3D MRI Studies of Neuroanatomic Changes in Unipolar Major Depression: The Role of Stress and Medical Comorbidity

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Increasing evidence has accumulated for structural brain changes associated with unipolar recurrent major depression. Studies of neuroanatomic structure in early-onset recurrent depression have only recently found evidence for depression-associated structural change. Studies using high-resolution three-dimensional magnetic resonance imaging (MRI) are now available to examine smaller brain structures with precision. Brain changes associated with early-onset major depression have been reported in the hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex, structures that are extensively interconnected. They comprise a neuroanatomic circuit that has been termed the limbic–cortical–striatal–pallidal–thalamic tract. Of these structures, volume loss in the hippocampus is the only consistently observed change to persist past the resolution of the depression. Possible mechanisms for tissue loss include neuronal loss through exposure to repeated episodes of hypercortisolemia; glial cell loss, resulting in increased vulnerability to glutamate neurotoxicity; stress-induced reduction in neurotrophic factors; and stress-induced reduction in neurogenesis. Many depressed patients, particularly those with late-onset depression, have comorbid physical illnesses producing a high rate of hyperintensities in deep white matter and subcortical gray matter and brain damage to key structures involved in the modulation of emotion. Combining MRI studies with functional studies has the potential to localize abnormalities in blood flow, metabolism, and neurotransmitter receptors and provide a better integrated model of depression. Biol Psychiatry 2000;48: 791–800 © *2000 Society of Biological Psychiatry*

Key Words: Depression, MRI, atrophy, limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuit, hippocampus, stress

Introduction

Until recently, the major psychiatric illnesses, including major depression, have been described as "functional," unassociated with structural brain pathology. In the last two decades with the development of new imaging tools, increasing evidence has accumulated that challenges this assumption. Studies have found both generalized and localized structural brain changes in major depression. In this review, brain changes associated with early-onset recurrent depression (EORD) and potential etiologic mechanisms are described, with emphasis on the role of stress and the hypothalamic–pituitary–adrenal (HPA) axis. Brain changes associated with late-onset depression and potential causal factors, primarily medical comorbidity, are also described, and a neuroanatomic circuit associated with depression is discussed. For the past decade there have been a number of studies that revealed brain changes in late-onset depression including diffuse cortical atrophy, loss in regional volumes, and increases in white matter hyperintensities. Late-onset depression typically occurs in the setting of age-related illnesses, such as Parkinson's disease, Alzheimer's disease, poststroke syndromes, and myocardial infarction (see below for a discussion of late-life depression).

Early-Onset Recurrent Depression

There is now emerging evidence for brain changes associated with EORD as well. Differences in three-dimensional magnetic resonance imaging (MRI) volumes have been identified in the frontal cortex (Coffey et al 1993; Drevets et al 1997; Krishnan et al 1992), caudate nucleus (Krishnan et al 1992), putamen (Husain et al 1991), pituitary gland (Axelson et al 1992), hippocampus (Bremner et al 2000; Shah et al 1998; Sheline et al 1996, 1999), and the core nuclei of the amygdala (Sheline et al 1998). In addition, some studies have reported negative findings for the amygdala/hippocampus complex (Ashtari et al 1999; Axelson et al 1993; Pantel et al 1997; Swayze et al 1992) and for the caudate nucleus, putamen, and lentic-

