

Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders

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An extensive literature stretching back decades has shown that prolonged stress or prolonged exposure to glucocorticoids—the adrenal steroids secreted during stress—can have adverse effects on the rodent hippocampus. More recent findings suggest a similar phenomenon in the human hippocampus associated with many neuropsychiatric disorders. This review examines the evidence for hippocampal atrophy in (1) Cushing syndrome, which is characterized by a pathologic oversecretion of glucocorticoids; (2) episodes of repeated and severe major depression, which is often associated with hypersecretion of glucocorticoids; and (3) posttraumatic stress disorder. Key questions that will be examined include whether the hippocampal atrophy arises from the neuropsychiatric disorder, or precedes and predisposes toward it; whether glucocorticoids really are plausible candidates for contributing to the atrophy; and what cellular mechanisms underlie the overall decreases in hippocampal volume. Explicit memory deficits have been demonstrated in Cushing syndrome, depression, and posttraumatic stress disorder; an extensive literature suggests that hippocampal atrophy of the magnitude found in these disorders can give rise to such cognitive deficits.

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Glucocorticoids (GCs), the adrenal steroids secreted during stress, typify the double-edged quality of the stress-response. When secreted transiently (during the brief physical challenge typical of mammalian stress), GCs aid survival. Glucocorticoids mobilize energy, increase cardiovascular tone, suppress unessentials such as growth, tissue repair, and reproduction, and potentiate aspects of immunity while preventing activity to the point of autoimmunity.^{1,2}

However, excessive GCs, can have deleterious consequences, including increased risks of hypertension, insulin-resistant diabetes mellitus, amenorrhea, impotency, ulcers, and immune suppression.^{1,2} In addition, GCs can also have adverse effects in the nervous system, disrupting learning and memory, and synaptic plasticity.³ Glucocorticoids can also have adverse morphologic effects, particularly in the hippocampus, a primary neural GC

target site, with plentiful corticosteroid receptors. These effects include impairing neurogenesis, causing atrophy of dendritic processes and, at an extreme, a neurotoxic effect.

These data have been derived from studies of laboratory animals. This article reviews the possibility that GCs have adverse morphologic effects in humans with Cushing syndrome, depression, or posttraumatic stress disorder (PTSD); specifically, these disorders all seem to involve a volume loss in the hippocampus.

ADVERSE EFFECTS OF GCs ON HIPPOCAMPAL MORPHOLOGIC FEATURES IN ANIMALS

In reviewing this subject, it is worth beginning with a brief overview of hippocampal anatomy and function. The hippocampus is a bilateral subcortical structure in the temporal lobe, with a laminar organization. Each such lamella has a characteristic circuitry. Axonal inputs from the entorhinal cortex enter the hippocampus and form synapses on granule neurons in the dentate gyrus.

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Such neurons, in turn, send axonal projections to CA3 pyramidal neurons that project, in turn, onto pyramidal neurons in the CA2, CA1, and subicular regions. Such neurons then send their projections outside of the hippocampus. While there are additional connections to, from, and within the hippocampus, this “trisynaptic circuit” is the best characterized.

The hippocampus has a variety of functions, but its best documented one is in the realm of learning and memory. A vast literature shows that the structure plays a critical role in the consolidation of short-term into long-term explicit memory.⁴ “Explicit memory” can most readily be thought of as conscious factual memory (such as the recall of what month it is for a human or the correct route in a maze for a laboratory animal), and it is typically contrasted with “implicit memory” (such as the knowledge of riding a bicycle for a human or a conditioned response in an animal). The instances of hippocampal atrophy that will be considered are likely to be of clinical significance in the cognitive realm. This is because subtle hippocampal damage has been shown often to give rise to explicit memory deficits, and such deficits are found in all 3 of these disorders to be discussed.

Atrophy of Dendritic Processes

(In the interest of brevity in this and the next 2 sections, readers are directed to more detailed reviews, and only pertinent studies published since those reviews will be cited.) Complexly arborized dendritic processes are prerequisites for the formation of elaborate neural networks, and GCs can atrophy such processes. Prolonged stress decreases numbers of apical dendritic branch points and the length of apical dendrites in hippocampal CA3 neurons in rodents and nonhuman primates.^{5,6} This effect is GC-dependent and can emerge after a few weeks of GC overexposure in rodents. Moreover, such atrophy correlates with impaired explicit memory.

Glucocorticoid-induced atrophy seems to be mediated by an excess of excitatory amino acid (EAA)

neurotransmitters such as glutamate. Glucocorticoids increase EAA concentrations in hippocampal synapses. Pharmacological blockade of EAA release or EAA receptors (particularly, the *N*-methyl-D-aspartic acid receptor) prevent GC-induced atrophy. In addition, GCs can have adverse effects on levels or efficacy of neurotrophins, particularly brain-derived neurotrophic factor, that normally play a role in the maintenance of normal dendritic arborization.

Thus, transient GC overexposure can alter neuronal morphologic features in a manner deleterious to explicit memory. Critical to evaluating some human data to be discussed, with the abatement of the stressor or GC exposure, there is regrowth of dendritic processes.

Inhibition of Adult Neurogenesis

Long-standing dogma is that adult neurons are postmitotic and, as such, a neuron lost cannot be replaced. Thus, the recognition that neurogenesis does, in fact, occur in the adult brain is revolutionary^{6,7} (although the extent and relevance of the phenomenon has been questioned by some investigators⁸). Such neurogenesis is particularly pronounced in the hippocampal dentate gyrus, occurs in rodents, nonhuman primates, and humans, and can be stimulated by manipulations such as environmental enrichment. Perhaps most remarkably, there is evidence that new neurons can support hippocampal function.

