Neuroimaging Studies of Mood Disorder Effects on the Brain

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Studies of early-onset recurrent depression, late life depression associated with neurologic disorders, and bipolar illness have revealed structural brain changes within a neuroanatomical circuit. This circuit, originally described by Nauta (1972), has been termed the limbic-cortical-striatal-pallidal-thalamic tract and is comprised of structures which are extensively interconnected. In three-dimensional magnetic resonance imaging studies of affective illness, many of the structures that comprise this tract have been found to have volume loss or structural abnormalities. Mechanisms proposed to explain volume loss in depression include glucocorticoid neurotoxicity, decreased brain-derived growth factor, decreased neurogenesis, and loss of plasticity. Biol Psychiatry 2003;54:338–352 © *2003 Society of Biological Psychiatry*

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Introduction

This article will briefly review the evidence for depression-associated brain changes in bipolar illness, stroke, Parkinson disease, epilepsy, and dementia of the Alzheimer type (DAT), illnesses characterized by tissue loss in the hippocampus, amygdala, basal ganglia, and frontal cortex. Then, evidence for brain changes occurring in this same limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit in early-onset recurrent depression (EORD) will be summarized. Brain changes associated with early-onset major depression have been reported in the hippocampus, amygdala, caudate, putamen, and frontal cortex, the same areas as reported in neurologic illnesses commonly associated with depression. Finally, potential mechanisms for structural brain loss in EORD will be explored and the question of whether depression is the cause or effect of abnormalities in brain structure will be addressed.

Limbic-Cortical-Striatal-Pallidal-Thalamic Tract

We and many others have proposed that both primary and secondary mood disorders often involve abnormalities in specific neuroanatomic circuits (Nauta and Domesick 1984; Swerdlow and Koob 1987; Drevets et al 1992; McDonald and Krishnan 1992; Mayberg 1994; Mega and Cummings 1994; Soares and Mann 1997; Sheline 2000). In addition to subserving important cognitive functions, the prefrontal cortex has an important role in modulating activity in basal ganglia and limbic regions, and there are extensive cortical-subcortical interconnections. A limbic-thalamic-cortical branch composed of the amygdala and hippocampus, mediodorsal nucleus of the thalamus, and medial and ventrolateral prefrontal cortex has been proposed as one arm of the LCSPT circuit and a limbic-striatal-pallidal-thalamic branch as the other arm of the circuit. The caudate and putamen (striatum) and globus pallidus (pallidum) are organized in parallel to connect with limbic and cortical regions. Given the multiple neurotransmitter systems involved and multiple interconnections, there are many ways in which lesions within this system could result in depression. One hypothesis (Swerdlow and Koob 1987) to account for depressive symptoms is underactive forebrain dopamine activity resulting in disinhibition of the limbic striatum. Disinhibition of the limbic striatum then produces overinhibition of the ventral pallidum with decreased inhibitory connection with mediodorsal thalamus and, in turn, results in disinhibition of the excitatory loop involving the mediodorsal thalamus, prefrontal cortex, and amygdala. This hypothesis is attractive since it could explain some characteristic emotional, cognitive, and motor activity in depression, for example, guilty ruminations, motoric slowing, and recurrent thoughts of death. This clearly is a simplification, since while it could explain some behaviors, it would not explain underactivation of other cognitive functions, such as decreased attention, and in some studies, impairment in executive control (Degl'Innocenti et al 1998). Thus, lesions within the LCSPT structures themselves or in the interconnections among them could result in malfunction predisposing to

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depression, but it is difficult to explain all of the manifestations of depression.

Brain Structural Changes in Bipolar Disorder

Table 1 summarizes the studies reporting structural changes in primary bipolar disorder.

Structural abnormalities reported in bipolar disorder have included diffuse gray matter tissue loss, enlarged ventricles, increased numbers of T2-signal hyperintensities (T2H), and regional tissue loss in basal ganglia, lateral and mesial temporal structures, and cortical regions. Structural changes in the same neuroanatomical circuit (LCSPT) as in major depression have been found in studies in bipolar subjects, but these changes have been less consistent and have involved increases in some structure volumes as well as decreases.

Magnetic resonance imaging (MRI) studies have not generally found diffuse cortical gray matter volume loss in bipolar disorder (Dupont et al 1995; Harvey et al 1994; Pearlson et al 1997; Schlaepfer et al 1994; Zipursky et al 1997); however, a recent study in geriatric bipolar disorder (Young et al 1999) found increased cortical sulcal widening which was related to age of illness onset. Enlarged cortical sulci were also found in a study in middle-aged bipolar subjects (Lim et al 1999). The same study found generalized decreased cortical gray volume in bipolar subjects, intermediate between control and schizophrenia values. Lateral ventricle findings in bipolar disorder have included increases (Swayze et al 1990; Figiel et al 1991; Strakowski et al 1993) and no difference from control (Harvey et al 1994; McDonald et al 1991). A recent study (Strakowski et al 2002) found significant lateral ventricular enlargement that was associated with multiple episodes of mania.

Structural abnormalities in regional volumes have also been identified. Studies have found temporal lobe volume changes in bipolar subjects. These include bilateral temporal lobe reductions (Altshuler et al 1991); loss of normal asymmetry (Swayze et al 1992); increased left temporal lobe volume (Harvey et al 1994); and no differences (Johnstone et al 1989). Strakowski et al (1999) found overall differences in the LCSPT circuit. Volumetric changes identified were both increases (amygdala, striatum) and decreases (prefrontal cortex, hippocampus). Results of amygdala volume determination in bipolar disorder have found larger (Altshuler et al 1998), smaller (Pearlson et al 1997), or equal (Swayze et al 1992) volumes. As stated below, amygdala volumes are difficult to compare between studies.

