviewed the literature about diffusion tensor imaging in MDD and childhood maltreatment and found in a

meta-analysis a significant reduction in fractional anisotropy (FA), in the left SLF in MDD (Murphy, 2011). FA is a measure for the diffusion of longitudinal to perpendicular white matter tracts and is often related to neural integrity. With respect to childhood maltreatment, some studies show evidence for decreased FA. Paul *et al.* showed a significant reduction in the genu of the corpus callosum in female individuals subjected to high levels of ELS compared to controls and these changes are also seen in the absence of psychiatric symptoms (Paul et al., 2008). A study by Choi *et al.* reported a significant decrease in FA in the left superior temporal gyrus in association with parental verbal abuse whereas Tomoda *et al.* reported a 14.1% increase in the grey matter of this area (Choi et al., 2009; Tomoda et al., 2010). Despite conflicting evidence, both studies concluded that parental verbal abuse causes alterations in the neural pathways responsible for language processing and development. A ROI and tractography study conducted in seven socioeconomically deprived children and matched controls found significant reductions in FA values of the uncinate fasciculus and suggested these changes may underlie the cognitive and behavioural changes occurring in children exposed to high levels of ELA (Eluvathingal et al., 2006).

HPA axis and the hippocampus assessed with structural neuroimaging

There has been much speculation about whether cortisol measures, either dynamic or static, correlate with hippocampal neuroimaging measures (Table 3). The first study that assessed the association between hippocampal volumes and cortisol measures was published in 1998 by Lupien and colleagues. This longitudinal study conducted over five years in older adults has demonstrated a correlation over time

between cortisol levels and hippocampal volume changes. The total hippocampal volume of 6 subjects with increasing or high cortisol levels was significantly reduced by 14% in comparison to that of 5 subjects with decreasing/moderate cortisol levels and the degree of hippocampal atrophy correlated strongly with both the degree of cortisol elevation over time and current basal cortisol levels (Lupien et al. 1998). Subsequent studies then used different measures of the HPA axis including the DST, cortisol awakening response, stress tests and basal as well as diurnal cortisol measures.

(Insert table 3 here)

DST and brain neuroimaging studies

In a study 20 drug-free first episode female patients with depression were investigated. The volumes of the left and right hippocampus did not correlate with basal or post-dexamethasone cortisol levels, although the depressed sample had smaller hippocampal volumes compared to 15 healthy controls (Kaymak et al., 2010). No significant association between DST and hippocampal volumes either were detected in a depression study (Vythilingam et al., 2004). Thus, it might be that the association between DST cortisol measures and hippocampal volumes is very weak. Larger samples in patients with MDD are necessary here to explore the association between DST suppression and hippocampal volumes.

Other studies have used the DST to evaluate the association between HPA axis functioning and hippocampal volumes in other disorders, but none of these have

looked at early life adversity. In the largest and best powered study investigating 575 patients with arteriosclerotic disease, participants with higher awakening levels after dexamethasone had smaller hippocampal volumes (Knoops et al., 2010). However, five independent studies with smaller samples did not show an association between DST and hippocampal volumes. In one of these studies, 10 healthy elderly nonsuppressors to dexamethasone did not show changes in the hippocampus, but had significantly smaller left anterior cingulate cortex volumes than 10 suppressors (MacLulich et al., 2006). Another study, examining 41 middle-aged type2 diabetes mellitus patients, did not report any association between results from the DST test and hippocampal volumes (Bruehl et al., 2009b). Neither was any association found between post-DST cortisol and hippocampal volume in mild to moderate Alzheimer's Disease (Elgh et al., 2006).

Stimulation with cortisol and brain neuroimaging studies

Tessner et al. 2007 investigated the association of cortisol levels before and after hydrocortisone challenge on hippocampal volumes. There was no significant difference between hydrocortisone and placebo on the hippocampal volume suggesting that a single administration of low-dose hydrocortisone does not alter the volume of the hippocampus. The post challenge cortisol levels were inversely associated with hippocampal volumes (Tessner et al., 2007). In another study of 20 healthy subjects, the ACTH feedback was measured after 0.5 mg/kg cortisol or placebo injection. Neither hippocampal nor cingulate cortex volumes were associated with post cortisol measures (Wolf et al., 2002) indicating no association between ACTH feedback and hippocampal volumes.

Awakening and daily cortisol measures and brain neuroimaging studies**Negative correlations between cortisol levels during the day and hippocampus**

Studies in healthy subjects, patients with arteriosclerotic disease, multiple sclerosis, schizophrenia and alcohol dependency found smaller hippocampal volumes to be associated with increased levels of cortisol during the day. Mean cortisol levels measured 4 times a day during 3 consecutive days were significantly negatively correlated with right hippocampus volumes at follow-up and with hippocampal changes over time in a MRI follow-up study over 12-18 months of 15 children with a history of maltreatment (Carrion et al., 2007). This longitudinal study supports animal data about negative effects of corticosterone on neurons in the hippocampus as described above. In the already mentioned study in 575 patients with arteriosclerotic disease, participants with higher evening levels of cortisol had smaller hippocampal volumes, whereas the CAR did not show significant associations (Knoops et al., 2010). In the above mentioned study on ACTH feedback after cortisol injection in 20 healthy subjects, hippocampal volumes were inversely associated with 24-hour urinary cortisol (Wolf et al., 2002). Smaller volumes in the CA23-dendate gyrus subfield of the hippocampus were linked to depressive symptoms in 29 patients with multiple sclerosis and were associated with hyper-reactivity of cortisol secretion during the day (Gold et al., 2010). Vythilingam et al. examined hippocampal-related cognitive tasks, hippocampal volume and cortisol measures in 38 subjects with depression and no adverse experiences in childhood, and 33 healthy subjects, and repeated the tests in a sub-group of 22 of the depressed group following treatment with antidepressants. Hippocampal volume was not related to

