

Stress Controversies: Post-Traumatic Stress Disorder, Hippocampal Volume, Gastroduodenal Ulceration*

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Stress in mammals triggers a neuroendocrine response mediated by the hypothalamic–pituitary–adrenal axis and the autonomic nervous system. Increased activity of these two systems induces behavioural, cardiovascular, endocrine and metabolic cascades that enable the individual to fight or flee and cope with the stress. Our understanding of stress and stress-response mechanisms is generally robust. Here, however, we review three themes that remain controversial and perhaps deserve further scrutiny and investigation before they achieve canonical status. The themes are, first, hypocortisolaemia in post-traumatic stress disorder (PTSD). A reduction rather than a stress-induced increase in adrenal glucocorticoid levels, as seen in major depressive disorder (MDD), is puzzling and furthermore is not a consistent feature of PTSD. Overall, studies on PTSD show that glucocorticoid levels may be normal or higher or lower than normal. The second theme concerns the reduction in volume of the hippocampus in MDD attributed to the neurotoxicity of hypercortisolaemia. Again, as for hypocortisolaemia in PTSD, reduced hippocampal volume in MDD has been found in some but not all studies. Third, the discovery of a causal association between *Helicobacter pylori* and peptic ulcers apparently brought to an end the long-held view that peptic ulceration was caused predominantly by stress. However, recent studies suggest that stress can cause peptic ulceration in the absence of *H. pylori*. Predictably, the aetiological pendulum of gastric and duodenal ulceration has swung from 'all stress' to 'all bacteria' followed by a sober realisation that both factors may play a role. This raises the question as to whether stress and *H. pylori* interact, and if so how? All three controversies are of clinical significance, pose fundamental questions about stress mechanisms and offer important areas for future research.

Key words: post-traumatic stress disorder, hippocampus, major depressive disorder, peptic ulceration, glucocorticoids, noradrenaline.

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Introduction

The neurobiological response to stress in mammals involves three key mechanisms (1–9). First, the stress is perceived and processed by higher brain centres. Second, the brain mounts a neuroendocrine stress response by way of the hypothalamic–pituitary–adrenal axis (HPA) and the autonomic nervous system (ANS). These two systems trigger behavioural, cardiovascular, endocrine and metabolic cascades that enable the individual to fight, flee and/or cope with the stress. Third, except in the case of extreme stress, feedback mechanisms restore homeostasis within the HPA and ANS.

A major breakthrough in our understanding of the HPA response to stress came from the characterisation by Vale *et al.* (10) of corticotrophin-releasing factor (CRF), a 41-amino acid residue peptide

that mediates neural control of adrenocorticotrophin (ACTH) release from pituitary corticotrophs. A series of physiological studies, including measurements of neurohormone release into hypophysial portal blood *in vivo*, have confirmed earlier views that arginine vasopressin (AVP) acts synergistically with CRF to control ACTH release (11,12). The actions of CRF and AVP on pituitary corticotrophs are mediated by way of the CRF receptor-1 (CRFR1) and the vasopressin receptor 1B (V1B also termed V3), respectively (13–15). In addition to its neurohumoral actions, CRF is considered to play a role in mediating stress-induced anxiety, and possibly depressed mood (13–20). The urocortins, members of the CRF peptide family, have recently been shown to exert metabolic effects (21).

Stressful life events can induce depression. The precise mechanisms involved remain to be determined, although genomic data

suggest that some individuals may be more susceptible than others to stress-induced depression. Susceptibility to stress is currently associated with polymorphisms in the genes for monoamine oxidase A, the serotonin transporter and CRFR1 (22–28).

The HPA and ANS responses to stress are the subject of numerous reviews (1–9,29–33). Stress concepts and stress data are generally robust. Here, however, we review three themes that remain controversial and deserve further scrutiny and investigation. The themes, hypocortisolaemia in post-traumatic stress disorder (PTSD), hippocampal volume in mood disorders, and the role of stress versus *Helicobacter pylori* in the causation of peptic ulcers, are of clinical and fundamental significance. In selecting these three areas, I am aware that other stress themes are also contentious. One such theme, the mechanisms by which stress, genotype, neurotransmitters and neurohormones interact to precipitate mental illness, is the subject of a seminal review by de Kloet *et al.* (34).

Post-traumatic stress disorder and hypocortisolaemia?

