

# Structural Changes in the Brain in Depression and Relationship to Symptom Recurrence

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## ABSTRACT

*Depression is an important public health problem affecting about 15% of the general population; however, little is known about possible changes in the brain that might underlie the disorder. Neuroimaging has been a powerful tool to map actual changes in the brain structure of depressed patients that might be directly related to their symptoms of depression. Some imaging studies of brain structure have shown smaller hippocampal volume with the chronicity of depression correlating to a reduction in volume. Although the meaning of these findings is unclear, other studies have shown increased amygdala volume. Studies have found reductions in volume of the frontal cortex, with some studies showing specific reductions in subregions of the frontal cortex, including the orbitofrontal cortex. Findings of an increase in white matter lesions in elderly patients with depression have been replicated and correlated with late-onset depression, as well as impairments in social and cognitive function. These findings point to alterations in a circuit of brain regions hypothesized to include the frontal cortex, hippocampus, amygdala, striatum, and thalamus, that underlie symptoms of depression.*

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## INTRODUCTION

Major depression is an important public health problem; however, we still do not understand the biological causes of depression. This paper will review the evidence that changes in the brain underlie the symptoms of depression, and how chronicity of depression might be related to changes in the brain. The disorder affects about 15% of the population at some time in their lives and is twice as common in women as in men. In the United States, depression is the disorder most likely to be associated with major morbidity. It is clear that patients with a history of depression are more likely to develop depression in the future, and that reducing the number of recurrent episodes of depression could lead to significant savings.

One way to reduce the recurrence of depressive episodes or to prevent the development of initial episodes is to understand the biological mechanisms involved in depression. There is evidence to support the idea that, following an initial episode of depression, there is an increased risk of developing a subsequent episode of depression. One explanation for this finding is that there is a genetic risk for depression. This makes it more likely that someone who has been depressed will be depressed again in the future. Another possibility is that the depressive episode itself will cause changes in the brain or neurobiology that will increase the risk for subsequent episodes of depression.

Over time a working model of the neuroanatomical basis of depression has developed. This includes a circuit involving the hippocampus (it plays a critical role in memory), amygdala (mediating fear responses and emotion), thalamus, caudate, and various subregions of the frontal cortex (involved in cognition, social behavior, and emotional regulation). Understanding structural changes in these regions can help us understand how disruptions in these circuits can lead to symptoms of depression. This paper will review studies of changes in brain structure in depression and the relationship with severity and recurrence of illness.

## STRUCTURAL NEUROIMAGING STUDIES IN LATE-LIFE DEPRESSION

Several studies have looked at changes in brain structure of patients with depression (Table 1).<sup>1</sup> Early studies using computed tomography in patients with bipolar disorder found ventricular enlargement and widening of the cortical sulci.<sup>2,3</sup> More recently, using magnetic resonance imaging (MRI), smaller caudate<sup>4,7</sup> and putamen<sup>8</sup> volumes were found in some studies of patients with unipolar depression, but not others.<sup>9-11</sup> Consistent with increased glucocorticoid release are findings of increased pituitary volume<sup>12</sup> and adrenal gland size<sup>13</sup> in unipolar depression.

Alterations in brain structure have been associated with late-life depression. MRI studies in elderly patients with

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both unipolar and bipolar depression showed subcortical white matter areas of increased signal intensity on T2 weighted images, which may be related to ischemic abnormalities.<sup>10,14-25</sup> Patients with later-onset depression (after age 50 years) have been shown to have more subcortical hyperintensities than patients with an early onset of depression. Greater subcortical hyperintensities were observed in late-onset depression even after controlling for age, sex, and cerebrovascular risk factors.<sup>19,20</sup> Subcortical white matter hyperintensities were also associated with an absence of a family history of depression.<sup>21</sup> The presence of subcortical hyperintensities predicts poor response to treatment. These changes have been associated with deficits in cognition and social function.<sup>18,21-26</sup> It has been hypothesized that these lesions could lead to disruptions of circuits connecting the frontal cortex with other regions such as the thalamus, and that they may underlie symptoms of depression in a select group of elderly patients with depression.<sup>10,15</sup>