24 hour urinary cortisol levels, or post DST cortisol levels in patients with MDD, but a negative association was seen between urinary cortisol and hippocampus in healthy controls (Vythilingam et al., 2004). Of interest also are studies examining the relationship between cortisol secretion and hippocampal volume in schizophrenia. AUC of diurnal cortisol was found to be correlated negatively with hippocampal volumes in 24 patients with first episode psychosis (Mondelli et al., 2010). Small but significant inverse associations were also found between cortisol levels and the thickness of left dorsolateral (superior frontal gyrus, left rostral middle frontal gyrus) and ventrolateral (pars opercularis, pars triangularis, pars orbitalis) prefrontal regions, and right dorsolateral (superior frontal gyrus) and medial orbital frontal cortex in 388 middle-aged male twins who were 51-59 years old (Kremen et al., 2010).

Seven studies including the large study by Knoops (Knoops et al., 2010) found that hippocampal volumes were smaller in subjects with higher cortisol levels during the day. Four studies however, could not repeat these findings. No significant associations between baseline cortisol measures and hippocampal volumes were found in 24 patients with MDD and healthy controls (Colla et al., 2007). Also an association between evening levels of cortisol and hippocampal volumes could not be seen in 24 traumatized police officers (Lindauer et al., 2006). In 59 young men and women no significant association was found between hippocampal volumes and AUC neither in the whole group nor in subsamples at risk for depression based on their current depression ratings (Dedovic et al., 2010). In a study on subjects with first episode schizophrenia and healthy controls there was no significant association

found between daily cortisol measured as the AUC and hippocampal volumes (Gunduz-Bruce et al., 2007). There are no obvious methodological differences between these studies that did not find the association and those who found the association so that most likely the lack of finding is due to chance. Altogether there seems to be an effect of daily cortisol on hippocampal volumes, although when altogether this effect appears to be relatively small.

Positive correlations between CAR or TSST and hippocampus

Studies investigating CAR found a significant positive association between CAR and hippocampal volumes. In 18 subjects with type2 diabetes mellitus and 12 healthy controls, fasting insulin and hippocampal volume were found to be positively associated with higher CAR responses, independent of diagnosis (Bruehl et al., 2009a). A positive correlation was found between salivary cortisol level in early morning and right hippocampal volume in 24 traumatized police officers (Lindauer et al., 2006). Larger hippocampal volumes were also found to be associated with a significantly stronger cortisol increase in response to the TSST and a significantly greater CAR in 13 healthy males (Pruessner et al., 2007).

However, another study found significant inverse correlations between awaking cortisol concentrations and total hippocampal volume in 8 healthy controls, but not in 8 patients with severe alcohol dependency (Beresford et al., 2006). Interestingly, in a study of 17 healthy children, morning cortisol levels were not associated with total hippocampal volumes (Wiedenmayer et al., 2006). However, with hippocampal morphology analysis, associations were found between hippocampal subregions and cortisol levels. Positive associations between morning cortisol and hippocampal

surface morphology were found focally for the anterior segment of the hippocampus (CA3 and dentate gyrus). Inverse associations were found along the lateral aspects of the anterior, medial, and posterior segments of the hippocampus (CA1) (Wiedenmayer et al., 2006). These data indicate that just measuring cortisol in the morning at awakening is not a very stable index of cortisol functioning as linked to brain structures, whereas CAR with several measures after awakening and cortisol responses after stress tests might have a better potential to reflect the physiology of the system possibly reflecting that the hippocampus might have some regulatory influences.

Discussion

More light can be shed into the relationship between HPA axis function and hippocampal structure and volume. It is obvious that this is not a simple story. What is emerging is a complex system of interconnected factors that need to be separated out before the contribution of the component systems can be understood.

In the review we first focused on the role of childhood adversity on HPA axis function and hippocampal structure. The importance of childhood adversity for the development of psychiatric diseases like depression has consistently been shown. Supported by a recent meta-analysis, childhood maltreatment not only predicts the onset of depression, it is also associated with a lack of response in clinical trials and with a higher risk to develop recurrent MDD or persistent depression (Nanni et al., 2011). It has to be critically addressed that in the studies in adult populations,

childhood maltreatment was assessed retrospectively with questionnaires, and was therefore subject to recall bias. As reviewed above child maltreatment commonly is associated with abnormal cortisol secretory patterns. Interestingly, early life adversity resulted in higher cortisol levels during the day in infants (Saridjan et al., 2010) and lower cortisol levels in children (Cicchetti et al., 2010; van der Vegt et al., 2010). Adults with early life maltreatment had higher levels of cortisol in the CAR (Gonzalez et al., 2009) and lower levels after stimulation in the TSST (Carpenter et al., 2007; Carpenter et al., 2011). However, more studies and also longitudinal studies are required to determine how HPA axis functioning would change during development in children with early life maltreatment.