Small but significant prefrontal cortex volume decreases (Coffman et al 1990; Schlaepfer et al 1994; Strakowski et al 1993) have been seen in bipolar disorder and are supported by postmortem findings of decreased glia in prefrontal cortex in bipolar subjects (Ongur et al 1998). Mixed results were obtained in studies of the basal ganglia, including larger caudate volumes in males (Aylward et al 1994) and larger globus pallidus volumes but not striatal volumes (Strakowski et al 1999). Some MRI studies did not find any differences in bipolar subjects compared to control subjects in caudate, putamen, or lenticular nuclei (Dupont et al 1995; Strakowski et al 1993; Swayze et al 1992). Results have also been mixed for hippocampus (Altshuler et al 1998; Hauser et al 1989; Swayze et al 1992) and thalamus (Dupont et al 1995; Strakowski et al 1993). In analyzing reports of volume loss in bipolar patients, it may be critical to know the cumulative medication history, especially regarding lithium. Chronic lithium treatment has been reported to be neuroprotective and may prevent volume loss in treated patients (Manji et al 2000).

There is a complex relationship between bipolar disorder and increased hyperintensities seen on T2-weighted MRI scans (T2H). Hyperintensities have been associated with hypertension; however, T2H also are increased in asymptomatic elderly. Fujikawa et al (1995) found that compared with age- and gender-matched subjects who had developed affective illness before age 50, manic patients who developed bipolar disorder after age 50 had a significantly higher incidence of T2H, comparable to the incidence in subjects with late-onset depression. Similar results were obtained by McDonald et al (1991), who found a higher incidence of subcortical hyperintensities in late-onset bipolar disorder. Strakowski et al (1993) found a rate of subcortical hyperintensities 1.7 times higher in younger subjects with new-onset bipolar illness than in control subjects, but this was not significant. Aylward et al (1994) also found a higher rate of hyperintensities in bipolar subjects; however, the bipolar subjects were 12 years older on average. In contrast, Figiel et al (1991) and Dupont et al (1990) found higher rates of hyperintensities in age-matched comparisons and one study did not find differences in T2H between bipolar subjects and control subjects (Brown et al 1992).

From Comorbid Disease to Depression

Unusually high rates of depression are found in neurologic illnesses associated with both cortical and subcortical atrophy. These include Huntington's disease (Folstein et al 1983), poststroke syndromes (Starkstein and Robinson 1989), dementia of the Alzheimer's type (Burns et al 1990), epilepsy (Sawrie et al 2001), and Parkinson's disease (Cummings 1992). These illnesses involve damage to brain structures critical in emotional functioning,

Table 1. Brain Structural Changes Reported in Major Depression and Bipolar Disorder

Author	Brain Region	Sample (Number and Diagnosis)	Age (Mean ± SD)	Methods and Resolution	Findings
Frontal cortex					
Coffman et al 1990	Frontal lobe	52 NC	28.8 ± 7.2	1.5 T	Decrease in frontal cortex volume in bipolar group
		30 MDD-bipolar (with psychotic features)	32.0 ± 6.2	3 mm	
Krishnan et al 1992	Frontal lobe	50 NC	49.3 ± 18	1.5 T	Bifrontal distances smaller
		50 MDD	48.3 ± 17	5 mm	Bifrontal brain widths smaller
Coffey et al 1993	Frontal lobe	76 NC	62.4 ± 16.4	1.5 T	Smaller frontal lobe volumes in major depression
		48 MDD	61.6 ± 15.9	5 mm	
		44 unipolar; 4 bipolar ECT referred		5.2 interval	
Bell-McGinty et al 2002	Frontal lobe	47 NC	66.9 ± 7.3	1.5 T	Smaller bilateral middle frontal gyrus gray matter volume in MDD
		30 MDD	69.3 ± 5.7	8 mm	Smaller left anterior cingulate and right middle frontal gyrus white matter volume
Sax et al 1999	Prefrontal cortex	12 NC	27 ± 5	1.5 T	Smaller PFC volume in bipolar group
		17 MDD-bipolar (hospitalized)	27 ± 6	1 mm	
Strakowski et al 1999	Prefrontal cortex	22 NC	28 ± 6	1.5 T	No significant difference
		24 MDD-bipolar	27 ± 6	1 mm	
Strakowski et al 1993	Cingulate gyrus	16 NC	30.9 ± 7.3	1.5 T	No significant difference
		17 MDD-bipolar (first episode)	28.4 ± 6.8	6 mm	
Drevets et al 1997	Subgenual prefrontal cortex	33 NC	36.2 ± 8.9	1.5 T	Smaller subgenual prefrontal cortex volumes in major depression
		13 MDD	33.6 ± 10.0	1 mm	
		10 MDD, remitted	30.1 ± 7.8		
Brambilla et al 2002	Subgenual prefrontal cortex	38 NC	37.0 ± 10.0	1.5 T	No significant difference in the SGPFC in either familial or non-familial unipolar or bipolar disorder
		18 MDD-unipolar	42.0 ± 10.0	1.5 mm	
		27 MDD-bipolar	35.0 ± 11.0		
Temporal cortex					
Hauser et al 1989	Temporal lobe	21 NC	33.8 ± 6.2	.5 T	Smaller bilateral temporal lobe volumes in bipolar
		17 MDD-bipolar	40.5 ± 12.8	10 mm	
Johnstone et al 1989	Temporal lobe	21 NC	36.0 ± 6.1	.15 T	No significant difference
		20 MDD-bipolar	38.9 ± 8.2	8 mm	
		21 Schizophrenic	36.2 ± 6.4		
Altshuler et al 1991	Temporal lobe	10 NC	37.0 ± 12	.5 T	Smaller bilateral temporal lobe volumes in bipolar
		10 MDD-bipolar	39.8 ± 9	10 mm	
Harvey et al 1994	Temporal lobe	34 NC	31.6	.5 T	Increase in left temporal lobe volume in bipolar group
		26 MDD-bipolar	35.6	5 mm	
		48 Schizophrenic	31.1		
Pearlson et al 1997	Temporal lobe	60 NC	31.6 ± 8.0	1.5 T	No significant difference in bipolar group
		27 MDD-bipolar	34.9 ± 8.6	3 mm	
		46 Schizophrenic	31.8 ± 7.8		
Pearlson et al 1997	Superior temporal gyrus	60 NC	31.6 ± 8.0	1.5 T	Larger STG in the bipolar group
		27 MDD-bipolar	34.9 ± 8.6	3 mm	
		46 Schizophrenic	31.8 ± 7.8		
Hippocampus					
Sheline et al 1996	Hippocampus	10 NC	68.0 ± 9.5	1.5 T	Decreased hippocampal gray matter volume in major depression
		10 MDD, remitted	68.5 ± 10.4	.5 mm	
Altshuler et al 1998	Hippocampus	18 NC	53.4 ± 11.1	1.5 T	No significant difference in the bipolar group
		12 MDD-bipolar	50.8 ± 13.3	1.4 mm	
		14 Schizophrenic	48.9 ± 7.0		
Shah et al 1998	Hippocampus	20 NC	49.3 ± 11.8	1.0 T	Decreased hippocampal volume in treatment-resistant depression
		20 MDD	47.7 ± 9.9	2 mm	
		20 TRD	48.9 ± 9.8		
Sax et al 1999	Hippocampus	12 NC	27 ± 5	1.5 T	No significant difference
		17 MDD-bipolar (hospitalized)	27 ± 6	1 mm	
Sheline et al 1999	Hippocampus	24 NC	52.8 ± 17.8	1.5 T	Decreased hippocampal volume in major depression
		24 MDD, remitted	52.8 ± 18.4	.5 mm	