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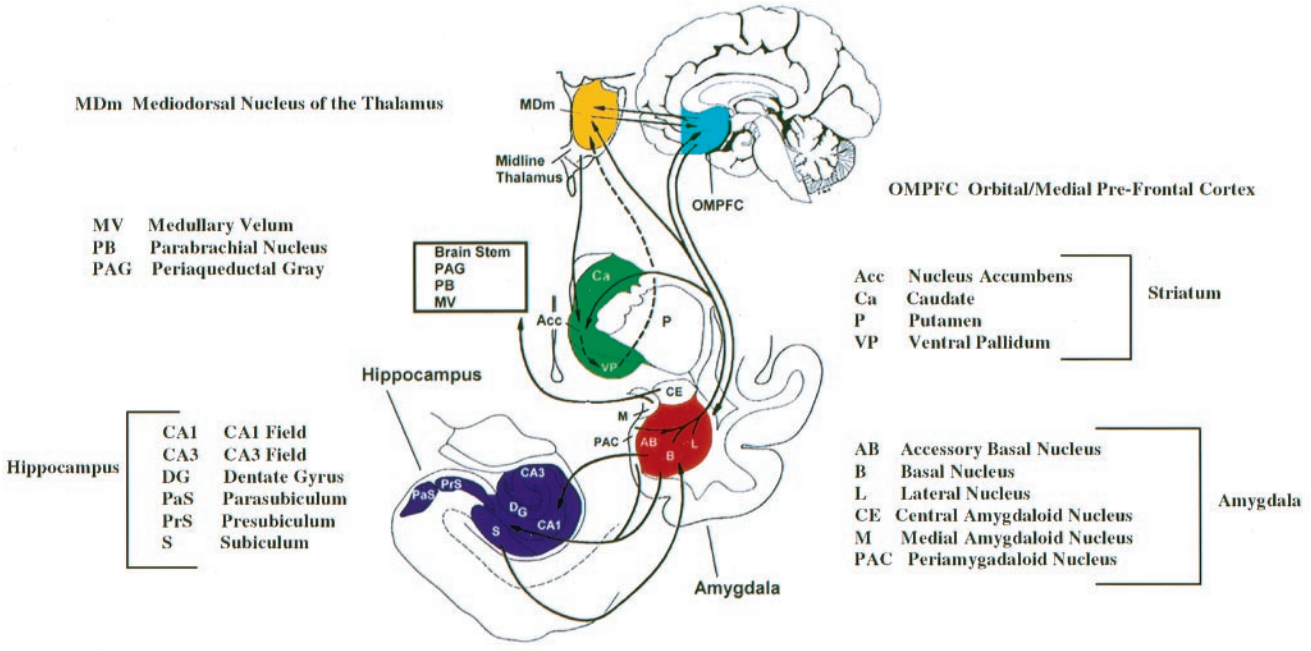

Figure 1. Reciprocal connections are depicted between the components of the limbic–cortical–striatal–pallidal–thalamic tract, including the orbital/medial prefrontal cortex, mediodorsal nucleus of the thalamus, caudate, ventral pallidum, amygdala, and hippocampus. (Reproduced with permission from Aggleton 1992; Bjorklund and Hokfelt 1987; DeArmond et al 1989.)

ular nucleus (Dupont et al 1995; Lenze and Sheline 1999). The studies reporting negative findings typically had lower resolution, ranging from 3 to 10 mm (Ashtari et al 1999; Axelson et al 1993; Dupont et al 1995; Swayze et al 1992), compared with 0.5–2 mm (Bremner et al 2000; Drevets et al 1997; Shah et al 1998; Sheline et al 1996, 1998) for studies reporting significant differences in major depression in these same structures, although one study reporting negative findings in the caudate nucleus and putamen (Lenze and Sheline 1999) also had high resolution. In addition, a study reporting negative findings (Dupont et al 1995) measured the amygdala/hippocampus complex in bipolar subjects with major depression rather than in subjects with unipolar depression. Many of the reported changes occur in structures comprising a neuroanatomic circuit that has been called the limbic–cortical–striatal–pallidal–thalamic (LCSPT) tract (Swerdlow and Koob 1987; Figure 1). Depression appears to involve abnormalities in specific components of this brain circuit. There is extensive interconnectivity between these structures, including the prefrontal cortex, amygdala, hippocampus, basal ganglia, thalamus, and the connecting white matter tracts (Price et al 1987).