A consistent finding is that previous history of early childhood maltreatment is associated with smaller hippocampal volumes in adult subjects. This is true for all studies investigating the effect of early childhood maltreatment using manual hippocampal tracing. Two studies investigated the effect of trauma later during the life in pre-pubertal children populations and did not find an effect on hippocampal volumes (Golier et al., 2005; Pederson et al., 2004). Studies in children on the effect of childhood maltreatment on brain structure are rare and often have been carried out in small samples, which may explain the mixed results. The only study in a larger sample of children found larger hippocampal volumes in those with maltreatment compared to those without (Tupler and De Bellis, 2006). The children in this study, however, had PTSD and not depression. PTSD is associated with HPA axis responses that frequently differ from those in depression (115). A history of childhood sexual abuse with adult PTSD, compared to childhood sexual abuse without the

development of adult PTSD, is associated with afternoon hypocortisolism (Bremner et al., 2003). The presence of PTSD may thus alter the direction of the HPA system abnormalities and should be controlled for in studies examining childhood adversity and the HPA axis. Similarly, chronic depression may be associated with normal or even exaggerated DEX/CRH responses (O'Keane et al., 2005; Watson et al., 2002). This raises two important issues: that of the clinical syndrome, depression versus PTSD; and that of age, child versus adult. One possible interpretation of the data might be that childhood maltreatment may render the individual more vulnerable for structural brain changes that occur later in life due to further negative stress and these changes then in turn could have effects on the functioning of the stress hormone system. However such speculative ideas need to be explored more in future.

The most consistent findings from this review demonstrate that an association between higher cortisol levels and smaller hippocampal volumes arise from a continuous measure of the cortisol levels over a day, rather than measures taken at one time of the day only. Continuous measures of cortisol over a day are natural measures of feedback mechanisms. Here studies in healthy controls, those with alcohol dependency, multiple sclerosis, atherosclerosis and schizophrenia indicate inverse associations. Only one study in MDD investigated the association between 24-hour urinary cortisol and the hippocampus and failed to find a significant result, while it was seen in the healthy comparison group (Vythilingam et al., 2004). Therefore, studies of depression in the future should use measures of the HPA axis that incorporate daily cortisol measures. Up to date this had not been done using

salivary cortisol measures at multiple time points during the day. Lastly, hippocampal volume is a crude measure of hippocampal function and, particularly in depression where changes over time are likely, would be better measured repeatedly over time in relation to hippocampal-related cognitive tasks and to HPA axis measures. Studies in MDD with reasonable samples for imaging studies between 20 to 40 patients usually used the DST and did not show such an association between DST cortisol measures and the hippocampal volume. However, since a study in the largest sample of patients with arteriosclerosis detected associations between hippocampus and DST cortisol (Knoops et al., 2010), the use of the DST in a larger sample of patients with depression might still be worthwhile considering.

Nearly all these studies measured the whole hippocampal volume. Hippocampal subregions like the dentate gyrus and the cornu ammonis have different functions and seem to have different stress sensitivities. Stress has been found to suppress neurogenesis and cause atrophy of the CA subfields in animal studies (McEwen and Magarinos, 2001), which are mostly present in hippocampal head and tail. In line with this we recently found that childhood maltreatment was associated with smaller hippocampal head volumes in subjects at risk for MDD (Carballedo, 2011). Moreover, smaller volumes in the CA23-dentate gyrus subfield of the hippocampus were linked to depressive symptoms and were associated with hyper-reactivity of cortisol secretion during the day in MS patients (Gold et al., 2010) suggesting region specific effects of stress and daily cortisol levels at least in subjects vulnerable for depression. Thus future studies should look with high-resolution methods in subregions of the hippocampus.

Our review also indicates that we would need to consider multiple factors interacting over time to explain the associations between early childhood maltreatment, hippocampus and HPA-axis functioning. Other influences, like genetic and temperamental, factors, probably also play a significant role. Key personality traits that have been demonstrated to predict HPA axis stress responses are self esteem and an internal locus of control. In healthy subject of all ages these traits are significantly correlated with hippocampal volume (Pruessner et al., 2005). Environmental factors like stress and genetic variation are linked together via epigenetic processes. Animal models tracking the trajectory from early life stress to adult depression indicate that sustained stress during development leads to hypermethylation of the GR promoter gene, leading to reduced function of the GR and inability to shut down stress responses (McGowan et al., 2011). An impact of parental care on epigenetic regulation of hippocampal GR was demonstrated in a study observing that suicide victims with a history of early life adversity (ELA) display decreased GR mRNA expression and increased cytosine methylation of a neuron-specific GR (NR3C1) promoter in postmortem hippocampus compared to either suicide victims with no ELA or controls (McGowan et al., 2009).