Glucocorticoids or stress inhibit such neurogenesis.^{6,7} This seems to be physiologically significant, in that the decreased neurogenesis in aged rats is eliminated by removing the elevated GC levels typical of aging.⁹ Of possible relevance to understanding this effect, GCs cause cell cycle arrest in peripheral tissues.^{10,11} In addition, *N*-methyl-D-aspartic acid–receptor activation by glutamate inhibits dentate neurogenesis¹² and, as noted, GCs elevate synaptic concentrations of glutamate in the hippocampus.

Neurotoxic Effects

As the most extreme example of the adverse effects of GCs in the cen-

tral nervous system, the hormone has neurotoxic effects in the hippocampus in some circumstances.^{5,6,13,14} Prolonged exposure to the levels of GCs achieved during major stressors for weeks to months in the rodent can kill CA3 neurons and cause explicit memory deficits and impaired synaptic plasticity in the hippocampus. Exposure to stress itself (eg, restraint, aversive learning tasks) for similar periods can cause loss of CA3 neurons in both rodents and primates. Finally, manipulations which reduce lifelong GC exposure (adrenalectomy or behavioral manipulations that chronically decrease GC concentrations) decrease neuron loss in the aging hippocampus, as well as protect from some of the cognitive deficits of aging.

Thus, cumulative lifelong GC exposure can act as a significant pacemaker of hippocampal aging and neuron loss. However, there is considerable strain and individual differences in this phenomenon, and even differences in the amount that neonatal rats are handled can alter the susceptibility to GC-induced neurotoxic effect during aging.

Few studies have examined the cellular mechanisms underlying these instances where GC excess causes neuron loss over the course of months, because of the obvious technical difficulties of such studies. Glucocorticoids can compromise the ability of neurons to survive a variety of neurologic insults that involve excesses of glutamate and calcium (a subject not pertinent to the present review), and it has been speculated that prolonged exposure to GCs is not actually directly neurotoxic, but rather sensitizes neurons to extremely mild insults. However, this idea remains to be tested.

Finally, while an excess of GCs can have a neurotoxic effect in the hippocampus, the complete elimination of GCs by adrenalectomy leads to apoptotic loss of dentate granule neurons.¹⁵ This underlines the use of the complex negative feedback regulation of GC secretion, in that both pathologic hypersecretion and hyposecretion can be damaging to the hippocampus. As this short review indicates, GCs

have a variety of adverse effects in the hippocampus.

HIPPOCAMPAL ATROPHY IN 3 HUMAN NEUROPSYCHIATRIC DISORDERS

Cushing Syndrome

Cushing syndrome arises from adrenocorticotrophic hormone- or corticotropin-releasing hormone-secreting tumors, resulting in hypercortisolism. The numerous pathogenic consequences of this now seem to include loss of hippocampal volume.

In the initial report,¹⁶ subjects were patients with Cushing syndrome (10 women, 2 men) whose disorder was estimated to have gone undiagnosed for 1 to 4 years (based on patient self-reports and photographic evidence of when the disease became apparent). Magnetic resonance imaging (MRI) indicated no change in total intracranial volume but bilateral hippocampal atrophy, expressed as a percentage of total intracranial volume. As a problematic issue, no control group was imaged. Instead, subjects were compared with published norms derived from healthy age-matched individuals. Such comparisons indicated that 27% of subjects had hippocampal volumes below the 95% confidence interval. However, as an important within-group finding, more severe atrophy was associated with more severe hypercortisolism.

In a second report,¹⁷ patients with Cushing syndrome (17 women, 5 men) were imaged at the time of corrective surgery, and at an average of 17 months later (range, 5-52 months). Hippocampal volume increased bilaterally following the abatement of the hypercortisolism. The increase averaged a significant 3% (10% in one case) and was predicted by the extent to which cortisol levels normalized after surgery. Again, no control group was imaged, making it unclear whether the increase completely normalized the volume. Neither estimated disease duration nor time after surgery predicted the extent of expansion; however, extent of expansion negatively correlated with age. Finally, in

one subject, surgery did not reverse the hypercortisolism; in this individual, hippocampal volume decreased after surgery. Thus, the hypercortisolism of Cushing syndrome seems to be accompanied by reversible bilateral hippocampal atrophy in both sexes in the 2 studies that have examined the issue.

Depression

Severe, chronic depression may also be associated with morphologic brain changes. In the first article to be considered,¹⁸ volumetric MRIs were studied from 10 women with a history of prolonged, severe depression, but in remission from 6 months to 4 decades. Control subjects were matched for age, sex, height, education, and handedness. Subjects did not differ from controls in basal cortisol concentrations or responsiveness to dexamethasone therapy. There was no change in overall cerebral volume, but a significant 15% reduction in left hippocampal volume, and a significant 12% reduction in right hippocampal volume. Patients with former depression also showed large low-signal foci throughout the hippocampus. Atrophy was still demonstrable after controlling for history of alcohol use, antidepressant treatment, depression severity, and history of electroconvulsive therapy.