Introduction

Science is a debate especially when data are subjective as is often the case with disorders of mood and mental state and when hormonal and neurotransmitter changes may be relatively subtle. This is the case for PTSD in which there are several areas of uncertainty. Early studies suggested that PTSD is characterised by hypocortisolaemia rather than hypercortisolaemia as tends to occur in major depressive disorder (MDD). The purported hypocortisolaemia of PTSD was widely accepted (33,35); however, several recent studies have failed to demonstrate that hypocortisolaemia is a robust and consistent feature of PTSD. Clinical and genetic studies show that PTSD is an anxiety disorder (36–38) and is formally classified as such by DSM-IV of the American Psychiatric Association. Thus, the apparent prominent focus on the HPA at the expense of the ANS and especially the sympathetic adrenomedullary (SAM) system might not be warranted. Indeed, PTSD is frequently associated with SAM activation resulting in significant increases in noradrenergic and adrenergic activity. The neuroendocrine picture is often muddled by the fact that a proportion of patients with PTSD also have MDD. Furthermore, the symptomatology and neuroendocrine correlates of PTSD are complicated by gender and context differences.

Definitions and background

PTSD is a condition in which a traumatic event is persistently re-experienced in the form of intrusive recollections, dreams or dissociative flashback episodes. Cues to the event lead to distress and are avoided, and there are symptoms of increased arousal. To meet the diagnostic criteria of the DSM-IV, the full symptom picture must be present for more than 1 month, and the disturbance must cause clinically significant distress or impairment in social, occupational or other areas of functioning.

PTSD has only been accepted officially as a mental disorder since 1980, when it was included, amid considerable controversy,

in DSM-III. References to the after effects of psychological trauma date back as far as the third century BC and were regarded as the basis for hysteria at the turn of the 19th Century by neurologists and psychiatrists such as Jean-Martin Charcot, Pierre Janet and Sigmund Freud (4,39). Interest in PTSD increased dramatically during World War I. Charles Samuel Myers (40) was the first to coin the term and report case histories of 'shell shock', which described a condition that afflicted many troops who screamed and wept uncontrollably, froze and could not move, became mute and unresponsive, and lost their memory, sensations and capacity to feel. The condition occurred again in vast numbers of people as a consequence of World War II. However, it was the psychological trauma experienced by US Vietnam veterans and their demand for compensation that led to the inclusion of PTSD in the DSM-III as a condition that occurred both in civilian (e.g. rape trauma syndrome, battered woman syndrome and abused child syndrome) and in military trauma response syndromes. The reality of PTSD has been buttressed by studies on identical twins that demonstrate that the majority of psychiatric symptoms reported by combat veterans with PTSD would not have been present were it not for their exposure to traumatic events (41,42).

Neuroendocrine (HPA) correlates: no consistent evidence for hypocortisolaemia in PTSD

Mason *et al.* (43) first reported that mean urinary free cortisol concentrations during hospitalisation of Vietnam combat veterans were significantly lower in PTSD than in MDD, bipolar I, manic disorder and undifferentiated schizophrenia, although they were similar to those in paranoid schizophrenia. The low, stable cortisol levels in these PTSD patients were remarkable because the overt signs in PTSD of anxiety and depression would on first principles be expected to be associated with cortisol elevations. Mason *et al.* (43) concluded that 'the findings suggest a possible role of defensive organization as a basis for the low, constricted cortisol levels in PTSD and paranoid schizophrenic patients'. The findings of Mason *et al.* (43) were broadly confirmed by subsequent independent studies. Low dose dexamethasone suppression test in some studies suggested that hypocortisolaemia associated with PTSD reflected increased central sensitivity to glucocorticoids with a consequent greater negative feedback inhibition (35,44,45). By 2002, the concept that PTSD was associated with hypocortisolaemia had almost achieved canonical status (33,44).

The observation of low cortisol in PTSD, precipitated by extreme stress, appeared to contradict the popular 'glucocorticoid cascade hypothesis' which posits that stress-induced increased plasma cortisol concentrations (hypercortisolaemia) result in damage to brain regions such as the hippocampus that are involved in memory and cognition (1,33). However, of greater concern is that the early findings of Mason *et al.* (43) have not been universally replicated. Thus, when compared with levels in normal controls, ambient cortisol levels in PTSD over a 24-h period have been reported as significantly lower, significantly higher or not significantly different