In postmortem studies of the prefrontal cortex in major depression (Rajkowska et al 1999), depressed subjects differed significantly from control subjects in several prefrontal cortical areas. They had decreases in cortical thickness, neuronal size decrease, and loss of glial cells in layers II–IV of the rostral orbitofrontal cortex. Caudal orbitofrontal cortex findings were reductions in glial cells in layers V and VI and decreases in neuronal sizes. In the dorsolateral prefrontal cortex depressed subjects had reductions in glial and neuronal cells throughout all layers as well as reduction in cell size. Ongur et al (1998) have also reported glial cell loss in the subgenual region of the prefrontal cortex in major depression. These neuropathologic changes may account for MRI volumetric findings in the frontal cortex. Substantial volume reduction of 39–48% in the subgenual prefrontal cortex has been reported (Drevets et al 1997), as well as a much smaller 7% overall reduction in frontal lobe volume in major depression (Coffey et al 1992). The prefrontal cortex is a particularly important component of the LCSPT tract as a target of monoamine projections, and there is substantial evidence for disturbances in monoamine receptors, transporters, and second messenger systems (Arango et al 1995; Duman 1998; Mintun et al 2000; Price 1999). In addition, it is possible to speculate that overactivation in one part of this interconnected neuroanatomic circuit may lead to overexcitation in the other components, resulting in excitotoxic damage. The orbitomedial prefrontal cortex has high concentrations of glucocorticoid (GC) receptors, potentially rendering it vulnerable to stress-mediated damage (see below). Mechanisms involving stress and elevated GC concentrations may be more relevant in EORD than in late-onset depression.

Hippocampal Volume Loss

Some recent articles have utilized high-resolution MRI technology to examine hippocampal volumes in individuals whose depressions were in remission, thus avoiding studying brain changes potentially due to hypercortisolemia of depression and revealing changes that persisted beyond the acute depression. The first study (Sheline et al 1996) involved volumetric MRIs from 10 women with histories of severe, recurrent depression but in current remission for at least 6 months and a mean of 82.8 months. Case–control matching and exclusion of other physical illness or any current or past drug or alcohol abuse were important aspects of the study design. Subjects were matched within 2 years for age and education, and all were female and right-handed; the groups were matched for height. The study found reductions of 15% in left hippocampal volume and 12% in right hippocampal volume. Exdepressives also showed low signal foci throughout the hippocampus. The extent of left hippocampal atrophy and numbers of foci correlated with depression duration, with a similar trend for right hippocampal volume. Differences in hippocampal volume were still demonstrated after controlling for depression severity and for a history of electroconvulsive therapy (ECT). Subjects did not differ from control subjects in basal cortisol concentrations or cortisol response to dexamethasone, and there was no difference in overall cerebral volume.

A follow-up study of 24 women with histories of severe depression and remission for a minimum of 4 months (Sheline et al 1999) employed an identical case–control design. The study reported 10% and 8% reductions in left and right hippocampal volumes, respectively, with no change in total cerebral volumes. Exdepressives also had smaller volumes of the core nuclei of the amygdala, which correlated with the extent of hippocampal atrophy. In this study also, longer total duration of depression predicted greater atrophy. Post hoc analyses showed that hippocampal atrophy remained after controlling for a history of ECT, for postmenopausal status, and for history of estrogen replacement therapy, and the mean duration of remission was 51.7 months. Exdepressive subjects also had deficits on neuropsychologic tests of verbal memory, which are dependent on hippocampal function. There was no relationship between age and hippocampal volume reduction in either exdepressives or in control subjects, differing from several prior reports. Since the study had carefully ruled out any depressed or control subjects with medical problems, it was speculated that the subjects constituted “supernormals.”