In a follow-up study of 24 women with histories of severe depression and remission for a minimum of 4 months,¹⁹ controls were matched for age, sex, height, education, and adrenocortical profiles. Results indicated 10% and 8% reductions in left and right hippocampal volumes, respectively, with no change in total cerebral or total amygdaloid volumes. There was no relation between age and hippocampal volume reduction in patients with former depression. (Nor had there been in controls, counter to prior reports; the authors had excluded subjects with any medical problems and speculated that their controls constituted "supernormal" aged.¹⁹) Again, longer-duration depressions predicted greater atrophy. Patients with former depression also had smaller volumes of the core nuclei of the amygdala, which correlated with the extent of hippo-

campal atrophy. The hippocampal atrophy persisted after controlling for a history of electroconvulsive therapy, or of estrogen replacement therapy.

A third report concerned 6 women and 10 men with a history of severe, repeated depressive episodes but in remission for an average of 7 months (range, 1½-28 months).²⁰ Controls were matched for age, sex, education, handedness, and history of alcohol abuse. Magnetic resonance imaging scans revealed atrophy averaging a significant 19% in the left hippocampus, and a nonsignificant 12% in the right hippocampus. There was no change in overall brain volume, or volumes of left amygdala, caudate, or frontal or temporal lobe. Surprisingly, there was increased absolute volume of the right amygdala in patients with former episodes of depression. The extent of hippocampal atrophy was unrelated to the number of depressive episodes, of hospitalizations, duration of remission, age, or severity of alcohol abuse.

In one study,²¹ patients with former episodes of depression constituted a control group, and showed no evidence of hippocampal atrophy, in comparison with controls with no depressive history. However, it was not indicated how severe or chronic the depressions were, making comparison with the other 3 studies impossible. Finally, a number of studies²²⁻²⁵ failed to observe any volume change in the hippocampus of patients with severe depression. However, all of these studies used older and less sensitive MRI technology with approximately an order of magnitude of less anatomical resolution than in the more recent studies just discussed, such that it was impossible to differentiate between hippocampus and amygdala in any of these studies.

To summarize, all 3 studies that have used MRI technology that can image the hippocampus alone, and that have examined volumetric correlates of severe and repeated depression that persist after depressions have resolved all reported hippocampal atrophy. That extent of atrophy was not predicted by duration of remission (in the sole study examining this²⁰) suggests that the atrophy does not resolve over time.

Instead, tentatively, it appears to be irreversible.

Posttraumatic Stress Disorder

An initial report²⁶ involved 26 male Vietnam combat veterans with PTSD. Control subjects were matched for age, sex, race, education, body size, socioeconomic status, and years of alcohol abuse. This final factor was critical, given high rates of alcoholism in patients with PTSD, and the neurotoxic effect of alcohol.²⁷ Results indicated a significant 8% right hippocampal atrophy, and a nonsignificant 3.8% left hippocampal atrophy. Neither caudate nor temporal lobe volumes differed.

Gurvits et al²⁸ examined 7 male Vietnam combat veterans with PTSD, and included 2 control groups: one a trauma-free nonveterans (n=8) and the second, veterans exposed to combat trauma but without PTSD (n=7). Hippocampal volume did not differ between the 2 control groups and data were combined; subjects with PTSD had 26% and 22% atrophy of the left and right hippocampi, respectively. Such atrophy remained after adjusting for age and whole brain volume, and was weakened, but still significant for the left hippocampus, when adjusted for cumulative alcohol exposure. In contrast, whole brain volume, ventricular volume, ventricular-brain ratios, and amygdaloid volume did not differ. As an important covariance in these data, the subjects with PTSD had more severe combat exposure (as measured by a standard instrument, the Combat Exposure Scale) than did the combat controls. Furthermore, the significant relation between severity of combat exposure and hippocampal volume included data from both veterans with and without PTSD, and while the article did not analyze the relation within the group, my own analysis indicates no significant relation in either population alone. Thus, hippocampal atrophy may be more a function of the severity of the trauma, rather than of succumbing to PTSD following trauma.

Two studies considered PTSD arising from childhood sexual abuse. One²⁹ concerned 21 women with a self-reported history of severe abuse.

Control subjects were trauma free and matched for age, sex, height, weight, education, handedness, and socioeconomic status. No subjects had histories of head injury. Abused subjects had higher rates of histories of substance abuse than did controls, but did not differ in active alcohol abuse. Left hippocampal volumes (as a percentage of brain slice volume) in abused subjects were a significant 4.9% smaller than in controls, while right hippocampal volumes were a nonsignificant 2.9% smaller. Atrophy remained after controlling for alcohol and drug histories. There was no relation between hippocampal volume and age, severity of abuse, or neuropsychological scores. Smaller hippocampi among abused subjects predicted more severe dissociative symptoms. Importantly, only 15 of those 21 abused subjects had PTSD. If atrophy were a function of the PTSD, there should be a significant difference in volume between those 6 abused subjects and those with PTSD. Instead, there was no differences between those 6 and either the remaining 15, or controls (M. Stein, MD, e-mail communication, October 22, 1999). Given the caveat of the extremely small sample size, this again raises the issue of whether atrophy is a function of trauma or of developing PTSD following trauma.

The final study³⁰ compared 5 women and 12 men with PTSD arising from severe childhood sexual or physical abuse with controls matched for age, sex, race, education, body size, handedness, and years of alcohol abuse. Subjects with PTSD had a significant 12% left hippocampal atrophy and a nonsignificant 5% right hippocampal atrophy. Temporal lobe, caudate, and amygdala volumes were not different. There were no correlations between hippocampal volume and age of onset or duration of abuse and the time since it had stopped when controlling for age, sex, height, weight, education, or for substance abuse history. Importantly, atrophy was still demonstrable when controlling for a history of major depression along with the PTSD. Thus, with the exception of one recent abstract to be considered below, all studies that have examined hippocampal volume changes in PTSD have reported atrophy.