Table 1. Continued

Author	Brain Region	Sample (Number and Diagnosis)	Age (Mean ± SD)	Methods and Resolution	Findings
Strakowski et al 1999	Hippocampus	22 NC 24 MDD-bipolar	28 ± 6 27 ± 6	1.5 T 1 mm	No significant difference
Bremner et al 2000	Hippocampus	16 NC 16 MDD (1 panic disorder)	45.0 ± 10.0 43.0 ± 8.0	1.5 T 3 mm	Decreased hippocampal volume in major depression
Mervaala et al 2000	Hippocampus	17 NC 34 MDD (6 bipolar, 28 monopolar)	42.1 ± 14.6 42.2 ± 12.2	1.5 T 3 mm	No significant difference
Vakili et al 2000	Hippocampus	20 NC 38 MDD	40.3 ± 10.4 38.5 ± 10.0	1.5 T 3 mm	No significant difference
Frodl et al 2002a	Hippocampus	30 NC 30 MDD (first episode)	40.6 ± 12.5 40.3 ± 12.6	1.5 T 1.5 mm	Smaller left hippocampal total and gray matter volume in males Smaller bilateral hippocampal white matter volume in all subjects
MacQueen et al 2003	Hippocampus	20 NC 20 MDD (first episode) 17 NC 17 MDD (multi episode)	28.4 ± 11.5 28.4 ± 11.8 36.2 ± 11.9 35.9 ± 11.1	1.5 T 1.2 mm	No significant difference in the first episode group Smaller bilateral hippocampal volume in those with multiple episodes of major depression
Pearlson et al 1997	Hippocampus/ entorhinal cortex	60 NC 27 MDD-bipolar 46 Schizophrenic	31.6 ± 8.0 34.9 ± 8.6 31.8 ± 7.8	1.5 T 3 mm	No significant difference in bipolar group
Bell-McGinty et al 2002	Hippocampus/ entorhinal cortex	47 NC 30 MDD	66.9 ± 7.3 69.3 ± 5.7	1.5 T 8 mm	Smaller right hippocampal gray matter volume Hippocampus/entorhinal cortex is inversely associated with the number of years since the first lifetime depressive episode
Amygdala					
Pearlson et al 1997	Amygdala	60 NC 27 MDD-bipolar 46 Schizophrenic	31.6 ± 8.0 34.9 ± 8.6 31.8 ± 7.8	1.5 T 3 mm	Smaller left amygdala volume in the bipolar group
Sheline et al 1998	Amygdala	20 NC 20 MDD, remitted	53.8 ± 17.7 54.1 ± 18.1	1.5 T .5 mm	Decreased amygdala core nuclei volume in major depression
Altshuler et al 1998	Amygdala	18 NC 12 MDD-bipolar 14 Schizophrenic	53.4 ± 11.1 50.8 ± 13.3 48.9 ± 7.0	1.5 T 1.4 mm	Increased amygdala volume in bipolar group
Strakowski et al 1999	Amygdala	22 NC 24 MDD-bipolar	28 ± 6 27 ± 6	1.5 T 1 mm	Increased amygdala volume in the bipolar group
Tebartz van Elst et al 1999	Amygdala	20 NC 38 TLE 12 TLE with Dysthymia	36.5 32 30	1.5 T 1.5 mm	Increased amygdala volume in both the TLE and TLE with dysthymia groups
Bremner et al 2000	Amygdala	16 NC 16 MDD (1 panic disorder)	45.0 ± 10.0 43.0 ± 8.0	1.5 T 3 mm	Increased right amygdala volume in major depression
Mervaala et al 2000	Amygdala	17 NC 34 MDD (6 bipolar, 28 monopolar)	42.1 ± 14.6 42.2 ± 12.2	1.5 T 3 mm	Significant asymmetry in amygdalar volume (right smaller than left)
Tebartz van Elst et al 2000	Amygdala	20 NC 47 TLE 17 TLE with Dysthymia	36 33.3 32.8	1.5 T 1.5 mm	Increased amygdala volume in dysthymia females but not males and in the TLE with dysthymia group as a whole
Frodl et al 2002b	Amygdala	30 NC 30 MDD (hospitalized with first episode)	40.6 ± 12.5 40.3 ± 12.6	1.5 T 1.5 mm	Increased bilateral amygdala volume in the depressed group