**IMAGING THE HIPPOCAMPUS AND AMYGDALA IN DEPRESSION**

The hippocampus has long been of interest in studies of depression based on the aforementioned preclinical studies.<sup>27,28</sup> MRI studies showed smaller right hippocampal volume<sup>29</sup> and temporal lobe volume<sup>30</sup> in bipolar patients, and alterations in hippocampal T1 relaxation time (reflective of changes in water content)<sup>31</sup> with reductions in grey matter in the left temporal lobe<sup>32</sup> in unipolar depression. One MRI study in patients with unipolar depression that specifically concentrated on hippocampal volume found no evidence for reduction in amygdala/hippocampal volume (combined), although there was a correlation between 11PM cortisol levels and volume of left hippocampal/amygdala complex.<sup>33</sup> This negative finding might have been related to increased amygdala size in depression. In another study, elderly patients with depression showed medial temporal lobe atrophy (including the hippocampus) that correlated with cognitive impairments.<sup>7</sup>

More recently, there have been two or more studies specifically quantitating hippocampal volume that showed a

reduction in depression. Sheline and colleagues<sup>34,35</sup> examined hippocampal volume in elderly female patients with treated major depression (n=10, mean age=68 years) and age-, education-, and sex-matched controls (n=10). Depressed patients had an average of 4.5 prior episodes of depression. There was also a correlation between length of illness and hippocampal volume reduction.<sup>34,35</sup>

We studied 16 male and female outpatients with remitted major depression currently treated with antidepressant medication.<sup>11</sup> Depressed patients had an average of three (standard deviation [SD]=4, range=0-10) inpatient hospitalizations, their mean remission from depression was 31 weeks at the time of the study, and they had an average of two prior episodes of depression. Patients were treated with antidepressants including fluoxetine (n=10), paroxetine (n=3), and desipramine (n=3). Comparison subjects consisted of 16 healthy subjects who were matched a priori on a case-by-case basis; the patients were the same sex and handedness, and similar in age, years of education, and years of alcohol use.

We found a 19% smaller volume of left hippocampus in depressed patients versus comparison subjects, which was statistically significant (F=7.78; df=1.30; P=.009), while there was no significant difference in right hippocampal volume between the groups (Table 2, Figure 1, Figure 2). There continued to be significantly smaller left hippocampal volume in depressed patients after controlling for variations in whole brain volume (F=3.98; df=2.29; P<.05) as well as other factors, including age and education. There were no differences in the volumes of the left or right caudate, temporal lobe, frontal lobe, or whole brain. However, there was a pattern of relationship between left hippocampal volume and number of hospitalizations in the depressed patients that was not statistically significant (r=-0.44; P=.15) (the effect size for this relationship was 0.44, indicating that an effect would be shown with 37 subjects).<sup>11</sup> Vakili and colleagues<sup>36</sup> found that female patients with depression who did not respond to selective serotonin reuptake inhibitors (SSRIs) had smaller right hippocampal volume than

**TABLE 1. FINDINGS RELATED TO STRUCTURAL BRAIN ALTERATIONS IN AFFECTIVE DISORDERS**

| Brain Region                             | Supporting References                | Refuting References |
|--|--------------------------------------|---------------------|
| Decreased hippocampal volume             | 7,* 11, 29, 32,* 34, 35, 36,* 37, 38 |                     |
| Decreased temporal lobe volume           | 30†                                  | 39, 40, 52          |
| Increased amygdala volume                | 11, 46, 47, 48*                      | 11                  |
| Increased white matter lesions (elderly) | 1 (review), 10, 14, 15,† 16-25       | N/A                 |
| Decreased caudate volume                 | 6, 7                                 | N/A                 |
| Decreased putamen volume                 | 8                                    | 9-11                |
| Decreased whole frontal volume           | 52-54                                | 9                   |
| Decreased orbitofrontal volume           | 58, 59                               | 11                  |
| Decreased subgenual frontal volume       | 58                                   | N/A                 |
| Increased ventricular volume             | 2, 3, 4,† 5, 83, 82                  | 11<br>N/A           |

N/A=not applicable.  
 \*See text for full explanation.  
 † Also see reference 49.  
 ‡ Primarily bipolar patients.

responders, and men with depression had a negative correlation between depression severity and left hippocampal volume. However, in all patients with depression combined there was not a significant difference from controls.

Some studies in treatment-resistant depression<sup>37</sup> and elderly patients with depression<sup>38</sup> found hippocampal volume reduction, although other studies have not.<sup>39,40</sup> We recently found hippocampal volume reduction in women with childhood abuse and depression (without posttraumatic stress disorder [PTSD]), but not depression without a history of childhood trauma (Vythilingam, et al, unpublished data, December 2001). These findings, in conjunction with findings of hippocampal volume reduction in PTSD,<sup>41-45</sup> suggest that not all patients with depression may have hippocampal volume reductions. Perhaps specific factors, including a history of traumatic stress as well as chronicity and recurrence of depression, could be required for the finding.