(35,46–49). In a meta-analysis across 37 studies and 828 people with PTSD and 800 controls, Meewisse *et al.* (50) found no systematic difference in basal cortisol levels between people with PTSD and controls. Meewisse *et al.* (50) conclude, 'Although the general assumption is that cortisol levels are low in PTSD, we could not confirm this hypothesis even though we used homogeneous groups as a result of strict exclusion criteria'. Subgroup analysis revealed that cortisol levels were significantly lower in people with PTSD as a result of physical or sexual abuse (50). This type of trauma is generally chronic and often starts in early development. Plasma cortisol levels were also significantly lower in people with PTSD compared to controls who were not exposed to trauma; however, there was no significant difference in cortisol levels in people with PTSD compared with trauma-exposed controls. Meewisse *et al.* (50) conclude, 'This suggests that differences in cortisol levels relate to being exposed to trauma generally rather than to PTSD'. There is also a gender difference in that females with PTSD had lower levels of cortisol than female controls: no such difference was found in males. The time of assessment can also play a role in that cortisol levels in people with PTSD were lower in the afternoon, but not in the early morning (50).

Metzger *et al.* (45) postulate that the between-study discrepancies in cortisol levels might be a result of hypocortisolaemia and increased HPA sensitivity to glucocorticoid negative feedback generally being present in 'relatively homogeneous PTSD and trauma-exposed groups (e.g. combat veterans, Holocaust survivors, victims of domestic violence)', whereas normal or higher cortisol levels were reported in 'studies in which more heterogeneous samples have been compared with a control group consisting of non-trauma-exposed persons without PTSD'. However, the influence of homogeneity among PTSD and trauma-exposed groups on cortisol levels is not a universal finding (48,50).

Gender, it appears, is a potentially 'important variable in differentiating between different cortisol-related phenotypes' (45,50). Metzger *et al.* (45) tested this hypothesis in a homogeneous sample of female nurse veterans who served in Vietnam. Their study closely paralleled previously studied male Vietnam combat veterans with respect to age at time of trauma (early adulthood), exposure to the culture of the Vietnam War experience, time elapsed since trauma and duration of PTSD (30+ years). They found no significant differences in cortisol levels in the nurses with PTSD compared to those without any (current or lifetime) PTSD, and no cortisol hyper-suppression following administration of low dose (0.50 mg) dexamethasone. These negative findings led Metzger *et al.* (45) to conclude 'that PTSD alone is insufficient to produce low basal cortisol and/or cortisol hyper-suppression' and 'suggests that the previously reported low basal cortisol and enhanced HPA axis negative feedback inhibition in the PTSD literature reflect risk factors beyond the mere presence of PTSD'. In an independent study of male war veterans, de Kloet *et al.* (51) found that there were no significant differences between PTSD compared to trauma control patients in the HPA responses to the combined dexamethasone-CRF test. 'PTSD patients with co-morbid MDD showed an attenuated ACTH response compared to PTSD patients without co-morbid MDD,

suggesting the presence of subgroups with different HPA-axis regulation within the PTSD group' (51).

In reflecting on the between-study variance in cortisol levels in PTSD, Yehuda (35) points out that most cortisol levels, high or low, in individuals with PTSD are within the normal endocrine range, and not suggestive of endocrine pathology. That is, in endocrine disorders, Yehuda (35) argues, pathological hormonal changes are generally strikingly obvious and robust, whereas in psychiatric disorders, neuroendocrine alterations may be subtle and therefore difficult to determine with any degree of certainty or reproducibility.

Autonomic correlates of PTSD: robust evidence for increased sympathetic activity in PTSD

By contrast to the significant between-study differences in HPA function and responsiveness to dexamethasone and CRF in patients with PTSD, hyperarousal and increased SAM activity (e.g. increased skin conductance, heart rate, blood pressure and catecholamine secretion) appear to be robust and consistent features of PTSD (46,52–63). Hyperactivity of the peripheral sympathetic and central adrenergic system in PTSD is supported by the clinical improvement that occurs in patients with PTSD in response to agents that reduce the centrally hyperactive noradrenergic state. This is exemplified by the beneficial effects of clonidine, the α_2 adrenergic receptor agonist that reduces noradrenaline release, and prazosin, the α_1 postsynaptic adrenergic receptor blocker (54,64–66). Furthermore, the noradrenergic α_2 -antagonist, yohimbine, which increases peripheral and central noradrenergic activity in man, increases flashbacks, intrusive thoughts, emotional numbness, difficulty in concentrating and panic symptoms in combat veterans with PTSD (54,63,64). Recent genetic and functional magnetic resonance imaging (fMRI) studies have shown that a functional deletion variant of *ADRA2B*, the gene encoding the α_2b -adrenergic receptor, is related to enhanced emotional memory in healthy humans and enhanced traumatic memory in war victims (67). The *ADRA2B* deletion variant, which acts primarily as a loss-of-function polymorphism, is related to increased responsivity and connectivity of brain regions implicated in emotional memory (67,68). In normal subjects, only carriers of *ADRA2B* deletion variant showed increased phasic amygdala responses to acute psychological stress, illustrating that genetic affects on brain function can be context (state) dependent (69).