Table 1. Continued

Author	Brain Region	Sample (Number and Diagnosis)	Age (Mean ± SD)	Methods and Resolution	Findings
Hippocampus/Amygdala Complex					
Swayze et al 1992	Amygdala/ hippocampus complex	55 Schizophrenic 48 MDD-bipolar 47 NC	32.3 ± 35.4 33.4 ± 34.6	.5 T 1-cm thick slices 8 cuts	No significant difference
Axelson et al 1993	Amygdala/ hippocampus complex	30 NC 19 MDD	46.7 ± 20.4 56.6 ± 19.1	1.5 T 5 mm	No significant difference
Pantel et al 1997	Amygdala/ hippocampus complex	13 NC 19 MDD 27 AD	68.2 ± 5.3 72.4 ± 8.8 71.9 ± 8.0	1.5 T 1.25 mm	No significant difference
Ashtari et al 1999	Amygdala/ hippocampus complex	46 NC 40 MDD	71.4 ± .3 74.3 ± 6.0	1.0 T 3.1 mm	No significant difference
Hauser et al 1989	Hippocampus complex	21 NC 17 MDD-bipolar	33.8 ± 6.2 40.5 ± 12.8	.5 T 10 mm	No significant difference
Basal Ganglia					
Krishnan et al 1992	Caudate	50 NC 50 MDD	49.3 ± 18 48.3 ± 17	1.5 T 5 mm	Decreased caudate volumes in major depression
Strakowski et al 1993	Caudate	16 NC 17 MDD-bipolar (first episode)	30.9 ± 7.3 28.4 ± 6.8	1.5 T 6 mm	No significant difference
Greenwald et al 1997	Caudate	30 NC 36 MDD	72.8 ± 6.6 75.9 ± 6.7	1.0 T 3 mm	Decreased left caudate volume in major depression
Sax et al 1999	Caudate	12 NC 17 MDD-bipolar (hospitalized)	27 ± 5 27 ± 6	1.5 T 1 mm	No significant difference
Husain et al 1991	Putamen	44 NC 41 MDD	56.4 ± 19.2 55.3 ± 18.8	1.5 T 5 mm (2 patients with 7 mm)	Decreased putamen volume in major depression
Strakowski et al 2002	Putamen	32 NC 18 MDD-bipolar (first episode) 17 MDD-bipolar (multi episode)	24 ± 6 22 ± 6 25 ± 6	1.5 T 1.5 mm	Increase in putamen volume in the first episode bipolar group
Dupont et al 1995	Caudate and lenticular nucleus	26 NC 36 MDD-bipolar 30 MDD-unipolar	39.1 ± 9.4 36.6 ± 10.8 38.6 ± 10.6	1.5 T 5 mm - 2.5 mm gap	No significant difference
Lenze and Sheline 1999	Caudate and putamen	24 NC 24 MDD-remitted	52.8 ± 17.8 52.8 ± 18.4	1.5 T .5 mm	No significant difference
Strakowski et al 1999	Caudate and putamen	22 NC 24 MDD-bipolar	28 ± 6 27 ± 6	1.5 T 1 mm	Trend toward larger striatum volume in the bipolar group
Strakowski et al 1999	Globus pallidus	22 NC 24 MDD-bipolar	28 ± 6 27 ± 6	1.5 T 1 mm	Trend toward larger globus pallidus volume in the bipolar group
Thalamus/Pituitary					
Strakowski et al 1993	Thalamus	16 NC 17 MDD-bipolar (first episode)	30.9 ± 7.3 28.4 ± 6.8	1.5 T 6 mm	No significant difference
Sax et al 1999	Thalamus	12 NC 17 MDD-bipolar (hospitalized)	27 ± 5 27 ± 6	1.5 T 1 mm	No significant difference
Strakowski et al 1999	Thalamus	22 NC 24 MDD-bipolar	28 ± 6 27 ± 6	1.5 T 1 mm	Trend toward larger thalamus volume in the bipolar group
Axelson et al 1992	Pituitary	21 MDD (1 bipolar; 1 adjustment disorder; 1 multi-infarct dementia; 1 schizophrenic affective)	47.9 ± 18.4 39.6 ± 13.2	1.0 T 3 mm	Increase in pituitary volume in major depression
Ventricles/Sulci					
Johnstone et al 1989	Lateral ventricle	21 NC 20 MDD-bipolar 21 Schizophrenic	36.0 ± 6.1 38.9 ± 8.2 36.2 ± 6.4	.15 T 8 mm	No significant difference
Swayze et al 1990	Lateral ventricle	47 NC 48 MDD-bipolar 54 Schizophrenic	34.8 34.0 33.8	.5 T 1 cm	Larger lateral ventricle in bipolar men but not women
McDonald et al 1991	Lateral ventricle	12 NC 12 MDD-bipolar	68.7 ± 7 68.3 ± 7	1.5 T 5 mm	No significant difference