One unexpected finding has been an increase in amygdala volume in depression. We found a significant increase in amygdala volume in middle-aged patients with depression relative to controls (Table 2).<sup>11</sup> This has also been found in

patients with affective disorders and comorbid epilepsy<sup>46</sup> and bipolar disorder.<sup>47,48</sup> The amygdala has been shown in preclinical studies to play a critical role in fear responses, and by extension could modulate pathological emotional responses in depression. Alterations in the amygdala, reflected by structural alterations, could underlie symptoms of depression. The mechanism of increased amygdala volume in depression is unknown, but we speculated it might be due to increased synaptic connections in the amygdala of patients with depression. Studies looking at subregions of the amygdala have also found reductions in specific areas, including the core volume.<sup>49</sup> The significance of this finding relative to increases in total volume are unclear. However, findings related to amygdala volume should be replicated.

### STRUCTURAL NEUROIMAGING STUDIES OF THE MEDIAL PREFRONTAL CORTEX IN DEPRESSION

More recently, there has been interest in the medial prefrontal and orbitofrontal cortex in depression (Figure 3). Medial portions of the prefrontal cortex, including the orbitofrontal cortex and Brodmann's areas (BAs) 24, 25, and 32 have been

TABLE 2. VOLUME\* OF COMPARISON REGIONS IN MAJOR DEPRESSION AND CONTROLS

| Region              | Major Depression |         | Comparison      |         |
|---------------------|------------------|---------|-----------------|---------|
|                     | Subjects (n=16)  | SD      | Subjects (n=16) | SD      |
| Left caudate        | 2,668            | 710     | 2,767           | 571     |
| Right caudate       | 2,712            | 765     | 2,802           | 613     |
| Left amygdala       | 1,652            | 455     | 1,347           | 448     |
| Right amygdala      | 1,699            | 493     | 1,335           | 450     |
| Left frontal lobe   | 140,856          | 41,597  | 154,267         | 24,141  |
| Right frontal lobe  | 143,101          | 45,265  | 164,471         | 27,150  |
| Left temporal lobe  | 17,931           | 4,170   | 18,227          | 1,791   |
| Right temporal lobe | 18,207           | 4,260   | 19,475          | 2,707   |
| Whole brain         | 1,404,586        | 179,994 | 1,390,789       | 153,948 |

\*Volumes expressed in cubic mm.  
SD=standard deviation.

Adapted from Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry*. 2000;157:115-118.

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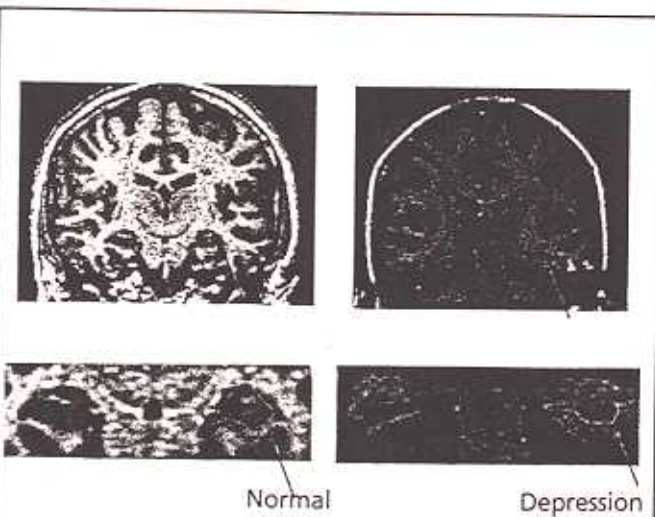


FIGURE 1. Atrophy of the hippocampus in depression.

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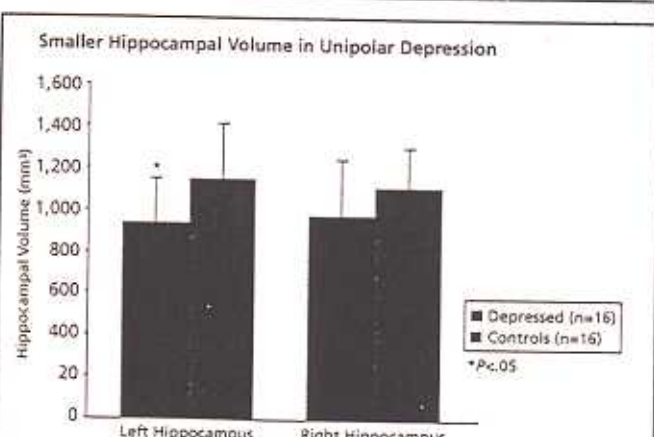


FIGURE 2. Hippocampal volume in patients with unipolar depression and controls. There was a 19% smaller volume of the left hippocampus in patients with depression compared to controls ( $P<.05$ ).