Noradrenergic neurones interact with several neuronal types, including GABAergic, dopaminergic and serotonergic, and serotonin reuptake inhibitors are sometimes helpful in moderating PTSD. Indeed, notwithstanding the importance of noradrenergic mechanisms, it is important to emphasise that the neurobiology of PTSD is complex and involves several central neurotransmitter systems (64). The mechanism of noradrenergic action remains uncertain, as does the precise neural circuitry involved in PTSD. Adrenergic receptors in the hypothalamus, glucocorticoid and CRF receptors in the locus coeruleus and adrenergic innervation of the adrenal gland suggest that both central and peripheral catecholamine systems and the HPA axis may be linked in a way that could subserve

PTSD-related changes in the two arms of the stress response system (53,70). Liberzon *et al.* (53) posit that PTSD might represent a syndrome, or 'final common pathway', which reflects abnormalities in a number of different neurobiological modalities. However, in their study of Vietnam veterans with and without PTSD, Liberzon *et al.* (53) found that, although challenges activated multiple stress response systems in the PTSD patients, the systems were not activated in an integrated fashion. This may be consonant with the pharmacological and cognitive findings in man which suggest that under normal circumstances noradrenergic systems can influence the magnitude of the HPA axis response to stress, but that in major depression HPA axis activation appears to be autonomous of noradrenergic influence (70).

Experimental studies in animals and fMRI in man are making some headway in elucidating the central neural circuits involved in arousal and PTSD. Thus, for example, neuroimaging studies in PTSD have led to a neurobiological model in which reductions in the inhibitory activity of the ventromedial prefrontal cortex are considered to lead to heightened amygdala activity in response to threat (71). Recent fMRI studies suggest that PTSD is associated with a reduction in activity of the ventral anterior cingulate gyrus that is specifically linked to engagement of arousal networks as assessed by increases in skin conduction in response to neuropsychological challenge (71).

Conclusions

In summary, although often associated with depression, PTSD is an anxiety disorder characterised by intense arousal with concomitant activation of the ANS, especially the SAM. By contrast, the role of the HPA and cortisol in PTSD remains uncertain as a result of major differences between studies and patient groups. Indeed, based on their longitudinal 90-day study of 51 Vietnam combat veterans hospitalised with PTSD, Mason *et al.* (72) concluded, 'At a more general level, the marked lability of cortisol levels demonstrated in the present study does not support pursuing the simplistic, polarized conceptualization of a static "hypocortisolaemia" vs. a static "hypercortisolaemia" in PTSD, but rather supports pursuing the dynamic concept of a more complex regulatory dysfunction of the HPA axis involving a propensity for relatively large swings of cortisol levels, probably in both downward and upward directions'.

Until such time as the cause for the inconsistent data on cortisol levels in PTSD remains unresolved, there is perhaps a case for taking a skeptical view of 'hypocortisolaemia' as a pathognomonic sign for PTSD. Given that PTSD has the clinical features of an anxiety rather than a mood disorder, it is perhaps surprising that clinicians and laboratory scientists have, in their research on PTSD, apparently focused on the HPA at the expense of the ANS and especially central noradrenergic and serotonergic mechanisms that are involved in PTSD and anxiety (61). Indicators of altered ANS activity (e.g. electrodermal, cardiac and blood gas measures) may prove to be useful supplementary diagnostic markers and possible endophenotypes in genetically focused studies of PTSD (59).

Human hippocampus and MDD: does hippocampal size matter?

Introduction

The short answer to this question is 'possibly, although the present data are inconsistent and the mechanism is uncertain'. Much is made of hippocampal volume and MDD. Indeed a current Medline search draws down approximately 300 papers on the subject. The present consideration is not meant to be a detailed meta-analysis. Rather, we review what appears to be a rather confused status of whether hippocampal volume is a consistent feature of MDD.