Table 1. Continued

Author	Brain Region	Sample (Number and Diagnosis)	Age (Mean ± SD)	Methods and Resolution	Findings
Harvey et al 1994	Lateral ventricle	34 NC	31.6	.5 T	No significant difference
		26 MDD-bipolar	35.6	5 mm	
		48 Schizophrenic	31.1		
Zipursky et al 1997	Lateral ventricle	17 NC	29.9 ± 6.6	1.5 T	Larger lateral ventricle volume in bipolar group
		23 Schizophrenic	33.7 ± 7.9	5 mm	
		14 MDD-bipolar	35.9 ± 7.2		
Strakowski et al 1993	Lateral ventricle	16 NC	30.9 ± 7.3	1.5 T	Trend toward larger lateral ventricle volume in bipolar group
		17 MDD-bipolar (first episode)	28.4 ± 6.8	6 mm	
Lim et al 1999	Lateral ventricle	16 NC	44.3 ± 6.8	1.5 T	Larger lateral ventricle volume in bipolar group
		9 MDD-bipolar	44.0 ± 9.4	5 mm	
		9 Schizophrenic	44.4 ± 9.2		
Young et al 1999	Lateral ventricle	18 NC	74.4 ± 10.1	Non-contrast	Increased lateral ventricle in bipolar group
		30 MDD-bipolar	71.4 ± 7.7	CT	
Strakowski et al 2002	Lateral ventricle	32 NC	24 ± 6	1.5 T	Increase in lateral ventricle volume with repeated manic episodes
		18 MDD-bipolar (first episode)	22 ± 6	1.5 mm	
		17 MDD-bipolar (multi episode)	25 ± 6		
Strakowski et al 1993	Third ventricle	16 NC	30.9 ± 7.3	1.5 T	Larger third ventricle volume in the bipolar group
		17 MDD-bipolar (first episode)	28.4 ± 6.8	6 mm	
Pearlson et al 1997	Third ventricle	60 NC	31.6 ± 8.0	1.5 T	Larger third ventricle volume in the bipolar group
		27 MDD-bipolar	34.9 ± 8.6	3 mm	
		46 Schizophrenic	31.8 ± 7.8		
Lim et al 1999	Cortical sulci	16 NC	44.3 ± 6.8	1.5 T	Increased cortical sulci by determination of increased CSF in bipolar group
		9 MDD-bipolar	44.0 ± 9.4	5 mm	
		9 Schizophrenic	44.4 ± 9.2		
Young et al 1999	Cortical sulci	18 NC	74.4 ± 10.1	Non-contrast	Greater cortical sulci widening in the bipolar group
		30 MDD-bipolar	71.4 ± 7.7	CT	
Cortical Gray Matter					
Strakowski et at 1993	Cortical matter	16 NC	30.9 ± 7.3	1.5 T	Trend toward less white matter and increased gray matter in the bipolar group
		17 MDD-bipolar (first episode)	28.4 ± 6.8	6 mm	
Harvey et al 1994	Cortical matter	34 NC	31.6	.5 T	No significant difference in cortical gray matter volume in the bipolar group
		26 MDD-bipolar	35.6	5 mm	
		48 Schizophrenic	31.1		
Schlaepfer et al 1994	Cortical matter	60 NC	31.6 ± 8.0	1.5 T	No significant difference in cortical gray matter volume in the bipolar group
		46 Schizophrenic	31.8 ± 7.8	5 mm	
		27 MDD-bipolar	34.9 ± 8.6		
Zipursky et al 1997	Cortical matter	17 NC	29.9 ± 6.6	1.5 T	No significant difference in cortical gray matter in bipolar group
		23 Schizophrenic	33.7 ± 7.9	5 mm	
		14 MDD-bipolar	35.9 ± 7.2		
Lim et al 1999	Cortical matter	16 NC	44.3 ± 6.8	1.5 T	Less cortical gray matter in bipolar group
		9 MDD-bipolar	44.0 ± 9.4	5 mm	
		9 Schizophrenic	44.4 ± 9.2		

NC, normal control; MDD, major depressive disorder; ECT, electroconvulsive therapy; T, Tesla; TRD, treatment resistant depression; AD, Alzheimer's disease; PFC, prefrontal cortex; SGPFC, subgenual prefrontal cortex; STG, superior temporal gyrus; TLE, temporal lobe epilepsy, CSF, cerebrospinal fluid; CT, computed tomography.

namely frontal cortex, hippocampus, thalamus, amygdala, and basal ganglia. Further, these same brain structures are involved in more classical or early-onset major depression. In temporal lobe epilepsy, not only is there hippocampal and amygdala sclerosis from the epilepsy itself, but postsurgical volume loss associated with depression has been reported in connected structures, the medial-dorsal thalamus, and putamen (Parashos et al 1993). Different subtypes of Parkinson's disease have neuronal loss in a variety of subcortical brain regions, with some evidence for an association with clinical syndromes in postmortem studies (Jellinger 1999). Decreased volumes of caudate and putamen have been demonstrated in vivo in Parkinson's disease (Lisanby et al 1993). Further, in depressed compared with nondepressed Parkinson's patients, fluorodeoxyglucose metabolism studies using positron-emission

tomography (PET) have demonstrated selective hypometabolism in the caudate and orbital-inferior frontal lobe (Mayberg et al 1990). In groundbreaking work, Robinson et al (1983) and Lipsey et al (1983) reported that ischemic lesions located in the anterior frontal cortex were associated with more severe depression. Subsequently, inconsistent results have been reported on the relationship between infarct site and depression after stroke, with systematic review of the numerous studies not supporting the hypothesis that stroke lesion location predicts depression (Carson et al 2000). A recent study in a large, well-defined series of patients with ischemic stroke, however, found a strong correlation between lesions affecting the prefrontosubcortical circuits, particularly on the left, and subsequent depression (Vataja et al 2001). Patients with dementia of the Alzheimer's type have been shown in postmortem studies to have profound atrophy of the hippocampus and frontal and parietal cortex, and atrophy in each of these areas is associated with a specific neuropsychological profile (Kanne et al 1998). Studies have found that in individuals with cognitive impairment, baseline depression was associated with a threefold increased risk of incident dementia. In vivo MRI studies (Steffens et al 2002) have shown that small left hippocampal size on neuroimaging predicts later dementia. In summary, neurologic diseases have been associated with structural changes in the LCSPT tract.