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implicated in emotion, cognition, and social behavior (all functions that are abnormal in patients with depression). Using MRI, Drevets and colleagues<sup>50</sup> found a reduction in subgenual cortex volume (BA 24) in depression. Reductions in glia have been found in this area based on the postmortem brains of patients with depression.<sup>51</sup> Studies in patients with late-life depression<sup>52-54</sup> and children with depression<sup>55</sup> found a reduction in whole frontal lobe volume, although other studies in late-life<sup>40</sup> and mid-life<sup>41</sup> depression did not find such a reduction. In our positron emission tomography study of tryptophan depletion in patients with major depression on SSRIs, we found a decrease in orbitofrontal cortical function during tryptophan-depletion-induced depressive relapse.<sup>56</sup> Rajkowska and colleagues<sup>57</sup> followed up on this study by looking in this area in the postmortem brain of patients with depression and found a decrease in neurons and glia. Based on these findings, our group<sup>58</sup> (Figure 3) and the group at Duke (Lai and colleagues)<sup>59</sup> measured orbitofrontal cortical volume on MRI in both middle-life (our group) and late-life (Lai and colleagues)<sup>59</sup> depression and found significant reductions in volume in this area (up to 30%). Spectroscopy studies have also shown a reduction in glutamate and glutamine in the anterior cingulate.<sup>60</sup>

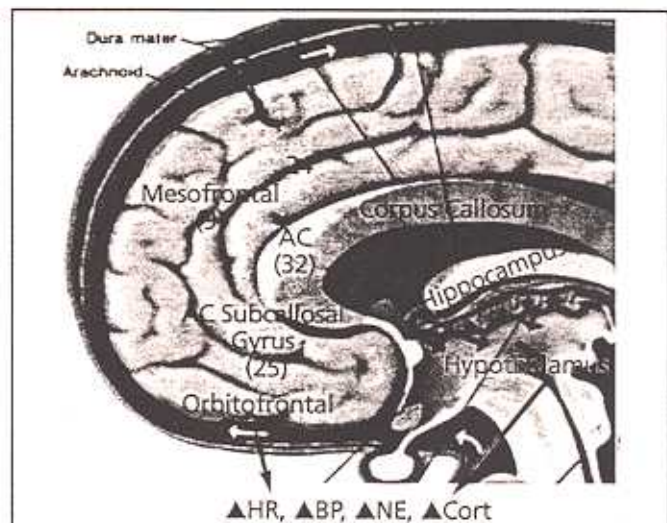
In a second study involving essentially the same sample of patients we used in our study of the hippocampus in depression, we measured volumes of subregions of the prefrontal cortex, including the orbitofrontal cortex (gyrus rectus) and anterior cingulate (BAs 24 and 25). We found that patients with major depression had 32% smaller volume of the medial orbitofrontal cortex (gyrus rectus) compared to controls, which was statistically significant based on analysis of variance (ANOVA). This difference was also seen after controlling for differences in whole brain size using ANOVA, with whole brain volume added as a factor in the analysis ( $F=6.77$ ;  $t=2.32$ ;  $P<.05$ ). There were no differences in size of other prefrontal cortical regions measured in this study, including BA 25 (subcallosal gyrus), BA 24 (subgenual gyrus), or BA 32. There were no differences between patients and controls in whole brain volume (Table 3).

There was no correlation between orbitofrontal cortical volume and clinical variables, including the number of weeks in remission, number of prior episodes of depression, or number of hospitalizations for depression. When potentially confounding factors, including age, years of education, and years of alcohol abuse were entered into the model,

there continued to be a difference in orbitofrontal cortical volume between patients and control subjects.<sup>58</sup>

## NEUROCHEMICAL BASIS OF DEPRESSION

Animal studies on the effects of stress on the brain are relevant to understanding changes in the brain during depression. Stress has been linked to the development and recurrence of depression. In addition, stress is associated with elevated levels of glucocorticoids (cortisol in humans), and elevated glucocorticoids are seen in a subset of patients with depression.<sup>61,62</sup> Stress has been associated with damage to neurons of the hippocampus (a brain area involved in learning and memory), an effect that has been hypothesized to be related to elevated levels of glucocorticoids with stress, increasing vulnerability to excitatory amino acids<sup>1,3,63-65</sup> and/or stress-induced decreases in brain-derived neu-