Epigenetic influences on the HPA system may also be trans-generational. One study has shown that maternal childhood abuse is associated with lower cortisol responses in their infants (Brand et al., 2010). Interestingly, HPA axis development commences *in utero*. For most of the duration of pregnancy the baby and mother share a common CRH-ACTH-cortisol axis because the placenta produces CRH (McLean et al., 1995). CRH production by the placenta is positively controlled by maternal and fetal

cortisol, so that if mother or baby is stressed CRH production will increase (Smith and Nicholson, 2007). Increased production of placental CRH will result in increased cortisol levels in baby and mother and, because of a positive feed-forward loop between cortisol and placental CRH, more CRH production (McLean et al., 1995). Babies born to women who were psychologically stressed during pregnancy tend to have disorganized sleep, to be less responsive emotionally (Field, 2011); and to have higher cortisol responses to stressors (Davis et al., 2011). The HPA axis seems to be “programmed” *in utero*, via GR mechanisms, so that the developing brain is primed to respond to a fixed “set point” in post uterine life (Glover et al., 2010). Interestingly children exposed to maternal depressive symptomatology showed larger amygdala volumes (Lupien et al., 2011), which have also been reported in depression (Frodl et al., 2002), suggesting further that low maternal caretaking is a predisposing factor for structural brain changes and in turn for psychiatric disease like depression.

These observations may also indicate that good maternal care could protect against excessive stress responses and result in larger brain structural volumes. Indeed, mothers who reported higher maternal care in childhood showed larger grey matter volumes in the superior and middle frontal gyri, orbital gyrus, superior temporal gyrus and fusiform gyrus (Kim et al., 2010). Birth weight significantly positively predicted hippocampal volume in adulthood in female subjects reporting low maternal care suggesting a complex picture with some protective factors (Buss et al., 2007). Thus, events post-birth may also reverse the damaging effects of a harsh intra-uterine environment; and the plasticity within the HPA system during

childhood can provide greater resilience for the developing adult (Fisher et al., 2006).

Conclusions

Despite the experimental findings involving neuroplasticity in the pathophysiology of MDD (Duman, 2002), to date this work has not been translated into the clinical setting in terms of elucidating a causal role for stress and inflammatory cytokines in mediating hippocampal changes. In the clinic it is commonly found that depressed patients hypersecrete cortisol (Vreeburg et al., 2009), have impaired glucocorticoid receptor (GR) functioning (Pace and Miller, 2009), have increased circulating concentrations of inflammatory cytokines (Simon et al., 2008) and C-Reactive Protein (CRP) (Howren et al., 2009) and have reduced hippocampal volumes (MacQueen and Frodl, 2011). In this review we report the evidence from studies that childhood maltreatment is associated with abnormalities of the HPA system sometimes in terms of basal secretion, sometimes in diurnal feedback mechanisms and sometimes in HPA challenge studies. Yet, the developmental pattern of these changes has to be determined. There is no consistent evidence that children with histories of maltreatment have altered hippocampal volumes; whereas there is evidence that adults with a history of childhood maltreatment have hippocampal volume reduction indicating that a sensitive stress system due to childhood maltreatment might later in life form the basis of structural brain changes. Most interestingly, there is evidence for a negative association between hippocampal volume and cortisol secretion during the day, thus providing evidence that the continuous cortisol profile may predict hippocampal volumes. From the data reviewed here we can conclude

that early life maltreatment results in hippocampal changes and most likely also changes in other brain regions like the OFC or medial prefrontal cortex. However, since there are only a few studies mostly in small samples and using different methods to assess stress hormone function it is not possible to conclude whether early life maltreatment would result in stress hormone axis changes. More research is clearly needed in this area. We might speculate from the studies reviewed that a change in hippocampal structures during brain development might have effects on HPA axis functioning later in life resulting in alterations of cortisol feedback regulation and thus higher cortisol levels, which in turn could have negative effects on brain structure and functioning leading subsequently to higher vulnerability for stress-related psychiatric diseases like depression.

To conclude it is becoming increasingly clear that the cascade theory, while being a reasonably evidence-supported hypothesis, needs to be expanded into a model that incorporates genetic and epigenetic, temperamental, and time phase effects to explain the increasingly complex story of how stress affects the brain.

Acknowledgement:

We would like to thank Science Foundation Ireland for a fund to conduct the present research to TF (Grant Number: SFI/07/SK/B1214C Science Foundation Strokes Professorship Grant).

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Table 1 Effects of early childhood maltreatment on cortisol measures:

Study	Sample	Test used	Results
children			
Saridjan et al. 2010 (Saridjan et al., 2010)	366 infants, 12-20 months old 10% of infants were classified as having parenting stress compared to 90% without parenting stress	Area under the curve (AUC), cortisol awakening response (CAR), the diurnal cortisol slope: Immediately after awakening, 30 min later, around noon, between 3-4pm, and at bedtime. Dutch version of the Parenting Stress Index-Short Form	Infants of mothers experiencing parenting stress showed higher AUC levels
Van der Vegt et al. 2010 (van der Vegt et al., 2010)	102 international adoptees with severe childhood maltreatment, 327 without maltreatment	Area under the curve (AUC): shortly after waking up, 30 minutes later, at 3 pm, just before going to bed. Abuse and neglect was measured on a 3-point Lickert scale	In adoptees with an anxiety disorder, severe maltreatment was associated with lower daily cortisol secretion compared with nonmaltreated adoptees. In adoptees without an anxiety disorder, no difference in cortisol secretion was found between persons who did or did not experience severe maltreatment early in life
Chicchetti et al. 2010 (Cicchetti et al., 2010)	265 school-aged maltreated, 288 non-maltreated children	Morning and late afternoon saliva samples on 5 consecutive days Children with maltreatment identified by the Department of Human Services (DHS)	Children experiencing physical/sexual abuse and high depressive or internalizing symptoms uniquely exhibited an attenuated diurnal decrease in cortisol
adults			
Tyrka et al. 2009 (Tyrka et al., 2009)	91 adults with no or minimal maltreatment, 38 adults with moderate or severe maltreatment	Dex/CRH test and cortisol and cortisol receptor gene 28 item version of the Childhood Trauma Questionnaire (CTQ)	<i>CRHR1</i> SNPs rs110402 and rs242924 showed a significant interaction with maltreatment in the prediction of cortisol response to the DEX/CRH test ($p < .05$).
Gonzalez et al. 2009 (Gonzalez et al., 2009)	36 postpartum mothers with no early life adversity, 36 postpartum mothers with one	Cortisol awakening response (CAR): at awakening and 30 min after awakening over two consecutive days	Women who reported experiencing adverse early life experiences exhibited a tendency towards higher cortisol levels in the CAR compared to women who reported no

	type of early life adversity (maltreatment or consistency of care), 16 with both types of early life adversity	Diurnal cortisol rhythm: after awakening at 8 am, 8:30 am, 10:00 am, 4:00 pm, 6:00 pm, and 9:00 pm 28 item version of the Childhood Trauma Questionnaire (CTQ)	adverse early life experiences
Using the Trier Social Stress test			
Carpenter et al. 2007 (Carpenter et al., 2007)	23 healthy adults with childhood maltreatment, 27 healthy adults without childhood maltreatment	Plasma adrenocorticotropin hormone (ACTH) and cortisol reactivity to the Trier Social Stress Test (TSST): Plasma samples were collected at time points 0, 15, 30, 45, 60, 75, 90 minutes after TSST 28 item version of the Childhood Trauma Questionnaire (CTQ)	Childhood maltreatment was associated with significantly lower cortisol and ACTH baseline-to-peak deltas. Lower cortisol concentrations were found in subjects with childhood maltreatment. Emotional neglect and sexual abuse strongly predicted maximal cortisol release.
Carpenter et al. 2011 (Carpenter et al., 2011)	20 healthy women with childhood abuse, 90 healthy women without childhood abuse	Salivary cortisol before, 15, 30, 45, 60, 75 and 90 minutes after the Trier Social Stress Test (TSST) 28 item version of the Childhood Trauma Questionnaire (CTQ)	Women reporting childhood adversity displayed a significantly blunted cortisol response to the TSST compared with subjects without PA

Table 2 Structural MRI studies on the effect of childhood maltreatment in humans.

Study	Population	Method	Results	Comment
Studies in adults				
Bremner et al. 1997 (Bremner et al., 1997)	17 adults , childhood physical or sexual abuse, 17 healthy controls matched by age, sex, race, handedness, education, body size and alcohol	1.5 Tesla MRI 5 sections of a mid-hippocampal segment were analysed Early Trauma Inventory	12 % smaller left hippocampal volume in abused subjects No significant difference in the right hippocampus	left hippocampus smaller
Stein et al. 1997 (Stein et al., 1997)	21 adult women , sexual abuse during childhood, 21 healthy controls	1.5 Tesla MRI manual hippocampal segmentation Early life adversity	5 % smaller left hippocampal volume in abused subjects No significant difference in the right hippocampus	left hippocampus smaller
Vythilingam et al. 2002 (Vythilingam et al., 2002)	21 women with MDD and a history of perpubertal physical or sexual abuse, 11 women with MDD without abuse, 14 healthy controls	1.5 Tesla MRI manual segmentation of hippocampus Early Trauma Inventory	Subjects with childhood abuse had 18% smaller mean left hippocampal volumes than the nonabused depressed subjects and 15% smaller mean left hippocampal volume than the healthy subjects. No significant difference in the right hippocampus	left hippocampus smaller
Pedersen et al. 2004 (Pederson et al., 2004)	17 women with prepubertal abuse without PTSD, 17 women with prepubertal abuse with PTSD, 17 controls	1.5 Tesla MRI manual segmentation of hippocampus Childhood Trauma Questionnaire (CTQ), Trauma Symptom Inventory (TSI);	No significant difference in hippocampus between groups	n.s.
Golier et al. 2005 (Golier	27 elderly Holocaust survivors , 20 non exposed	1.5 Tesla MRI	No significant difference in hippocampus or other regions between groups	n.s.