In addition to an association of specific neurologic illnesses with increased rates of depression, late-life depression itself is associated with an increased prevalence of structural brain changes due at least in part to the increased prevalence of comorbid illness with age. Compared with EORD, depression onset in late age is characterized by lower familial frequency of affective disorders (Baron et al 1981), greater medical morbidity and mortality (Jacoby et al 1981), and higher rates of neuroradiological abnormalities, particularly white-matter hyperintensities (Coffey et al 1988; Figiel et al 1991). Some studies have found late-onset depression to be associated with higher rates of neuropsychological impairment and greater treatment refractoriness (Alexopoulos et al 2002; Simpson et al 1998).

Magnetic resonance imaging and computed tomography (CT) 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). In addition to neurologic illnesses, conditions which have been associated with brain atrophy include hypertension (Kobayashi et al 1991), Cushing's disease (Starkman et al 1992), diabetes (Aronson 1973), and alcohol abuse (Charness 1993). Any condition which produces neuronal ischemia or neurotoxicity can potentially contribute to brain atrophy. Some studies do not find evidence for generalized atrophy in addition to volume loss in structures of the LCSPT circuit. For example, Kumar et al (1998) found prefrontal lobe volume loss in late-onset depression in the absence of generalized atrophy, suggesting that as in early-onset depression, some subjects with late-onset depression may also have focal volume loss. It is not known whether this focal volume loss occurs by the same etiologic mechanisms as EORD.

Another phenomenon in late-life depression is the presence of hyperintensities seen on T2-weighted scans (T2H). Increased numbers of T2H (Coffey et al 1990; Howard et al 1993; Krishnan et al 1993; Lesser et al 1991; Rabins et al 1991) is a well-replicated finding in elderly depressed subjects. Younger subjects with depression have also been found to have increased T2H (Coffey et al 1993; Hickie et al 1995), although negative findings have also been reported with younger groups (Dupont et al 1995; Guze and Szuba 1992). Etiologic mechanisms for T2H are unknown; however, it is important to note that T2H also occur at rates of up to 60% in healthy elderly (Fazekas et al 1991), in whom their significance is also unknown (Mirsen et al 1991). A higher rate of "silent" cerebral infarctions (T2H) in late-onset compared to early-onset major depressive disorder (MDD) was found by Fujikawa et al (1993, 1994). Older age, vascular risk factors, neuropsychological impairment, and late age of onset (Krishnan et al 1988; Coffey et al 1993; Simpson et al 1998) are the clinical correlates of MRI-defined T2H in late-life depression. The concept of "vascular depression" with increased cardiovascular disease (CVD) risk factors and increased T2H has been proposed (Krishnan et al 1997). Interestingly, in late-life depression, T2H have been found to cluster in the frontal cortex (Macfall et al 2001), as well as in subcortical areas.

While this section has summarized the evidence for structural brain changes leading to depression, there are important qualifications. Impairment of LCSPT structure in patients with diseases causing structural impairment and even in healthy persons with small structures does not always lead to depression. Thus, a direct correspondence between structural impairment in LCSPT structures and depression does not exist. Rather, it appears that a subset of people with such structural impairment have increased vulnerability to depression and that when depression occurs it may further contribute to additional damage.

From Depression to Structural Brain Changes

Table 1 summarizes the studies reporting structural changes in primary unipolar depression.

Frontal Cortex

Volume reductions in frontal cortex ranging from 7% overall reduction in frontal lobe volume in major depression (Coffey et al 1992) to 48% in the subgenual prefrontal cortex (Drevets et al 1997) have been reported. Significant differences from control subjects were reported in several prefrontal cortical areas in a postmortem study of prefrontal cortex in major depression (Rajkowska et al 1999). Abnormalities included rostral orbitofrontal cortex decreases in cortical thickness, neuronal size decrease, and loss of glial cells in layers II to IV. Caudal orbitofrontal cortex abnormalities were reductions in glial cells in layers V and VI and decreases in neuronal sizes. Reductions in glial and neuronal cells throughout all layers, as well as reduction in cell size, were reported in dorsolateral prefrontal cortex. Subgenual prefrontal cortex glial cell loss has also been reported in major depression (Ongur et al 1998). Some of the MRI volumetric findings in frontal cortex could be accounted for by neuropathological changes such as these. The prefrontal cortex is particularly important as a target of monoamine projections and abnormalities in monoamine receptors, transporters, and second messenger systems (Arango et al 1995; Biver et al 1997; Duman 1998; Mintun et al 2000; Price 1999) are reported to occur in major depression. Another possibility is that overactivation in one part of the interconnected LCSPT neuroanatomical circuit may lead to overexcitation in the other components, resulting in excitotoxic damage. The orbitomedial prefrontal cortex has high concentrations of glucocorticoid receptors, potentially rendering it vulnerable to stress-mediated damage (see below).

Hippocampus

Several studies have examined hippocampal volume in depression. Some (Bell-McGinty et al 2002; Bremner et al 2000; MacQueen et al 2003; Shah et al 1998; Sheline et al 1996, 1999) but not all (Ashtari et al 1999; Axelson et al 1993; Mervaala et al 2000; Swayze et al 1992; Vakili et al 2000) found significant reductions in hippocampal volumes in depression. The volume loss appears to have functional significance with an association between acute depression and abnormalities of declarative memory (Burt et al 1995) and recollection memory (MacQueen et al 2003), as well as an association between depression in remission and lower scores on tests of verbal memory (Sheline et al 1999). In one study (Shah et al 1998), hippocampal atrophy was found in patients with chronic depression but not in patients with remitted depression. Vakili et al (2000) also observed correlations between depression severity and hippocampal volumes, although no group differences between depressed and control subjects. In one study (Frodl et al 2002a), white matter changes were noted but no overall differences in hippocampal volume. In most of these studies that assessed depression severity in unipolar subjects and used high-resolution MRI techniques, depression was associated with hippocampal volume loss, ranging from 8% to 19%. Studies which only measured the hippocampus/amygdala complex found no differences. A recent postmortem study (Bowley et al 2002) has found glial cell loss in the dentate gyrus of the hippocampus as well as in the amygdala in major depression. In addition, a recent study has found increased neuronal and glial cell packing density (Stockmeier et al, unpublished data), suggesting a decrease in the hippocampal neuropil in MDD.