Collectively, hippocampal atrophy can be associated with Cushing syndrome, prolonged major depression, and PTSD following combat trauma or childhood abuse. Such atrophy is demonstrable in both sexes and ranges from 5% to 26%. (There is profound hippocampal atrophy in Alzheimer disease, as well as reports of such atrophy in schizophrenia; neither are considered herein, in that the atrophy in Alzheimer disease is well understood and the defining feature of the disease, while the atrophy in schizophrenia is far from consistently demonstrated.)

SOME KEY ISSUES

Are These Effects Lateralized?

While there is not an asymmetry in volume in the normal human hippocampus, there is evidence for lateralization of function in that the left hippocampus seems to play more of a role in verbal performance on cognitive tasks whereas the right hippocampus plays more of a role in spatial tasks.³¹ Thus, it becomes of interest to determine whether the hippocampal volume loss reported in these disorders is symmetric. Some investigators³² suggest that right hippocampal atrophy predominates in PTSD arising from adulthood (as in Bremner et al²⁶ but not Gurvits et al²⁸), whereas left atrophy predominates in PTSD arising from childhood.^{29,30} Given the small number of studies, plus the minimal laterality in some cases (eg, 4.9% vs 2.9% atrophy in left vs right side²²), more study is needed. In depression, all 3 reports indicate greater atrophy in the left hippocampus¹⁸⁻²⁰; again, however, the differences are small (eg, 15% vs 12% atrophy in left vs right side¹⁸). Finally, data from patients with Cushing syndrome indicate no asymmetry.

How Much Anatomical Specificity Is There to the Hippocampal Atrophy?

Is the atrophy restricted to the hippocampus? (One might also ask whether atrophy is selective to specific hippocampal cell fields, but this requires an anatomical resolution beyond the means of current MRI

technology.) The Cushing syndrome study that demonstrated increased hippocampal volume after normalization of cortisol levels also demonstrated a significant, albeit smaller, increase in caudate volume. Furthermore, cortical and cerebellar atrophy and ventricular enlargement occurs in patients with Cushing syndrome.³³ Thus, the hippocampus seems to be one of a number of sites morphologically altered in Cushing syndrome.

In the case of patients with former episodes of depression, there were no changes in overall brain volume,^{18,20} or in volumes of the left amygdala, caudate, or frontal or temporal lobe.²⁰ One group reported smaller volumes of the core nuclei of the amygdala,^{18,34} while another reported increased absolute volume of the right amygdala.²⁰

Studies of individuals with ongoing chronic depressions indicate less consistent and more diffuse brain changes. Changes include enlarged ventricles and diffuse cortical and subcortical atrophy (including the hippocampus).^{21,35,36} One of those studies³⁵ concerned psychotic depression, which may well be a different illness with different pathology, while another study³⁶ concerned geriatric patients with depression, where there was the confound of comorbid medical illnesses that were likely to have neurologic components). In one of those studies²¹ patients with depression had normal adrenocortical profiles at the time of the MRIs. Imaging studies have indicated volume loss in prefrontal cortex, and post-mortem studies suggest that these arise from loss and shrinkage of neurons and/or glia in prefrontal cortex.³⁷⁻⁴¹ The imaging studies of patients with former depression have not reported on frontal cortical volume; however, the postmortem demonstration of cell loss underlying the volume loss suggests that the latter should persist with the resolution of depression. Finally, bilateral loss of caudate or putamen volume in ongoing depression has been reported in some^{41,42} but not all studies.^{24,43}

Thus, studies of ongoing depressions report ventricular enlargement and loss of gray matter in the

cortical and subcortical regions. With the resolution of depression, the most consistent residual change reported by MRI is hippocampal atrophy, ranging from 8% to 19% (and with volume loss in frontal cortical regions likely as well). Finally, the hippocampal atrophy of PTSD appears to be fairly specific in that atrophy is not consistently observed in whole brain, temporal lobe, ventricular, caudate, or amygdaloid volume.

Thus, there is some suggestion of volume changes in many additional brain regions in these disorders. As one of the organizing ideas of this review, GCs may play a role in mediating the hippocampal atrophy demonstrated. Despite the evidence for that, to be discussed later, there is no reason to believe that the additional brain volume changes reported could have been predicted by the brain-wide distribution of GC receptors (ie, regions with great receptor concentrations are more likely to have shown atrophy). For example, atrophy has been reported in regions with both plentiful and sparse numbers of such receptors (frontal cortex and cerebellum, respectively), while there is evidence of both decreased and increased volume in another region rich in such receptors (the amygdala).

Does the Hippocampal Atrophy Have Functional Consequences?