et al., 2005)	healthy controls	Manual segmentation of the hippocampus, superior temporal gyrus, lateral temporal lobe		
Cohen et al. 2006 (Cohen et al., 2006b)	265 healthy adults, comparison between more than 2 events of early life adversity and no event of early life adversity, no other control group (e.g. healthy controls)	1.5 Tesla MRI region of interest based voxel-based morphometry ACC, the hippocampus, the amygdala and the caudate nucleus Early Life Stress Questionnaire (ELSQ)	Trend for smaller left and right hippocampal volumes in subjects with early life adversity compared to those without early life adversity Significant smaller anterior cingulate cortex and caudate volume in those adults with adverse childhood events No significant difference in the amygdala	trend for smaller left and right
Weniger et al. 2008 (Weniger et al., 2008)	10 women with severe childhood abuse and diagnosis of PTSD, 13 women with severe childhood abuse and dissociative disorder, 25 healthy controls	1.5 Tesla MRI manual segmentation of hippocampal and amygdala volume The Traumatic Antecedent Questionnaire (TAQ)	Smaller hippocampal and amygdala volumes in subjects with PTSD compared to controls, No significant differences in hippocampal volumes and larger amygdala volumes between dissociative disorder and controls	Smaller hippocampal volumes
Frodl et al. 2010 (Frodl et al., 2010)	43 patients with MDD and 44 healthy controls, median split with emotional neglect (low, high)	1.5 Tesla manual segmentation of hippocampus Childhood Trauma Questionnaire (CTQ)	Smaller hippocampal volumes in subjects with depression and emotional neglect during childhood compared to subjects (healthy or patients) without emotional neglect.	Smaller hippocampal white matter
Harmelen et al. 2010 (van Harmelen et al., 2010)	84 patients with depression and/or anxiety disorder, who reported childhood emotional maltreatment, 97 patient with depression or anxiety disorder without childhood maltreatment	3 Tesla MRI VBM multiple incidents (more than once) of emotional neglect and/or emotional abuse before age 16 years	5.14% reduction in the left dorsal mPFC no significant differences in hippocampus or amygdala	n.s. for hippocampus

Rao et al. 2010 (Rao et al., 2010)	30 adolescents with MDD, 22 adolescents at high-risk for depression (at least one parent with history for depression), and 35 control subjects (ages between 12-20)	1.5 Tesla Manual segmentation of hippocampus Semistructured interview of adolescents and parents	Higher scores on early-life adversity were associated with smaller hippocampal volumes in the control subjects and the high-risk subjects. In patients with MDD, the association between early-life adversity and hippocampal volume was moderated by parental depression	Smaller hippocampal volumes
Gerritsen et al. 2011 (Gerritsen et al., 2011)	568 healthy subjects , 51% in 1.5 Tesla cohort and 56 % in 3 Tesla cohort reported childhood adversity.	1.5 Tesla and 3 Tesla MRI VBM List of Threatening Life Events	History of childhood adversity was associated with smaller volumes in ACC and orbitofrontal cortex in the 1.5 Tesla cohort, but not in the 3 Tesla cohort. Hippocampus not altered	n.s. for hippocampus
Carballedo et al. 2011 (Carballedo, 2011)	20 adult unaffected first degree relatives of patients with MDD and 20 healthy controls	3 Tesla Manual segmentation of hippocampus and VBM Childhood Trauma Questionnaire (CTQ)	Unaffected first degree relatives of patients with MDD, who had a history of emotional abuse, had significantly smaller left and right hippocampal heads compared to those without emotional abuse. VBM also showed smaller dorsolateral prefrontal cortices (DLPFC), medial prefrontal cortices (MPFC) and anterior cortex cinguli in unaffected first degree relatives who had a previous history of emotional abuse.	Smaller hippocampus in emotional abuse modulated by parental history
Studies in Children				
De Bellis et al. 2001 (De Bellis et al., 2001)	9 maltreated children with PTSD, 9 healthy controls matched for age, sex, Tanner state, socioeconomic status, baseline and 2 year follow up	1.5 Tesla manual segmentation of hippocampus reported and indicated child maltreatment experiences by Child Protective Services	No significant differences between maltreated and non-maltreated subjects in hippocampus or amygdala at baseline, follow-up or in between baseline or follow-up	n.s.

Tupler et al. 2006 (Tupler and De Bellis, 2006)	61 children with childhood maltreatment related PTSD, 122 healthy controls	1.5 Tesla MRI landmark based method to obtain hippocampal volume Trauma defined by Child Protective Services [CPS]	Larger hippocampal volumes in children with maltreatment-related PTSD compared to healthy controls	Larger hippocampal volumes
Carrion et al 2007 (Carrion et al., 2007)	15 children with childhood maltreatment, follow-up study, no further controls	1.5 Tesla MRI manual hippocampal segmentation Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA)	Presence of PTSD symptoms predicted decrease of hippocampal volume over 12-18 months	Hippocampal volume decrease over time
De Bellis et al. 2010 (De Bellis et al., 2010)	49 children with maltreatment, 49 children with maltreatment and PTSD and 118 control children without maltreatment	3 Tesla MRI manual hippocampal tracing Modified Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL)	No significant effect of hippocampal volumes	n.s.
Lupien et al. 2011 (Lupien et al., 2011)	17 children exposed to maternal depressive symptomatology since birth, 21 control children not exposed to maternal depressive symptomatology	1.5 Tesla MRI Manual hippocampal and amygdala tracing Maternal depression symptomatology (MDS) was assessed at 5, 17, 30, 42, 60, and 84 month using the National Institute of Mental Health's Center for Epidemiological Studies-Depression (CES-D) scale	No significant group difference in hippocampal volumes Amygdala volumes were larger in children exposed to maternal depression	No change in hippocampus