Amygdala

Inconsistent results have been found in amygdala volumes in major depression. Studies have identified an increase in volume in the right amygdala (Bremner et al 2000), in bilateral amygdala in first episode subjects (Frodl et al 2002b), loss of normal asymmetry (Mervaala et al 2000), or reduction in the bilateral core nuclei (Sheline et al 1998). The amygdala is a difficult structure to measure, since in many areas the cortical amygdala merges with surrounding cortex, and specific boundaries selected varied greatly in different studies.

Basal Ganglia

Many studies have found decreased volumes of basal ganglia structures in major depression, especially in late-onset depression (Greenwald et al 1997; Husain et al 1991; Krishnan et al 1992; Steffens and Krishnan 1998), as discussed above. Negative findings were reported in caudate and putamen in depressed subjects who were otherwise physically healthy (Lenze and Sheline 1999), a criterion not clearly present in other studies.

Potential Mechanisms for Volume Loss in Recurrent Depression

Approximately half of depressive episodes are associated with elevated cortisol levels. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction can produce repeated episodes of hypercortisolemia in depression. Volume studies do not routinely include measures of cortisol and cannot determine past episodes of hypercortisolemia. In addition to elevated cortisol levels, several different mechanisms could potentially explain volume loss, including neuronal loss through exposure to repeated episodes of hypercortisolemia, stress-induced reduction in neurotrophic factors, stress-induced reduction in neurogenesis, and glial cell loss, resulting in increased vulnerability to glutamate

neurotoxicity. Glucocorticoid (GC)-mediated neurotoxicity (Sapolsky 2000) with repeated hypercortisolemic episodes of depression giving rise to atrophy of affected structures is a mechanism that could potentially account for hippocampal, amygdala, and prefrontal cortex volume loss, all areas which have high concentrations of GC receptors; however, it is also well known that the hippocampus has structural plasticity, driven by excitatory amino acids and facilitated by glucocorticoids. In animal studies (Watanabe et al 1992), hippocampal apical dendrites shortened by a single GC exposure or restraint stress returned to normal after 3 weeks. In Cushing's disease, following successful surgery and a return to normal for GC levels, previously smaller hippocampal volumes returned to normal (Starkman et al 1992; Bourdeau et al 2002). Thus, up to a point, plasticity may be at least partially reversible. Early life stress may produce a permanent hypersensitivity to stress, with the production of ongoing HPA axis dysregulation, particularly in subjects who develop depression (Heim et al 2000). With repeated episodes, plasticity may give way to permanent damage. Inverse correlations between the total amount of time patients have been depressed and hippocampal volume found in some studies (Bell-McGinty et al 2002; MacQueen et al 2003; Sheline et al 1996, 1999) but not all (Bremner et al 2000) support recurrent depressive episodes having an antecedent or causal relationship. In addition, a study by Lupien et al (1998) demonstrated a correlation between higher cortisol levels measured longitudinally and greater hippocampal volume loss in normal human aging. A study of first episode patients identified memory impairment on neuropsychological testing but no hippocampal volume loss, whereas multiple episode patients in the same study had both memory impairment and volume loss (MacQueen et al 2003). Thus, while neurotoxic damage may occur, plasticity would permit return of function if the right intervention were used in time.

Excitatory connections between the amygdala and hippocampus (White and Price 1993) raise the possibility that damage in one structure could produce damage in the connected structure. Also, interconnections between prefrontal cortex and 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). Thus, loss of glial cells could increase vulnerability to neurotoxic damage, supporting the idea that glutamate neurotoxicity may be involved in the volume loss in the limbic-cortical-striatal-pallidal circuit.

Either directly or indirectly, glial cell loss is another potential mechanism for producing volume loss. Gray matter atrophy has been reported in the prefrontal cortex in an area ventral to the genu of the corpus callosum (Drevets et al 1997), an area associated in postmortem studies with glial cell loss (Ongur et al 1998). Glial cell loss has been found in two different areas of prefrontal cortex (Rajkowska et al 1999), as well as in the amygdala and the hippocampus (Bowley et al 2002) in postmortem studies of major depression.

Stress-induced inhibition of neurogenesis (Gould et al 1997) may also explain depression-related volume loss. Psychosocial stress has been shown to suppress neurogenesis in the tree shrew (Gould et al 1997). Corticosterone treatment in adult rats also produced suppression of neurogenesis, which was reversed by removal of the adrenal gland (Cameron and Gould 1994). It is also possible (Gould et al 1999) that neurogenesis may occur in the frontal cortex in addition to the hippocampus and subventricular zone.

Depression—Cause or Effect of Structural Brain Abnormalities?

Whether depression is the cause or result of brain structural changes is not known. As discussed above and represented in Figure 1, there is evidence that medical illnesses such as Parkinson's disease, Alzheimer's disease, and stroke produce brain changes that are associated with the onset of depression. There is also evidence that stress produces neuronal damage and structural changes in animal models and potentially in humans, although to date evidence in humans derives from studies of posttraumatic stress disorder (PTSD). Finally, depression per se may produce structural brain changes, but this is an unproven hypothesis. There are several potential mediators, including genetic predisposition, stress, and illness. Thus, it may be that depression acts through these other mechanisms rather than having an independent effect on brain structure. Alternatively, depression may have an independent effect in producing changes in brain structure (represented in Figure 1 by the dotted arrow). The converse question, how brain structural changes might produce depression, is also highly speculative. Since the structures in the LCSPT circuit all are involved in emotional regulation, damage to any portion of this circuit could potentially produce depression, either directly by neuronal damage or indirectly by changes in neurotransmitter balance (again, represented by a dotted arrow). Why the symptoms produced would be the same, with disturbance in mood, sleep, appetite, energy, etc. from structural changes in disparate brain regions, is not clear. Nor is it obvious how structural changes would produce episodic disturbances. Finally, not all patients who have such structural changes get depressed.