Three types of evidence suggest this to be the case. First, in normative human aging a small hippocampus and deficits in consolidation of long-term explicit memory as well as and elevated cortisol concentrations all covary.^{44,45}

Second, reports preceding the MRI studies under discussion indicate explicit memory deficits in Cushing syndrome,⁴⁶ depression,⁴⁷ severe depression in remission,¹⁸ and PTSD.^{48,49}

A final form of evidence is the demonstration of cognitive deficits in the same studies demonstrating hippocampal atrophy. In patients with Cushing syndrome, the extent of hippocampal atrophy, of hypercortisolism, and of deficits in explicit memory all covaried.¹⁶ One

study of patients with former episodes of depression indicated explicit memory deficits¹⁹; however, this was not correlated with the extent of atrophy. Finally, in the case of PTSD, studies reporting the greatest degrees of atrophy (12%-26%^{26,28}) demonstrated explicit memory deficits, whereas the study reporting the least significant atrophy (4.9%²⁹) found no such impairments. Stein et al²⁹ speculated that the absence of cognitive problems could reflect the minimal degree of atrophy coupled with its presumed emergence early in life (this was a childhood abuse study), allowing for developmental compensation. Those authors observed that more severe hippocampal atrophy predicted more severe dissociative symptoms. Dissociation is thought to reflect a failure of integration of aspects of identity and consciousness with memory⁵⁰ and, thus, may reflect memory deficits more subtle than revealed by the neuropsychological tests employed.²⁹

These studies suggest that the hippocampal atrophy found in these disorders may have cognitive consequences. Moreover, similar cognitive impairments have been reported in response to excessive exposure to GCs.³

When Does Hippocampal Volume Loss Occur?

Does hippocampal atrophy emerge as a consequence of Cushing syndrome, prolonged depression, or PTSD, or is it possible that the atrophy precedes and predisposes toward those disorders?

In Cushing syndrome, there seems to be no plausible route by which a small hippocampus might predispose toward an adrenocorticotropic hormone-secreting carcinoma of the lungs, or a pituitary microadenoma (2 common causes of Cushing syndrome). This strongly implies that hippocampal atrophy emerges as a consequence of the syndrome.

In depression, investigators tacitly assume that atrophy is a consequence of depression.¹⁹ Speculations about the causality being reversed could involve the idea of the cognitive consequences of a small

hippocampus predisposing toward depression. Recall, however, that hippocampal atrophy in patients with former episodes of depression correlated with longer cumulative durations of, but not with more severe, depression, or more depressive episodes.¹⁸ It seems difficult to posit a model in which more severe hippocampal atrophy predisposes to more prolonged depression but not to more severe depression or more depressive episodes. This seems to argue against the idea of atrophy preceding depression.

In the more complicated situation of PTSD, the question becomes whether atrophy occurs prior to trauma, as a result of trauma, or as a result of the stress disorder following trauma. As the first possibility, a small hippocampus could precede the trauma and predispose toward developing PTSD in response to it, an idea aired in both combat trauma articles. This is because the prevalence of PTSD among combat veterans is only 15% at any given time and 30% lifetime,⁵¹ suggesting some sort of vulnerability among that subset of individuals arising from prior biological and/or environmental factors. Supporting this, there is a significant concordance among twins in vulnerability to PTSD following combat.⁵² Furthermore, succumbing to PTSD is more likely among combat veterans with childhood soft neurologic signs (ie, attention deficit, hyperactivity, learning problems, and enuresis),⁵³ or with lower IQ scores at the time of enlistment.⁵⁴ These findings make more plausible the idea of a smaller hippocampus preceding the trauma as well. It has been postulated that the smaller hippocampus and lower IQ may increase the likelihood of being exposed to certain types of trauma (eg, increasing the likelihood of being assigned to front line combat⁵⁵ or may limit coping mechanisms for dealing with trauma).⁵⁴

Some points argue against the predisposition idea, however. First, as discussed, some data suggest that hippocampal atrophy is more associated with trauma itself, than with succumbing to PTSD. Second, most victims (67%) of repeated rape develop PTSD.⁵⁶ These findings can be

reconciled with the predisposition idea only in the implausible situation where a small hippocampus increases the likelihood of being repeatedly raped (or of being a victim of childhood abuse). Finally, in a recent prospective study, MRIs were carried out near the time of a trauma (in most cases, a serious car accident) and at intervals thereafter; a demonstration that individuals destined to develop PTSD already had small hippocampi at the time of the trauma would confirm the predisposition idea. Instead, atrophy was not yet demonstrable among those succumbing to PTSD even 6 months after trauma.⁵⁷ As a second possibility, atrophy may arise as a result of the trauma itself. Such atrophy need not necessarily be demonstrable immediately after trauma; it must merely be that an even slowly emerging atrophy arises from biological features of the trauma, rather than of the posttraumatic period. Favoring this are findings hinting that atrophy is more a correlate of trauma itself, rather than of PTSD. One example concerned atrophy among victims of childhood abuse²⁹; PTSD developed in a subset of individuals, but hippocampal volume in the non-PTSD trauma survivors did not differ from volume in subjects with PTSD (M. Stein, MD, e-mail communication, October 22, 1999). As the second example, individuals who succumbed to PTSD following combat trauma were also those exposed to the most severe trauma. Thus, it is unclear whether it is trauma itself, or succumbing to PTSD afterward, which predicts atrophy.²⁸

Potentially arguing against atrophy being rooted in the trauma, rather than the posttraumatic period is the abstract reporting that at 6 months following the trauma of a serious car accident, there was still no difference in hippocampal volume between those with and without PTSD.⁵⁷ Again, those data will be pertinent only if those with PTSD ultimately do demonstrate atrophy.

Finally, some data argue against atrophy emerging as a consequence of the PTSD. Since PTSD is an ongoing pathology (ie, these are not studies of individuals “for-

merly with PTSD”), any atrophy caused by PTSD might well be an ongoing process as well. This would predict that the magnitude of atrophy should increase with time since trauma. Moreover, in atrophy in adults associated with childhood abuse, age should be a proxy for time since trauma, and atrophy should also increase as a function of age. However, extent of atrophy does not correlate with either age⁴⁹ or time since trauma.³⁰ This needs further study.