Bremner et al (2000) examined 10 men and 6 women with severe, recurrent depressive episodes who had been in remission for an average of 7 months. Control subjects were matched for age, gender, handedness, education, and history of alcohol abuse. Magnetic resonance imaging scan measurement revealed an average of a significant 19% volume loss in the left hippocampus and a nonsignificant 12% loss in the right. Of note, the method used by Bremner measured a portion of the hippocampus that includes most but not all of the structure (Bremner et al 1995). There was no change in overall brain volume or in left amygdala, caudate nucleus, or frontal or temporal lobe volumes. Exdepressives exhibited a surprising increase in volume in the right amygdala. Amygdala volumes are difficult to compare between studies because the cortical amygdala blends in with surrounding gray matter and anatomic boundaries may differ from one study to the next. Hippocampal atrophy in the Bremner study was not related to number of depressive episodes, duration of remission, hospitalizations, age, or severity of alcohol abuse. Finally, a study (Shah et al 1998) that examined brain volumes in three groups—chronic depression, remitted depression, and control subjects—found hippocampal atrophy in patients with chronic depression but no evidence of hippocampal atrophy in patients with remitted depression. Clinical characteristics of depression were not described in the remitted group, however, making comparison with other studies difficult. Two studies (Axelson et al 1993; Swayze et al 1992) did not find hippocampal volume loss in depression but used less sensitive MRI methodology that could not differentiate the hippocampus from the amygdala. In summary, in studies that assessed depression severity and used high-resolution MRI techniques, depression was associated with bilateral hippocampal atrophy, ranging from 8% to 19%. The volume loss appears to have functional significance with an association between acute depression and abnormalities of declarative memory (Burt et al 1995) as well as an association between severe depression in remission and verbal memory (Sheline et al 1999).

Stress and Depression

An important question is whether hypercortisolemia was responsible for the reported hippocampal volume loss. To understand the potential link, the analogy between depression and stress is important, particularly since neuroendocrine physiology has been better elucidated in stress. Stress physiology involves the study of either physical or emotional stressors that disrupt homeostasis and also the study of the bodily responses that operate to return the system to normal homeostasis. The first recognition that the stress response could be deleterious was made by Hans Selye, who pioneered the concept that chronic stress could cause disease (Selye and Tuchweber 1976). This is particularly appropriate in understanding the deleterious pro-

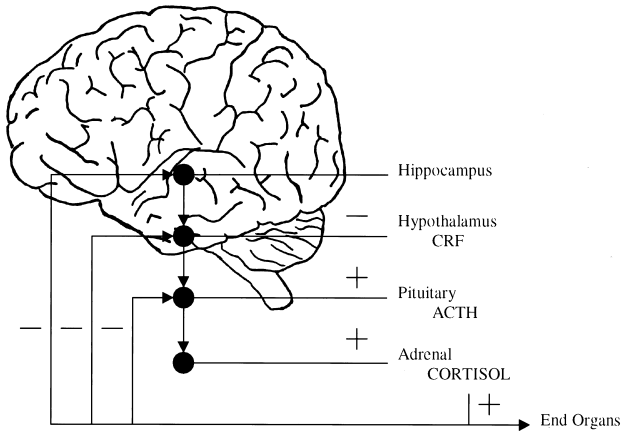

Figure 2. A representation of the relationship between the hippocampus and the hypothalamic–pituitary–adrenal (HPA) axis in response to stress. The activation of the HPA axis leads to elevated cortisol and to possible hippocampal damage. This hippocampal atrophy may interrupt inhibitory influence on the hypothalamus, in turn, resulting in increased corticotropin-releasing factor (CRF) levels with diminished adrenocorticotropic hormone (ACTH) response.

cesses that can affect the hippocampus. Under normal conditions the HPA axis carries out an appropriate acute response to stress (Figure 2); there is an endocrine cascade starting with the brain, continuing to the pituitary, and ending with secretion of GCs by the adrenal gland. Negative feedback loops operate at each of these levels to restore the system to normal homeostasis; however, during conditions of chronic stress, such as occurs in depression, alterations occur in the system so that the feedback mechanisms do not operate normally and there is damage to hippocampal neuronal cells (Gold et al 1984; Holsboer et al 1987; Sapolsky et al 1991; Young et al 1991).