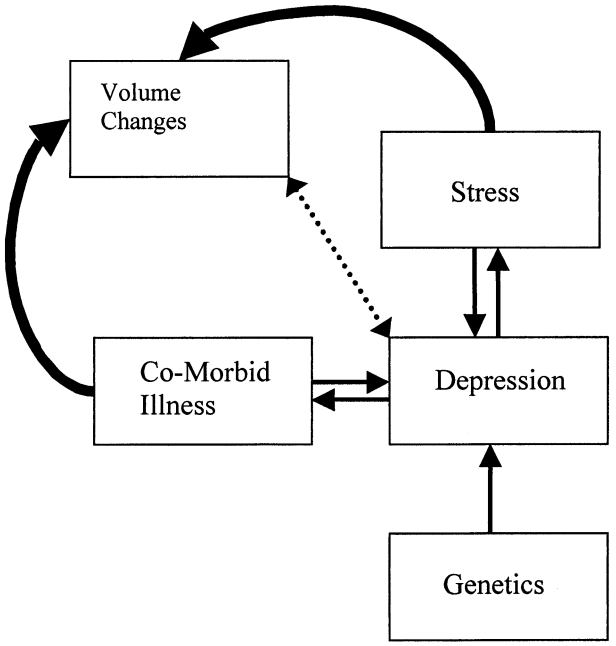

Figure 1. The figure shows hypothesized interactions accounting for some of the brain structural changes that have been reported in depression. It is well established that many comorbid illnesses are associated with structural brain changes (see text). This is represented as a solid arrow. In addition, animal models demonstrate stress-induced brain structural changes (solid arrow). Since depression is associated with both stress and higher prevalence of comorbid illnesses, it is not clear if there is an independent contribution of major depression to brain structural changes (dotted arrow).

Discussion and Future Directions

In summary, volumetric brain studies exhibit inconsistency in measurements from study to study. There are both 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 etiologies. In some studies, subjects were case control matched, whereas in other studies subjects were groupwise matched or the results were corrected statistically for significant covariates. Some, but not all, studies excluded subjects with other physical illness or any current or past drug or alcohol abuse.

Methodological differences can also contribute to study differences and include resolution, sampling, boundary determination, alignment, gray scale inconsistencies, and measurement technique. For example, many studies reporting negative findings for hippocampal volumes had lower resolution, ranging from 3 to 10 mm (Ashtari et al 1999; Vakili et al 2000; Dupont et al 1995; Axelson et al 1993; Swayze et al 1992), compared with .5 to 3 mm (Bremner et al 2000; MacQueen et al 2003; Shah et al 1998; Sheline et al 1996, 1999) for studies reporting significant differences. Sampling is also important; some studies sample every slice, whereas others may sample sparsely. Another issue is boundary determination. Given the complexity of the structures being measured, it is critical to have expert consultation in boundary determination. Some studies have used methodology that does not separate two adjacent structures, as when resolution is not sufficient to see a boundary of demarcation. Other studies have not measured an entire structure but just a subvolume. Scan alignment, lining up all scans to the same standard atlas space, is critical to preventing errors that may occur from rotation if there is no standardization. Likewise, gray scale normalization from scan to scan is important in providing standardized volumetric determination, since differences in gray scale can change the apparent volume from scan to scan. Finally, differences in volume determination methodology—unbiased stereological determination, edge-tracing, or automated computer segmentation—may produce different volume measurements.

The continuing development of automated tissue segmentation methods facilitates determination of gray and white matter volumes using computer generated algorithms and will provide faster and more standardized volume measures. With the development of noninvasive neuronal fiber tracking using water diffusion properties (Conturo et al 1999), it will be possible to obtain increasingly sophisticated reconstruction of fiber trajectories throughout the brain, providing a better understanding of the organization of brain systems. A recent study using diffusion-tensor imaging (DTI) (Alexopoulos et al 2002) has shown that in geriatric depression treatment nonresponse was associated with bilateral white matter disease in regions containing frontostriatal tracts. The combination of structural and functional studies will be important to determine the functional significance of brain structure changes. Combining MRI and functional studies such as PET, single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) will allow more precisely localization of abnormalities in blood flow/metabolism and neurotransmitter receptors. This integrated perspective will allow further development of a structural-functional model of depression. Additional postmortem studies in larger samples with careful clinical screening for comorbidity are also needed to examine ultrastructural correlates of volumetric and functional changes. Further, longitudinal studies will be important to determine the progression of brain structural

changes. It will be important to conduct longitudinal studies in neurologic illnesses alone, neurologic illnesses with depression, and depression alone.

Preclinical studies provide preliminary direction for neuroprotective strategies aimed at preventing stress-induced damage. Findings reported include prevention of stress-induced decreases in brain-derived neurotrophic factor with antidepressants (Nibuya et al 1995, 1996; Vaidya and Duman 1999), prevention of stress-induced excitotoxic injury with phenytoin (Dilantin) (Watanabe et al 1992), prevention of stress-induced decreases in neurogenesis with antidepressants (Czeh et al 2001; Duman and Malberg 1998), and increase in dendritic branching with serotonin reuptake inhibitors (Duman et al 1997). Currently lacking are imaging probes that could directly examine in vivo neurogenesis, BDNF, cyclic-AMP-response-element binding protein (CREB), and other potential targets of antidepressant-induced neuroplasticity. With the development of ligands for these targets, a dramatic increase in understanding of physiologic mechanisms would be possible.

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