Thus, at present, it seems most likely that atrophy emerges as a consequence of Cushing syndrome or prolonged depression. With PTSD, there are still insufficient data to distinguish among atrophy as predisposing, as a consequence of the trauma, or as a consequence of the posttraumatic period. Distinguishing among those possibilities will require more data indicating when atrophy is first demonstrable (with respect to the trauma), whether it worsens with time after trauma, and the extent to which atrophy is a correlate of trauma itself, as opposed to PTSD.

What Are the Likely Cellular Mechanisms Underlying the Hippocampal Atrophy?

Three broad possible cellular mechanisms might give rise to hippocampal atrophy: (1) a loss of neuropil volume, owing to regression of dendritic processes; (2) an inhibition of the genesis of new neurons and/or glia; and (3) the loss of preexisting neurons and/or glia. In addition, atrophy could result from a noncellular mechanism, namely, compression of the hippocampus owing to loss of brain water content or ventricular enlargement.

Which of these mechanisms likely contribute to the cases of atrophy discussed? Tissue compression could potentially give rise to the atrophy in Cushing syndrome. Glucocorticoids, through their anti-inflammatory effects, decrease brain water volume by inhibiting blood-brain barrier permeability.^{58,59} Commensurate with this, as noted, there is ventricular enlargement and diffuse cortical atrophy in Cushing syndrome.³³ Furthermore, the cerebrovascular effects of GCs are reversible;

as discussed, the hippocampal atrophy in Cushing syndrome is reversible as well, with the abatement of hypercortisolism.

Tissue compression is unlikely to play a role in the other 2 neuropsychiatric disorders. While ventricular enlargement has been reported in depression,^{21,35,36} there are no reports of it persisting decades after the resolution of depression. In the case of PTSD, there have been no reports of ventricular enlargement.

Regression of dendritic processes may play a role in hippocampal atrophy in Cushing syndrome. As noted, such stress- or GC-induced regression is reversible, and thus may account for the reversible atrophy in Cushing syndrome. However, it is unlikely to be relevant to the persistent atrophy of depression. Whether such regression might explain the atrophy in PTSD is complicated. Should atrophy, demonstrable long after the trauma, result from factors preceding or arising from trauma, it is unlikely that regression of dendritic processes would be a contributing factor. This is because of the reversibility of the regression, and the seeming lack of reversibility of the atrophy. However, if atrophy results from ongoing PTSD itself, it is unknown whether atrophy would reverse should the PTSD abate.

Loss of neurons and/or glia is unlikely to explain the atrophy in Cushing syndrome because of the reversible nature of the atrophy. However, it could help explain the persistent atrophy in depression. Supporting this is the reported loss of prefrontal cortical glia and neurons in depression³⁷⁻⁴⁰; equivalent studies are needed in the hippocampus. Cell loss could also be pertinent to PTSD, whether the atrophy precedes the trauma or emerges as a consequence of the trauma or of the PTSD. Should atrophy precede the trauma, a lack of neurons and/or glia could reflect a neurodevelopmental abnormality.

The volume loss could also be secondary to inhibition of neurogenesis and/or gliogenesis; while virtually nothing is known about the latter, neurogenesis in the adult brain is a subject of intense current research. Two findings are pertinent,

the first being the ability, as noted, of stress or GCs to inhibit neurogenesis; the second is the occurrence of neurogenesis alongside ongoing normative neuronal loss, resulting in a steady turnover of neurons. Inhibition of neurogenesis, with no change in the rate of normative neuronal loss, should produce a progressive depletion of neurons. The duration of the Cushing syndrome, of repeated depressions, of trauma, or of the posttraumatic period ranged from months to years in the studies discussed. Is this sufficient time for an excess of neuronal loss, relative to neuronal replacement, to produce hippocampal atrophy of up to 25%? While any answer is speculative, the extent of neurogenesis (and thus the consequences of its inhibition) appears to be quite large.^{9,12} Thus, inhibition of neurogenesis could be relevant to some instances of atrophy. As an important additional anatomical issue, such neurogenesis predominately occurs in the dentate gyrus of the hippocampus; thus, if inhibition of neurogenesis were a major contributor to atrophy, such atrophy should be centered in the dentate. At present, it is impossible to determine if this is the case, in that MRIs do not have the anatomical resolution to allow this to be determined, and there are only minimal suggestions in the literature that atrophy of the dentate would have different functional consequences than, say, atrophy of pyramidal neurons in the CA3 region in the hippocampus.

Evaluating which instances involve inhibition of neurogenesis relies on information currently unavailable, namely, what happens to rates of neurogenesis after the inhibition ceases. There are 3 broad possibilities. First, inhibition of neurogenesis might never recover back to baseline. In this scenario, the magnitude of atrophy should progressively worsen. This model would not apply to these instances of atrophy since there is no correlation between the extent of atrophy and time since normalization of cortisol levels in patients with Cushing syndrome, duration since the abatement of depressions, or time since trauma in the PTSD studies.

As a second possibility, neurogenesis rates indeed recover to the baseline. This results in no further atrophy, but no recovery either. This could thus be applicable to the persistent and stable atrophy in patients with former episodes of depression. It would also be applicable if the atrophy in PTSD arises prior to or during the trauma. Finally, it would not be applicable to the reversible atrophy in Cushing syndrome.