Animal Models of Stress and Hippocampal Damage

A substantial body of data in animal systems indicates that recurrent episodes of stress are associated with damage to hippocampal neurons. It has been demonstrated that repeated episodes of stress or elevated GC levels, also characteristic of depression, can produce neurotoxic damage to hippocampal pyramidal cells. Even 21 days of restraint stress in rats resulted in atrophy of apical dendrites of CA3 pyramidal neurons (Watanabe et al 1992a). Similarly, chronic multiple stressors (e.g., shaking in addition to restraint) produced dendritic atrophy of CA3 neurons. Multiple stressors produced a more robust increase in corticosterone, implicating a permissive role of another factor (excitatory amino acids) in producing damage (Magarinos and McEwen 1995). After repeated stressor episodes, ultrastructural changes (McEwen and Magarinos, 1997) occur in mossy fiber projections from the granule cells in the dentate gyrus, the major excitatory input to CA3 pyramidal neurons. It is important to note, however, that these changes in ultrastructure are reversible (Conrad et al 1999), and hence by themselves cannot explain the volume loss occurring in repeated major depression. A more severe social stress (Uno et al 1989) or long-term GC treatment produced hippocampal neuronal damage in primates. At autopsy, monkeys that died after exposure to severe stress were found to have multiple gastric ulcers and hypertrophy of the adrenal cortex, indicating ongoing GC release. Furthermore, the CA3 subfield of the hippocampus was found to be damaged, and follow-up studies indicated that this damage involved hippocampal exposure to GCs (Sapolsky et al 1990). In other studies, however (Leverenz et al 1999), primates exposed to GCs in the absence of stress did not exhibit hippocampal cell loss, indicating that, in the absence of stress, chronically elevated GC levels may not produce hippocampal neurotoxicity. A recent article by Starkman et al (1999) also found that the hippocampal atrophy induced by high levels of GCs in Cushing's disease patients was partially reversible with treatment of Cushing's disease and reversal of elevated GC levels.

The mechanisms leading to GC-induced hippocampal cell death are not fully delineated, but enhanced vulnerability to excitotoxicity may be a critical factor (Armanini et al 1990; for reviews, see McEwen 1992; Reagan and McEwen 1997; Sapolsky et al 1986). Glucocorticoid- or psychosocial stress–induced atrophy of hippocampal pyramidal neurons is attenuated by *N*-methyl-D-aspartate receptor blockers and by phenytoin, a sodium and T-type calcium channel blocker (Magarinos et al 1996). Collectively, these results support a hypothesis that an interaction between GCs and glutamate is involved in stress-induced neuronal atrophy.

HPA Axis and Depression

The relevance to depression of studies demonstrating that chronically elevated GCs damage hippocampal neurons depends on the assumption that depression is associated with dysregulation of the GC system, and also on the assumption that exdepressives with hippocampal volume loss had elevated GCs. Dexamethasone nonsuppression occurs in approximately half of individuals with major depression (Arana and Mossman 1988). Since baseline cortisol levels and dexamethasone suppression tests are not routinely obtained in clinical practice during acute depressive episodes, it is difficult to establish a history of hypercortisolemia. None of the volumetric studies in humans, which were all retrospective, reported cortisol data as well as hippocampal volume data, making a causal link with GC levels impossible. Subjects in

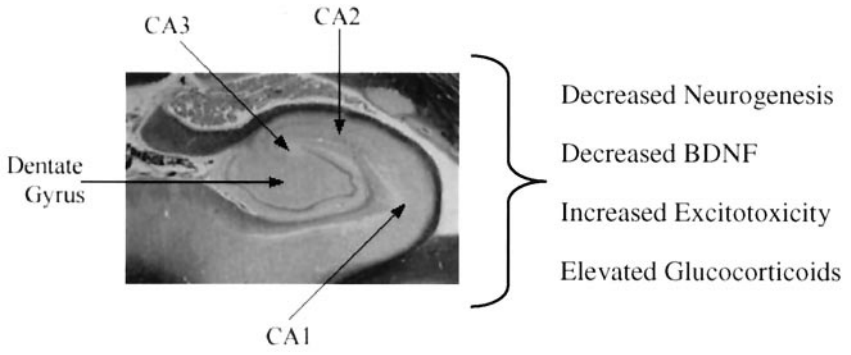

Figure 3. Potential mechanisms for decrease in hippocampal volume in depression. Includes stress-induced decrease of neurogenesis, stress-induced decrease of brain-derived neurotrophic factor (BNDF), increase in excitotoxicity from loss of glia, and elevated levels of glucocorticoids. (Reproduced with permission from Mai et al 1995.)