Table 3 Studies on Cortisol measurements and hippocampus, other brain region findings are also described in the table

Study	Subjects	Method	Result
Studies that only used or in addition used Dexamethason suppression test (DST)			
MacLulich et al. 2006 (MacLulich et al., 2006)	10 healthy elderly male non-suppressors and 10 healthy elderly suppressors to the DST	1.9 Tesla Semi-automated measure of ACC, superior frontal gyrus and hippocampus DST (0.25mg dexamethason, blood drawing at 9 am)	Non suppressors had smaller anterior cingulate cortex (ACC) volumes. No difference in hippocampal volumes between suppressors and non-suppressors.
Kaymak et al. 2010 (Kaymak et al., 2010)	20 drug-free female patients with first episode MDD , 15 healthy female controls	3 Tesla Manual hippocampal volume assessment Blood samples at 08 am and 4 pm to measure baseline cortisol concentrations + DST (1 mg dexamethason), blood collection at 8 am and 4 pm the following day	No correlation between hippocampal volumes and baseline nor post-dexamethasone cortisol levels in patients and controls.
Vythilingam et al. (Vythilingam et al., 2004)	38 subjects with MDD and 33 healthy subjects	1.5 Tesla Manual hippocampal segmentation Urin sample over 24 hours, DST: (1 mg of dexamethason at 11 pm) and blood was collected at 4 pm the following day	Baseline plasma or urinary free cortisol (UFC) was not related to either hippocampal volume in patients with major depression. A negative correlation between 24-hour UFC and both the right and left hippocampus was seen in healthy controls. There was no correlation between hippocampal volume and post-DST plasma cortisol or baseline DST plasma cortisol.
Elgh et al. 2006 (Elgh et al., 2006)	16 medication free Mild to moderate Alzheimer's Disease	0.5 Tesla MRI CA1, CA2/3 and total hippocampal areas, not volumes	No significant association between HPA feedback and hippocampal volume were found.

		DST: 0.25 or 0.5 mg dexamethason and blood cortisol measure at 8 am the following day, on 2 consecutive days	
Knoops et al. 2010 (Knoops et al., 2010)	575 patients with arteriosclerotic disease	1.5 Tesla Manual tracing of the hippocampus cortisol measures after awakening, after 30, 45, and 60 min. at 10 PM and 11 PM. + dexamethasone test	Participants with higher evening levels and higher awakening levels after dexamethasone had smaller hippocampal volumes. Cortisol awakening response was not significant associated with hippocampal volumes.
Bruehl et al. 2009 (Bruehl et al., 2009b)	41 middle-aged dementia-free volunteers with T2diabetes mellitus (on average 7 years since diagnosis) with 47 age-, education-, and gender-matched non-insulin resistant controls	1.5 Tesla Manual segmentation of hippocampus and prefrontal lobe Basal cortisol levels after a 10 hour overnight fast HPA axis feedback was assessed on a different day, using the short version of the DEX/CRH test.	No association was found between cortisol measures and hippocampal volumes. Diminished cortisol suppression after dexamethasone and dyslipidemia were associated with decreased cognitive performance, whereas obesity was negatively related to hippocampal volume
Studies using post cortisol injection measurements			
Wolf et al. 2002 (Wolf et al., 2002)	Nine young (24.0 +/- 1.2 years; mean +/- SE; range: 19-30) and 11 older (69.0 +/- 1.8 years; range: 59-76) healthy men	1.5 Tesla Manual hippocampal segmentation ACTH feedback after 0.5 mg/kg cortisol or placebo 24 hour Urinary cortisol measure, Baseline ACTH and post 0.5 mg/kg cortisol or placebo	Hippocampal volumes were inversely associated with 24-hour urinary cortisol and basal corticotropin (ACTH) levels, and the anterior cingulate gyrus volume was negatively correlated with baseline ACTH. No association between brain structure and ACTH feedback after cortisol
Tessner et al. 2007 (Tessner et al., 2007)	14 healthy male healthy controls	3 Tesla Manual segmentation of hippocampal volume received 100 mg of hydrocortisone and placebo on different days,	The hippocampal volume was not different between the hydrocortisone and placebo conditions Post-challenge cortisol levels were inversely associated with total and right hippocampus volumes.

		Saliva was then sampled at regular 15-min intervals, beginning at 130 min prior to entering the scanner. On average 10 saliva samples	
Studies that used cortisol awakening response (CAR) or daily cortisol profiles			
Lupien et al. 1998 (Lupien et al., 1998)	Healthy participants 6 subjects with progressive increase in cortisol levels and 5 subjects with progressive decrease in cortisol levels	1.5. Tesla MRI Manual hippocampal segmentation 24-hour period with sampling each hour of a blood sample For five to six years, plasma cortisol levels were measured annually over a 24-hour period.	Longitudinal study: Total hippocampal volume of the increasing/high cortisol group was significantly reduced by 14% in comparison to that of decreasing/moderate cortisol group. The degree of hippocampal atrophy correlated strongly with both the degree of cortisol elevation over time and current basal cortisol levels. No significant effect was seen in the parahippocampal gyrus, or fusiforme gyrus.
Wiedenmayer et al. 2006 (Wiedenmayer et al., 2006)	17 healthy children	1.5 Tesla Hippocampal volume and surface morphology Blood samples were obtained in the morning to measure cortisol levels	Cortisol levels were not associated with total hippocampal volumes. Positive associations between cortisol and hippocampal surface morphology were found focally for the anterior segment of the hippocampus (CA3 and dentate gyrus). Inverse associations were found along the lateral aspects of the anterior, medial, and posterior segments of the hippocampus (CA1).
Pruessner et al. 2007 (Pruessner et al., 2007)	13 healthy male subjects	1.5 Tesla manual segmentation of hippocampal volumes	Larger hippocampal volume was associated with stronger cortisol increase in response to the TSST and a significantly greater CAR.