Finally, neurogenesis rates might transiently overshoot baseline. Such supranormal rates would lead to a reversal of atrophy, thus, of relevance to Cushing syndrome. Thus, data regarding recovery rates of neurogenesis are needed to determine which of the 3 instances of atrophy may involve inhibition of neurogenesis.

Are GCs the Damaging Agents?

As reviewed, GCs have varied adverse effects in the hippocampus that could cause loss of hippocampal volume. How likely are GCs to contribute to atrophy?

The common theme across the various tumors underlying Cushing syndrome is hypercortisolism. Thus, GCs are plausible contributors to the atrophy, particularly given that the extent of hypercortisolism predicts the extent of atrophy, while the extent of recovery from the hypercortisolism predicts the extent of volume recovery.

The issue is more complicated in depression. Hypercortisolism occurs in approximately half of the patients with depression, with only a subset of them demonstrating basal hypercortisolism (as opposed to dexamethasone resistance).⁴⁴ Unfortunately, no studies reporting hippocampal atrophy were able to document adrenocortical histories, making it impossible to determine whether a history of hypercortisolism predicted atrophy. In the absence of such data, one might predict that atrophy should occur in well under 50% of patients with former episodes of depression (ie, those who had been basally hypercortisolemic for prolonged periods) were an excess of GCs to be critical to the atrophy.

In contrast, atrophy seems to be demonstrable in a far higher percentage of individuals under study, seemingly arguing against the relevance of GCs. However, subjects in these studies had long histories of repeated and severe depression, involving hospitalization and electroconvulsive therapy. Such depressive profiles most frequently involve hypercortisolism,⁶⁰ prompting the convincing assertion that despite the lack of cortisol data, most subjects in these studies were likely to have been hypercortisolemic when depressed.²⁰

The role of GCs in PTSD is controversial. To begin, if hippocampal atrophy precedes trauma and predisposes toward PTSD, GCs and stress are irrelevant, as that model does not require prior trauma. A role for GCs is more likely should atrophy arise from trauma itself, particularly if the trauma were chronic. (This is because the instances of GC-induced hippocampal damage require prolonged or repeated bursts of GC excess.) Such chronicity is a defining feature of childhood abuse, while GC hypersecretion in response to each incident can only be inferred. In the case of combat trauma, hypercortisolism has been demonstrated (eg, a 4-fold increase in urinary corticosteroid levels in soldiers being shelled⁶¹). Moreover, a high score on the Combat Exposure Scale (which predicts greater hippocampal atrophy) predominantly reflects exposure to multiple traumas, rather than to a single severe trauma,⁵¹ suggesting that the requirement for chronicity is met as well.

There are no data published testing whether hippocampal atrophy occurs in PTSD arising from singular traumas (such as a car crash). Were such atrophy to be demonstrated, it seems unlikely that GCs would play a role. Theoretically, a single trauma could produce GC-mediated atrophy if secretion was of an unprecedented magnitude, invoking previously unrecognized mechanisms of damage. Arguing against this, cortisol levels in women shortly after being raped, while elevated (276-1931 nmol/L^{56,62}) are within the physiological range. (Rape, while a singular event, pro-

duces sustained and profound distress, such distress, by definition constitutes posttraumatic features). Thus, GC excess may be contributory if atrophy arises from chronic trauma, but is less likely should atrophy be shown to arise from single traumas.

Could GC excess be contributory if atrophy arises from the posttraumatic period? This is controversial, because of uncertainty about GC concentrations in PTSD. Basal GC levels in PTSD have been reported to be lower than normal,⁶³⁻⁶⁷ and they may be due to enhanced adrenocortical sensitivity to feedback regulation, given reports of enhanced dexamethasone suppressibility in PTSD.^{68,69} Thus, if PTSD involves hyposecretion of GCs, the steroids can be candidates for damaging only if there is abnormal hippocampal sensitivity to GCs. While this is consonant with the enhanced feedback sensitivity to GCs, there is no direct evidence for this idea.

However, there have also been reports of normal levels of GCs,⁷⁰⁻⁷² or of hypersecretion,⁷³⁻⁷⁶ in PTSD even after controlling for depression in some cases. There have also been reports of normal dexamethasone responsiveness in PTSD.^{72,77} Some of these inconsistencies might be explained by differing control groups among studies (ie, trauma survivors without PTSD in some cases, nontrauma or non-PTSD in others), or failure to control for depression or alcohol abuse. Thus, because of these contradictory findings, it is unclear whether GC excess contributes to atrophy, should it arise during the posttrauma period.

To summarize this last section, there is good evidence for a role for GCs in the atrophy in Cushing syndrome, indirect evidence in the case of depression, and an unclear role in PTSD. Furthermore, there are no other disorders of hippocampal atrophy that do not involve elevated GC levels. Nevertheless, what might be mechanisms independent of GCs that could contribute to these instances of hippocampal atrophy? Should the atrophy precede any of these disorders, there is obviously a wide array of genetic and environmental factors, beginning with fetal life and running the gamut of de-

velopmental biology, that could explain individual differences in hippocampal volume. Should atrophy be emerging during or after the onset of these disorders, there are many non-GC mechanisms as well. As one example, an enormous literature now testifies to the key roles played by various neurotrophins in regulating the division, survival, and dendritic arborization of neurons, and it is of considerable interest that stress decreases the levels of brain-derived neurotrophic factor messenger RNA in the hippocampus. Importantly, some of this stress-induced inhibition is GC independent.⁷⁸ This is particularly interesting in light of an appealing theoretical model about the role of stress-induced inhibition of neurotrophin levels in the origin of depression.⁷⁹