these studies had long histories of recurrent, severe depression, often involving hospitalization and ECT. Since more severe depression frequently involves hypercortisolism (Whiteford et al 1987), it has been hypothesized that, despite the lack of cortisol data, many subjects in these studies were likely to have been hypercortisolemic when depressed (Sheline et al 1999). There have been many studies indicating that depression is accompanied by dysregulation of the HPA axis resulting in elevated cortisol levels. The first report of humans with depression secreting excessive quantities of cortisol and exhibiting insensitivity to GC feedback inhibition was in 1962 (Gibbons and McHugh 1962).

Hypercortisolism and insensitivity to feedback suppression during depression have been extensively investigated. These studies determined the contributions to HPA dysfunction of adrenal hypersensitivity to adrenocorticotropic hormone (ACTH; Amsterdam et al 1989), pituitary resistance to GC feedback (Holsboer et al 1987), abnormalities in pituitary response to corticotropin-releasing factor (CRF) and other hormones (Gold et al 1984), and resistance to negative feedback at the hippocampus (Sapolsky et al 1991; Young et al 1991). The hypercortisolemia of depression involves hypersecretion of CRF, a compensatory decrease in sensitivity of the pituitary, and increased sensitivity to ACTH by the adrenal. Gold et al (1986) hypothesized that during chronic depression with time the pituitary becomes less sensitive to CRF and the adrenal becomes hyperplastic, resulting in increased sensitivity to ACTH. Thus, HPA axis dysregulation in depression can produce repeated episodes of hypercortisolemia, which may result in hippocampal neurotoxicity. It is important to note that the role of cortisol may vary across diagnostic/biological groups and may be more critical in early-onset depression, particularly in cases in which early life trauma occurred, than in late-life mood disorders.

Mechanisms for Volume Loss in Early-Onset Recurrent Depression

Although follow-up studies of exdepressive subjects have not been conducted, the reported hippocampal volume loss appears to be persistent over years, and therefore any hypothesis proposed to explain hippocampal atrophy in exdepressives must account for its seeming irreversibility. Several different mechanisms could potentially explain these findings. A narrow interpretation of the endangerment model (McEwen 1992; Sapolsky et al 1986) of excess GC levels combined with another insult, such as hypoxia or ischemia, appears unlikely because there is no evidence for such an accompanying insult in depression. Applied more broadly, an endangerment model might encompass damage from excitatory amino acids or suppression of neurogenesis during episodes of stress. Atrophy of dendritic processes induced by excess GC levels (Watanabe et al 1992a) is unlikely as a sole etiology because of the demonstrated reversibility of dendritic atrophy (Conrad et al 1999); however, it is not known which cases of hippocampal atrophy are reversible versus irreversible, and over what period of time.

At least three potential mechanisms exist that could account for the findings to date (Figure 3). One is that the atrophy may reflect neurotoxicity (Bremner et al 2000; Sheline et al 1996, 1999), with repeated hypercortisolemic episodes of depressions giving rise to an irreversible atrophy. In the case of hippocampal volume loss, the inverse correlations between the total amount of time patients have been depressed and hippocampal volume provide evidence for recurrent depressive episodes having a causal relationship. Further, a recent study (Lupien et al 1998) has shown that in normal human aging higher cortisol levels correlated longitudinally with greater hippocampal volume loss. Another potential mechanism is glial cell loss either directly or indirectly producing volume loss. Several studies report gray matter atrophy in the prefrontal cortex, one in an area ventral to the genu of the corpus callosum, indicated by MRI findings (Drevets et al 1997), which were shown in postmortem studies to be due to glial cell loss (Ongur et al 1998). Another study found glial cell loss in postmortem studies of depressed subjects in two different areas of the prefrontal cortex (Rajkowska et al 1999). In addition, glial cell loss has been

reported in postmortem studies in the amygdala and in the entorhinal cortex of the hippocampus (Bowley et al, in press).