Background to hippocampal volume reduction in MDD

Three sets of inter-related findings led to the proposition that MDD is associated with reduced hippocampal volume. First, hypercortisolaemia and resistance to glucocorticoid suppression of the HPA (i.e. disruption of normal glucocorticoid negative feedback) was considered a key biological correlate of MDD (73–76). Second, work by Sapolsky, McEwen and associates confirmed earlier findings that high doses of glucocorticoids appeared to damage or destroy hippocampal neurones and/or render the neurones vulnerable to metabolic insult (77–80). Earlier, McEwen *et al.* (81) had demonstrated that corticosterone uptake in the brain was highest in the hippocampus, a finding that underpinned the topographical specificity of glucocorticoid action. Third, Sheline *et al.* (75) using MRI showed that hippocampal volumes in subjects with a history of MDD were significantly reduced bilaterally compared to those in nondepressed control subjects. The degree of hippocampal volume reduction correlated with total duration of major depression. Sheline *et al.* (75) concluded, 'These results suggest that depression is associated with hippocampal atrophy, perhaps due to a progressive process mediated by glucocorticoid neurotoxicity'.

The glucocorticoid neurotoxicity hypothesis would, in principle, offer a coherent biological basis for our understanding of MDD and its relationship to stress. Indeed, structural/neuroplastic changes in key components of the limbic system, such as the prefrontal cortex (PFC), amygdala and hippocampus, offer an alternative or additional mechanism to the chemical (i.e. monoamine) hypothesis of MDD (82,83). However, although several volumetric MRI studies (84–87) have confirmed the initial findings of Sheline *et al.* (75), a substantial number have failed to show significant hippocampal atrophy in subjects with major depression compared to healthy controls (85,88–91).

MRI findings in conflict

Vythilingam *et al.* (85), for example, report that, of 14 studies of hippocampal volume in MDD, eight were unable to find significant between-group differences, whereas six found significantly smaller left or left and right hippocampus. Reduced hippocampal volume was correlated with total duration of depression in some but not all studies. Differences in hippocampal volume in bipolar disorder (BPD) have also been mixed, with reports of increased, decreased,

and unchanged hippocampal volumes (85). Indeed, Ladouceur *et al.* (92) reported increased hippocampal and parahippocampal volume in individuals with high risk of BPD. Sheline (93), on the basis of a literature review, concluded that 'volumetric brain studies exhibit inconsistency in measurements from study to study'. These inconsistencies were attributed to clinical and methodological sources of variability. Clinical variables in subject selection that can contribute to different findings include mean age of subject, age of depression onset, duration of depression and depression severity. Most volumetric studies in depression have used a mixed group of subjects with early-onset and late-onset depression and may therefore have different contributing aetiologies. In some studies, subjects were case control matched, whereas, in other studies, subjects were group matched. Some, but not all, studies excluded subjects with other physical illness or any current or past drug or alcohol abuse. Methodological differences between-studies in MRI scanning include resolution, sampling, boundary determination, alignment, grey scale inconsistencies and measurement technique.

Recent reviews suggest that reduction in hippocampal volume, considered by some to reflect the neurotoxic effect of prolonged depression, PTSD or chronic stress (33), is not a consistent finding in major depression (76,94). In a meta-analysis of 2418 patients with MDD and 1974 healthy individuals, Koolschijn *et al.* (95) reported that MDD patients showed large volume reductions in frontal regions, especially in the anterior cingulate and orbitofrontal cortex with smaller reductions in PFC. The hippocampus, the putamen and caudate nucleus showed moderate volume reductions. Similarly, based on their monumental review of the literature, Savitz and Drevets (89) conclude that, although hippocampal volume reduction in MDD has been widely reported, a significant number of studies have failed to find evidence of hippocampal atrophy in depressed patients, and that 'the majority of studies reporting evidence of hippocampal atrophy have made use of elderly, middle-aged or chronically ill populations'. In patients with BPD, most studies found no reduction of hippocampal volume (89). Hypometabolism of the dorsal PFC is one of the most robust findings in both MDD and BPD (89). A reduction in hippocampal volume cannot automatically be attributed to high levels of cortisol: indeed, reduced hippocampal volume has also been reported in PTSD patients (96) in which cortisol levels are assumed to be normal or lower than normal (see section on PTSD, above), and in patients with cardiovascular disease (76). Twin studies of male Vietnam veterans with and without PTSD and their combat-unexposed identical (monozygotic) co-twins showed that subtle neurologic dysfunction in PTSD does not reflect brain damage acquired along with the PTSD but, instead, represents a familial vulnerability factor, which likely antedates the traumatic exposure (42).