		<p>CAR</p> <p>Samples were taken at 0, 30, and 60 min after awakening once in 4 consecutive weeks</p> <p>Trier Social Stress Test (TSST)</p> <p>A total of eight saliva samples for cortisol assessment were taken 45, 15 min and immediately before the TSST, and immediately, 10, 20, 40 and 60 min thereafter. All</p>	
Kremen et al. 2010 (Kremen et al., 2010)	388 middle-aged male healthy twins (51-59 years old)	<p>1.5 Tesla</p> <p>Cortical surface reconstruction using Freesurfer and hippocampal segmentation</p> <p>saliva samples were obtained at awakening, 30 minutes post-awakening, 10:00 am, 3:00 pm, and 9:00 pm or bedtime.</p>	<p>Higher mean cortisol level and AUC cortisol was significantly associated with thinner cortex in seven prefrontal regions: left and right superior frontal gyrus; left rostral middle frontal gyrus; left pars opercularis; left pars triangularis; left pars orbitalis; and right medial orbital frontal cortex</p> <p>No significant associations were detected between cortisol measures and hippocampal volumes.</p>
Dedovic et al. 2010 (Dedovic et al., 2010)	59 healthy young men and women	<p>1.5 Tesla MRI</p> <p>Manual segmentation of the hippocampus</p> <p>Cortisol awakening response, AUC: at the time of awakening, after 30 min, 60 min, at 4 PM, and at 9 PM over a span of three nonconsecutive workdays.</p>	<p>No significant association was found in the whole group.</p> <p>In men significant positive correlations between hippocampal volume and CAR were seen.</p>
Colla et al. 2007	24 patients with MDD , 14	1.5 Tesla	Baseline cortisol levels were not related to

(Colla et al., 2007)	healthy controls	manual segmentation of hippocampal volumes Saliva cortisol was measured at 0800 and 1600 h	hippocampal volumes.
Lindauer et al. 2006 (Lindauer et al., 2006)	12 traumatized police officers with PTSD and 12 traumatized police officers without PTSD	1.5 Tesla manual segmentation of hippocampal volumes cortisol level at early morning, 4:00 PM and bedtime	Smaller hippocampal volumes were found in those officers with PTSD compared to those without. A positive correlation was found between salivary cortisol level in early morning and right hippocampal volume. No significant association was seen between hippocampus and cortisol levels at bedtime or 4:00pm.
Gunduz-Bruce et al. 2007 (Gunduz-Bruce et al., 2007)	29 healthy controls, 16 subjects with first episode schizophrenia	1.5 Tesla manual segmentation of hippocampal volumes AUC 8 AM, 9 AM, 12 noon and at 4 PM	No significant association was observed between AUC cortisol measures and hippocampal volumes.
Mondelli et al. 2010 (Mondelli et al., 2010)	24 patients with first episode psychosis , 18 healthy controls	1.5 Tesla Stereologically unbiased measurement of the hippocampus using software MEASURE Saliva samples were collected at 0 min after awakening and at 12 pm and 8 pm.	AUC of diurnal cortisol was correlated negatively with hippocampal volumes in patients with first episode psychosis.
Beresford et a. 2006 (Beresford et al., 2006)	8 patients with heavy-drinking alcohol dependency , 8 comparison subjects	3 Tesla manual segmentation of hippocampal volumes Salivary cortisol samples at waking, waking + 30 minutes,	A significant inverse correlation was detected between waking cortisol concentration and hippocampal volume in the total sample group. However, when analyzed separately, only the control group maintained a strong, inverse association.

		noon, and 4 PM	
Gold et al. 2010 (Gold et al., 2010)	20 Healthy controls and 29 patients with multiple sclerosis (MS)	3 Tesla High-resolution MRI of temporal region Manual segmentation of cornu ammonis 1 (CA1), CA2–CA3, and the dentate gyrus (CA23DG), subiculum (Sub), and entorhinal cortex (ERC) Diurnal salivary cortisol was assessed at awakening, 4 PM, and 9 PM on 2 consecutive days	Cortisol slope was significantly associated with CA23DG volumes in the MS group. MS patients with depressive symptoms had significantly flatter cortisol slopes.
Bruehl et al. 2009 (Bruehl et al., 2009a)	18 T2diabetes mellitus and 12 healthy controls	1.5 Tesla Volumes of hippocampus, superior-temporal-gyrus, and frontal lobe at awakening, 15, 30, 60 min post-wake-up, and at 11 a.m. and 3 and 8 p.m.	Hippocampal volume was positively correlated with the CAR, independent of diagnosis, no association between AUC and the hippocampus.