It is possible, however, that through excitatory connections between the amygdala and hippocampus (White and Price 1993) damage in one structure could produce damage in the connected structure. Likewise, the interconnections between the prefrontal cortex and the hippocampus (Carmichael and Price, 1995) could produce excitotoxic damage. Glial cells sequester glutamate, maintain metabolic and ionic homeostasis, and produce trophic factors, including brain-derived neurotrophic factor (BDNF; Ransom and Sontheimer 1992; Szatkowski and Attwell 1994). Loss of glial cells could therefore increase vulnerability to neurotoxic damage and supports the idea that glutamate neurotoxicity may be involved in the volume loss in the limbic–cortical–striatal–pallidal circuit. In animal studies even brief kindled seizures may induce selective hippocampal volume loss (Cavazos et al 1994).

Finally, stress-induced inhibition of neurogenesis seems an attractive hypothesis, although high rates of baseline neurogenesis would be needed to produce atrophy of the scale required by hippocampal volume loss in depression. Gould et al (1997) have shown that in the tree shrew psychosocial stress suppressed neurogenesis. Likewise, corticosterone treatment in adult rats also produced suppression of neurogenesis, which was reversed by removal of the adrenal gland (Cameron and Gould 1994). Although neither suppression of neurogenesis nor dendritic remodeling appears to account for the seeming irreversibility of hippocampal volume loss, there could be a combination of irreversible damage and reversible atrophy that increasingly converted to damage with time.

Depression and Comorbid Illness

It is important to note factors that potentially confound or contribute to anatomic changes due to depression, particularly comorbid illness. This applies much more to late-life depression than to early-onset depression, due largely to the increased prevalence of comorbid illness with age; however, although comorbidity may contribute to a higher proportion of late-life depressions than in younger patients, there are other important factors as well. Several computed tomography and MRI studies have shown diffuse cortical and subcortical atrophy and ventricular enlargement in late-life depression (Pantel et al 1997; Rabins et al 1991; Rothschild et al 1989; Soares and Mann 1997). A likely explanation for some findings of generalized brain atrophy in some studies is the comorbidity of major depression with other illnesses, especially in the case of patients with late-onset depression. Clinically significant depressive symptoms are detectable in approximately 12–36% of patients with another nonpsychiatric general medical condition, compared with approximately 5% in the general population (U.S. Department of Health and Human Services 1993). Conversely, patients with depression have a significantly higher rate of other medical illnesses. Specific illnesses that have been determined to cause brain atrophy include hypertension (Kobayashi et al 1991), diabetes (Aronson 1973), Cushing's disease (Starkman et al 1992), and alcohol abuse (Charness 1993); however, any condition that produces neuronal ischemia or neurotoxicity is a potential candidate for producing brain atrophy.

Late-Onset Depression

Late age–onset depression frequently occurs in patients with medical and neurologic disorders. It is characterized by greater medical morbidity and mortality than early-onset depression (Jacoby et al 1981); higher rates of neuroradiologic abnormalities, particularly white matter hyperintensities (Coffey et al 1988; Figiel et al 1991); lower frequency of affective disorders in families of patients (Baron et al 1981); and, in some studies, higher rates of treatment refractoriness (Alexopoulos et al 1996).