To date, studies examining the hippocampus in MDD have been mostly cross-sectional (97). Longitudinal prospective studies that track patients over disease onset are required. In this respect, Chen *et al.* (98) appear to be the first to report smaller hippocampal volume in healthy girls at a high familial risk of depression. A recent longitudinal study of adolescents found that smaller hippocampal volumes preceded clinical symptoms of depression in

at-risk adolescents, particularly in those who experienced high levels of adversity during childhood (99).

On the basis of their human post-mortem brain studies, Swaab *et al.* (90) conclude 'In depressed subjects or in patients treated with synthetic corticosteroids the hippocampus is intact and does not show any indication of neuropathological alterations or major structural damage. We conclude that in the human brain there is no conclusive evidence that corticosteroids would be neurotoxic for the Hippocampus'. Other studies have confirmed the absence of hippocampal cell loss in MDD or steroid treated subjects (100).

Mechanisms of hippocampal volume changes and reversibility

The mechanisms responsible for hippocampal volume loss in some subjects with MDD remain unclear (82). Genetic factors such the long variant of the serotonin transporter promoter region polymorphism and the *met* allele of the brain-derived neurotrophic factor Val66Met polymorphism in MDD and single-nucleotide polymorphisms within the *DISC1* gene in schizophrenia have been associated with reduced hippocampal volume (98). Human post-mortem brain findings exclude obvious neuronal loss or significant neuropathology (90,100). Stockmeier *et al.* (100) found that MDD is associated with a significant increase in the packing density of glia, pyramidal neurones and granule cell neurones in all hippocampal subfields and the dentate gyrus. Pyramidal neurone soma size was also significantly decreased. Stockmeier *et al.* (100) suggest that a significant reduction in neuropil as well as hippocampal water loss (i.e. shift in fluid balance between the ventricles and brain tissue) may account for decreased hippocampal volume detected in some MRI studies in MDD.

Adult neurogenesis has been regarded as another mechanism that could conceivably affect hippocampal volume. However, neurogenesis adds relatively few neurones per day, and its suppression if such inhibition exists in depressed patients is likely to be too modest to provide a significant contribution to the hippocampal volume reduction reported in some depressed patients. Recent findings from behavioural studies in rodents argue against a role for neurogenesis in MDD. That is, inhibition of cell proliferation in the dentate gyrus is not associated with development of anhedonic-like symptoms in rats or sensitivity to unpredictable chronic mild stress in mice (101,102).

Neurotrophic and other growth factors have been implicated in hippocampal neuroplasticity and in the actions of antidepressants (103). Furthermore, changes in hippocampal structure when present in MDD would appear to be state rather than trait-dependent. Thus, Zhao *et al.* (104), using MRI shape analysis, reported significant differences in the mid-body of the left hippocampus between depressed and control subjects, although this difference was not apparent in subjects who had recovered from depression. Zhao *et al.* (104) suggest that their findings may support the neurogenic effects of antidepressants and their relation to successful treatment for depressive symptoms. The reversibility (and therefore state-dependence) of hippocampal volume reduction receives support from findings in patients with Cushing's disease in which effective

treatment resulting in reduction of plasma cortisol concentrations was associated with an increase of up to 10% in hippocampal volume (90,105).

Impact of normal variability of hippocampal volume

Assessment of the possible relationships between stress, hippocampal volume and depression is confounded by the normal variability in hippocampal volume. Thus, based on their seminal MRI study, Lupien *et al.* (96) reported that hippocampal volume is as variable in young as in older adults, suggesting that smaller hippocampal volume attributed to the ageing process could in fact be determined early in life. Furthermore, within similar age groups, the percentage difference in hippocampal volume between the individuals with the smallest hippocampal volume and the group average was greater than the percentage difference reported between psychiatric populations and normal controls (96). These observations led Lupien *et al.* (96) to conclude, 'Taken together, these results confront the notion of hippocampal atrophy in humans and raise the possibility that pre-determined interindividual differences in hippocampal volume in humans may determine the vulnerability for age-related cognitive impairments or psychopathology throughout the lifetime'.