A second possible GC-independent mechanism involves EAA neurotransmitters such as glutamate. An excess of EAAs is central to necrotic neuron death, and seems to play a role in reversible dendritic atrophy.^{5,6} There is ample evidence that GCs and stress can increase glutamatergic tone in the hippocampus (as discussed early in this review). However, the vast array of additional factors that regulate glutamate neurotransmission constitutes one of the most active areas of neurochemistry. As an intriguing possible link between glutamate excess and the neurobiology of depression, lamotrigine, traditionally an antiepileptic drug that inhibits the excitatory effects of EAAs,⁸⁰ has been used successfully in some cases as a mood stabilizer.^{81,82}

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Three neuropsychiatric disorders are associated with somewhat selective atrophy of the hippocampus. These findings begin to allow some insight as to the causes, parameters, and consequences of the atrophy in all 3 cases (**Table**).

This represents a considerable increase in knowledge, as compared with a few years ago.⁸³ The consistency of the atrophy is impressive, given inherent methodological difficulties (appropriately controlling for the high rates of co-

Features of Hippocampal Atrophy in 3 Neuropsychiatric Disorders*

Feature	Cushing Syndrome	Depression	PTSD
Range of notable atrophy	NA	8%-19%	5%-26%
Laterality of atrophy	None	Trend toward left-sided atrophy > right-sided atrophy	Conflicting data
Anatomical specificity	Volume loss reported in hippocampus, caudate, and cortex; ventricles enlarged	Volume loss reported in hippocampus; frontal cortical and cell loss reported; and conflicting data regarding amygdaloid volume	Volume loss reported in hippocampus
Functional consequences†	Strong evidence for deficits in explicit memory	Evidence for deficits in explicit memory	Strong evidence deficits in explicit memory
When atrophy occurs	No evidence for atrophy prior to disease onset	No evidence for atrophy prior to disease onset	Mixed evidence‡
Likely mechanisms underlying atrophy	Tissue compression, regression of dendrites, and inhibition of neurogenesis?	Cell loss and inhibition of neurogenesis?	Cell loss and inhibition of neurogenesis?
Role for glucocorticoids	Highly likely	Indirectly implicated	No role if atrophy precedes trauma; indirectly implicated if atrophy arises from trauma, conflicting evidence if trauma arises from PTSD

* Depression indicates patients who had former episodes of depression; PTSD, posttraumatic stress disorder; NA, not available because of the form of the presentation data.

† Strong evidence indicates that there is a correlation between the extent of hippocampal atrophy and the extent of cognitive impairments, either within or between studies. Evidence indicates cognitive impairments demonstrated, but not correlating, with the extent of atrophy. Explicit memory can be thought of as conscious factual memory, eg, the recall of what month it is.

‡ Mixed evidence indicates evidence both for and against atrophy preceding the trauma, atrophy arising as a result of the trauma, and atrophy arising as a result of the posttraumatic disorder.

morbidity in depression and PTSD, particularly the high rates of substance abuse and depression in the latter). What should be the focus of future studies?

In the case of Cushing syndrome, a first key requirement is that imaging studies be carried out with appropriate non-Cushingoid control groups, rather than reliance on published norms. While the atrophy reported to date is provocative, particularly in light of the correlation between the extent of hypercortisolism and of hippocampal volume, such intrastudy controls are essential. Should the atrophy be demonstrable under those conditions, post mortems are needed from individuals at the point where atrophy is demonstrable, as well as from later time points when successful treatment of the Cushing syndrome has resulted in a recovery of hippocampal volume. Such studies would aid in identifying the cell biology underlying the reversible atrophy in this disorder.

In studies with depression, postmortem studies would help determine whether there is indeed cell loss, much as with the similar cortical studies.³⁷⁻⁴⁰ It must also be determined whether it is basally hy-

percortisolemic depressions that predict hippocampal atrophy. Prospective MRI studies are needed, beginning at the time of initial diagnosis, to test the idea of atrophy as preceding and predisposing toward depression, as well as to test with longitudinal data whether atrophy worsens as depressive duration increases. Finally, MRI might be carried out on high-risk "never depressed" relatives of individuals with depression; this would help determine whether atrophy might exist prior to depression.

Posttraumatic stress disorder studies should test whether atrophy occurs in PTSD associated with single traumas. Prospective studies are needed to determine when, with respect to the trauma, atrophy occurs. More data are needed regarding GC levels during traumas and during PTSD itself. Clarification is needed as to whether atrophy is a function of trauma, or of succumbing to PTSD afterward. This will be particularly difficult since likelihood of succumbing to PTSD and severity of trauma tend to be highly correlated (see Gurvits et al²⁸); as such, controls exposed to trauma but not succumbing to PTSD typically have had less severe traumas than

the PTSD group. Postmortem studies indicating whether hippocampal volume loss involves cell loss are also needed. Finally, an understanding of the likely biological heterogeneity of PTSD is also essential.

Basic science findings stretching back decades suggest that stress, trauma, and, most broadly, experience can alter morphology of the adult brain in rodents and nonhuman primates. Amid the clear need for more human studies in this realm, those reviewed suggest that that adverse experience might also alter the morphology of the human brain as well.

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