It is well established that late-onset depression may be precipitated by damage to key brain structures caused by age-associated medical or neurologic disorders (Alexopoulos et al 1988). A number of neurologic illnesses associated with both cortical and subcortical atrophy are associated with unusually high rates of depression, including dementia of the Alzheimer's type (Burns et al 1990), poststroke syndromes (Starkstein and Robinson 1989), Parkinson's disease (Cummings 1992), and Huntington's disease (Folstein et al 1983). These findings suggest that late-onset depression often is associated with age-related illnesses, which can produce damage to key brain structures. In illnesses with high rates of depression, the same brain structures that have been implicated in more classic or early-onset major depression are involved—namely, the frontal cortex, hippocampus, caudate nucleus, thalamus, and basal ganglia. Not all studies find evidence for generalized atrophy in addition to volume loss in structures of the LCSPT circuit. For example, Kumar et al (1998) have found loss in prefrontal lobe volume in late-onset depression in the absence of generalized atrophy, suggesting that, as in early-onset depression, subjects with late-onset depression may also have focal loss in volume. Whether this focal volume loss involves the same etiologic mechanisms is not known.

The finding of increased numbers of hyperintensites seen on T_2-weighted scans (T2H) in elderly subject groups with depression has been well replicated (Coffey et al 1990; Howard et al 1993; Krishnan et al 1993; Lesser et al

1991; Rabins et al 1991; Zubenko et al 1990). This result has also been reported in studies that included younger subjects (Coffey et al 1993; Hickie et al 1995), though negative findings with younger groups have been reported as well (Dupont et al 1995; Guze and Szuba 1992); however, T2H are also noted to occur at rates of up to 60% in healthy elderly patients (Fazekas et al 1991), in whom their significance is unknown (Mirsen et al 1991). In late-life depression clinical correlates of MRI-defined T2H have included older age, vascular risk factors, and late-onset depressive illness (Coffey et al 1993; Krishnan et al 1988). Fujikawa et al (1993, 1994) found a higher rate of "silent" cerebral infarctions (T2H) in late-onset major depressive disorder than in early onset. A subtype of "vascular depression" with increased cardiovascular disease risk factors and increased T2H has been proposed (Alexopoulos et al 1996; Krishnan et al 1997).

Future Directions

Given the fairly small differences in brain structure volumes between depressed and control subjects, it is important to enhance the ability to detect these differences. Recent advances in MRI technology have allowed much finer resolution; it is currently possible to obtain a resolution of 0.5 mm, compared with the 3- to 5-mm resolution of many previous studies. At this resolution, for example, it is possible to distinguish the thin white matter layer separating the hippocampus from the amygdala, and to measure the hippocampal gray matter volume alone rather than the hippocampus/amygdala complex. The specific nature of the association between recurrent depression and volume reduction in regions of the LCSPT circuit is not known. The possibility cannot be excluded that these volume decreases precede the onset of depression or that the volume decrease is simply a marker of some other brain abnormality that predisposes to depression. Prospective studies are needed to examine this question more fully. Studies in high-risk populations, such as first-degree relatives of affected individuals, will assist in determining whether focal atrophy changes are genetic/neurodevelopmental or acquired and whether they predate or follow the development of depression. Additional postmortem studies are also needed. Studies are needed of individuals at the time of their initial diagnosis of depression, to test the idea of atrophy as preceding and predisposing toward repeated depression. In addition, it will be useful to test explicitly whether only depressives with baseline hypercortisolemia show hippocampal atrophy. Furthermore, it will be important to combine structural studies with functional studies to determine the functional significance of brain structure changes. Combining MRI and functional studies such as positron emission tomography, single photon emission computed tomography, and functional MRI has the potential to more precisely localize abnormalities in blood flow, metabolism, and neurotransmitter receptors. This integrated perspective will allow further development of a structural–functional model of depression. Neuroprotective strategies aimed at preventing the damage associated with depression are likely to be an important future direction for research. Preclinical studies provide preliminary strategies for preventing stress-induced hippocampal damage. These include, for example, prevention of stress-induced decreases in BDNF with antidepressants (Nibuya et al 1995, 1996; Vaidya and Duman 1999), prevention of stress-induced excitotoxic injury with phenytoin (Dilantin; Watanabe et al 1992b), prevention of stress-induced decreases in neurogenesis with antidepressants (Duman and Malberg 1998; Jacobs et al 1998), and increase in dendritic branching with serotonin reuptake inhibitors (Duman et al 1997).

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