Functional changes and relevance for cognition and dementia

Major depression is frequently associated with cognitive and especially memory deficits that are attributable to hippocampal dysfunction. Thus, for example, in their study of 38 medication-free non-elderly depressed outpatients without alcohol dependence or adverse experiences in childhood, Vythilingam *et al.* (85) found that MDD patients had normal hippocampal volumes but also had focal declarative memory deficits that reflect hippocampal dysfunction. Treatment with antidepressants significantly improved memory and depression but did not alter hippocampal volume, suggesting that antidepressants may improve hippocampal function in the absence of detectable structural changes (85). Similarly, hippocampal and parahippocampal gyrus volumes do not differentiate between elderly patients with mild to moderate depressive disorders and those without depression (106). This suggests that mechanisms other than hippocampal volume reductions are associated with cognitive and especially memory deficits in elderly depressed patients. Avila *et al.* (106) speculate, 'Future MRI studies involving larger samples, and taking into consideration genetic markers, clinical comorbidities and the age of the depressive symptoms onset, will likely shed further light on the pathophysiology of depression and its associated cognitive deficits in the elderly, as well as on the relationship between this clinical condition and Alzheimer's Disease'.

Lack of illness specificity

Structural hippocampal changes are not specific for MDD. Several groups have reported smaller hippocampal volumes in PTSD as well as in adults with early childhood trauma, depressed women with

childhood sexual or physical abuse and in subjects with alcohol dependence (85). Structural brain changes in the hippocampus have also been reported in patients with schizophrenia. Meisenzahl *et al.* (107) carried out a head-to-head comparison of hippocampal volume in patients with schizophrenia and those with MDD, with the same duration of illness. Bilateral hippocampal volume reductions were detected in both schizophrenic and depressed patients compared to healthy control subjects. Hippocampal volumes were significantly lower in schizophrenic patients compared to MDD patients. Perhaps related tangentially are the findings of Reif *et al.* (108) indicating that neural stem cell proliferation is decreased in schizophrenia but not in depression, leading to the conclusion that reduced neural stem cell proliferation may contribute to the pathogenesis of schizophrenia but not affective disorders. As in MDD, hippocampal volume changes in schizophrenia are reversible on illness remission (109), emphasising the fact that changes in hippocampal volume when present are state not trait-dependent.

Conclusions

The early seminal studies by Bruce McEwen and Robert Sapolsky, which suggested a biological substrate for the effects of glucocorticoids on mood and cognition (1,2,79,80), attained clinical relevance when Sheline *et al.* (75) and other groups provided MRI evidence for volume reduction in the hippocampus of patients with MDD. However, the reduction in hippocampal volume is not a consistent finding: a substantial number of studies of MDD and BPD report no significant reduction. Several meta-analyses point to heterogeneity of subjects as a possible cause for these inconsistencies. The duration of and the number of depressive illness episodes are also significant factors in determining hippocampal volume reduction (97,110).

The importance of patient homogeneity is illustrated by Sheline *et al.* (75) who confined their study to right-handed females with a mean and median age of 68 years recruited from the Memory and Aging Project of the Alzheimer's Disease Research Center and the outpatient psychiatry service at the Washington University School of Medicine. Each depressed subject was matched using a case-control design for age and educational level, and the groups were matched overall for height (a predictor of overall brain size). The choice was made to select all women because it eliminated brain differences due to gender, decreased the possibility of hypertension and occult cardiovascular disease, and increased the ability to obtain subjects, although at the cost of generalizability' (75). The study by Sheline *et al.* (75) has important heuristic value for future clinical studies on the possible relationship between hippocampal volume, mood disorders and cognition.

Additional concerns regarding the possible causal association between MDD, reduced hippocampal volume and hypercortisolemia are, first, the reversibility of reduced hippocampal volume suggesting that there is no permanent structural change and that any change in hippocampal volume is state rather than trait-dependent. Second, hippocampal volume reduction lacks illness-specificity: this applies equally to the salivary cortisol dexametha-

some suppression test, which cannot discriminate between different types of major mental illness (111). Further incisive research appears to be required to establish the clinical fidelity and significance of reduced hippocampal volume in mental illness, and, indeed, whether hippocampal atrophy may be a risk factor for or a consequence of depressive disorders (87). Such research might benefit at a mechanistic level from reversion to fundamental paradigms such as scatter-hoarding animals that need to remember the location of food caches (112–114), the London Cab driver for whom spatial memory is of paramount importance (115,116) and how hippocampal neurogenesis affects learning and memory in birds and other animals (113,117).

Gastroduodenal (peptic) ulcers: stress–*Helicobacter pylori* interactions

The aetiology of gastric and duodenal ulceration and the causal switch from all stress to all bacteria followed by a sober realisation that both factors may play a role and indeed interact have heuristic value for our understanding of disease pathogenesis. Gastric ulceration, together with shrinkage of the thymus and enlargement of the adrenal glands, is one of the key elements of Hans Selye's general adaptation syndrome (4,118). The (2005 Nobel Prize winning) discovery by Marshall and Warren that 80% of gastric and 90% of duodenal ulcers appeared to be caused by *H. pylori* overturned the long-held view that stress was the cause of peptic ulceration (119,120). However, several studies show that stress may still play a significant role in peptic ulceration, either alone, or as a factor that predisposes to ulcer induction by *H. pylori* (118,121,122). This is exemplified by the fact that the Hanshin-Awaji earthquake, which occurred on 17 January 1995, was followed by a significant increase in the number of people with peptic ulceration (121,123). In most people, ulceration developed in conjunction with *H. Pylori*. However, among the physically injured, stomach ulcers developed independently of this infectious agent. Extensive burns also lead to stress ulcers that are likely to be independent of *H. pylori* status (124). Creed (121) argues that there is a clear relationship with stress, which must be considered alongside other risk factors for peptic ulceration: *H. pylori* infection, nonsteroidal anti-inflammatory drugs, smoking and an inherited predisposition.

Most people living with *H. pylori* never develop ulcers, about 30% of patients with ulcer do not harbour *H. pylori* infection and some patients in whom *H. pylori* colonisation has been eliminated by antibiotics subsequently develop new ulcers (125). These facts suggest that other risk factors, including gastric acid hypersecretion, smoking, psychological stress and genetic predisposition, play a part in ulcer formation. In a critical review of the interaction between stress and *H. pylori* in the causation of peptic ulcers Susan Levenstein (126) concludes, 'Peptic ulcer is a valuable model for understanding the interactions among psychosocial, socioeconomic, behavioural, and infectious factors in causing disease. The discovery of *H. pylori* may serve, paradoxically, as a stimulus to researchers for whom the concepts of psychology and infection are not necessarily a contradiction in terms'. Just as high cholesterol is not 'the cause' of myocardial infarction but one of many risk factors,

H. pylori might be one among several risk factors for ulcer formation (125).

General conclusions and observations

Stress research has made huge advances since Hans Selye's note to *Nature* in 1936 (127). This is especially the case with respect to the fundamental neuroendocrinology of the stress response. However, there are still many unknowns. Thus, for example, our understanding of the apparently straightforward HPA/glucocorticoid response to stress has been confounded by PTSD in which patients may have either high, low or normal cortisol levels. The robustness of hypocortisolaemia as a pathognomonic sign of PTSD remains in question, as does the dexamethasone suppression test for MDD. Despite the power of modern functional brain imaging, our understanding of the relationships between changes in the nervous system and signals in the endocrine system remain poor. That is, the significance of changes in hippocampal volume for stress neuroendocrinology (and HPA activity in particular), mood and cognition remains uncertain. The glucocorticoid vulnerability and neurotoxicity hypothesis has almost achieved canonical status. However, although there is no doubt about the veracity of the experimental data, is the hypothesis correct for mood and cognitive disorders in the human? What precisely does a change in the volume of the hippocampus or other brain region signify functionally? Are we missing some major conceptual and factual points? The tension between concept, fact and dogma is illustrated by the interaction between stress and *H. pylori* in the causation of gastroduodenal (peptic) ulcers. It is likely that both stress and *H. pylori* play a role, but what are the biological mechanisms of this interaction and what determines whether stress or *H. pylori* is the dominant factor?

So, in terms of understanding stress and behaviour, have we progressed significantly beyond the century-old Yerkes-Dodson Law which, simply put, states that the relationship between arousal and behavioural performance can be linear or curvilinear depending upon the difficulty of the task (128)? This skeptical view has a brighter side, in that the stress field, far from settled, offers numerous opportunities and challenges for researchers, especially with respect to the interactions between emotion, cognition, memory, mental state, 'somatic disorders' and behaviour. And how does all this translate into molecular synaptology on the one hand and society, culture, economics and medical practice on the other?

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