**FIGURE 3.** The medial prefrontal cortex in depression:

- Brain areas implicated in depression include the orbitofrontal cortex, dorsolateral prefrontal cortex, portions of the anterior cingulate (subcallosal gyrus or BA 25, as well as BAs 24 and 32), and hippocampus
- Orbitofrontal cortex and medial orbitofrontal cortex have outputs to peripheral stress response
- Lateral nucleus of the hypothalamus and medial prefrontal cortex stimulate NE and cortisol release in the stress response

AC=anterior cingulate; ▲=increased; HR=heart rate; BP=blood pressure; NE=norepinephrine; Cort=cortisol; BA=Brodman's area.

Bremner JD. *CNS Spectrums*. Vol 7, No 2, 2002.

**TABLE 3. VOLUME\* OF PREFRONTAL CORTICAL REGIONS IN MAJOR DEPRESSION AND CONTROLS**

|                                     | Major Depression (n=15) |         | Comparison and Difference |         |       | Values* |     |
|-------------------------------------|-------------------------|---------|---------------------------|---------|-------|---------|-----|
|                                     | Mean                    | SD      | Subjects (n=20)           | SD      | Diff. | F       | P   |
| Orbitofrontal cortex (gyrus rectus) | 338                     | 125     | 495                       | 230     | -32%  | 5.65    | .02 |
| Subcallosal gyrus (BA 25)           | 464                     | 294     | 395                       | 147     | 17%   | 1.34    | .25 |
| Anterior cingulate (BA 24)          | 588                     | 296     | 634                       | 262     | -7%   | 0.23    | .63 |
| Anterior cingulate (BA 32)          | 6,317                   | 1,114   | 6,837                     | 2,118   | -8%   | 0.74    | .39 |
| Whole brain                         | 1,266,035               | 144,942 | 1,233,333                 | 152,098 | 3%    | 0.41    | .52 |

\*Volumes expressed in cubic mm.

†  $df=1,33$

‡ These differences were not statistically significant after controlling for differences in whole brain size ( $P>.05$ ).

SD=standard deviation; Diff=difference; BA=Brodman's area.

Adapted from Bremner JD, Vythilingam M, Vermetten E, et al. Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry*. 2002. In press.

Bremner JD. *CNS Spectrums*. Vol 7, No 2, 2002.

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rotrophic factor (a neuropeptide that has trophic effects on the hippocampus).<sup>66</sup> Antidepressants and electroconvulsive therapy blocked these effects.<sup>67</sup> SSRIs also increase dendritic branching within the hippocampus,<sup>68</sup> a finding with implications for treatment of depression. Recently, it has been found that the hippocampus has the capacity for neurogenesis (growth of new neurons) in adulthood, and that an enriched environment or SSRIs enhance neurogenesis,<sup>69</sup> while stress inhibits neurogenesis.<sup>70</sup>

### **GLUCOCORTICOIDS, DECLARATIVE MEMORY, AND DEPRESSION**

Glucocorticoids also have effects on memory that are not simply due to irreversible hippocampal damage. Glucocorticoid administration to healthy human subjects, even at physiological levels, resulted in impairments in verbal declarative memory function.<sup>71-73</sup> Memory deficits were demonstrated with stress-induced glucocorticoid elevations.<sup>73,74</sup> Glucocorticoids were also associated with changes in brain structure. Ventricular enlargement was shown with computed tomography in human subjects exposed to high levels of glucocorticoids secondary to glucocorticoid steroid therapy.<sup>75,76</sup> Patients with Cushing's disease had verbal memory deficits and a reduction in hippocampal volume based on MRI.<sup>77</sup> These findings show that glucocorticoids act reversibly to impair verbal declarative memory function in humans and could have effects on the human brain.

The effects of glucocorticoids on memory function, cognition, and the brain have implications for the pathophysiology of depression. Patients with depression show deficits in verbal declarative memory tasks, including delayed paragraph recall and word-list learning.<sup>78</sup> These memory deficits are reversible with antidepressant treatment.<sup>79</sup> As mentioned above, hypercortisolemia is found in a substantial number of patients with major depression, and stress (which is associated with increased levels of cortisol) has been implicated in the triggering of depressive episodes. High levels of cortisol seen during depressive episodes were correlated with deficits in memory and cognition<sup>80,81</sup> as well as changes in brain structure as measured with computed tomography or MRI.<sup>4,5,82,83</sup> Memory deficits associated with depressive episodes improved when cortisol levels were lowered following successful treatment.<sup>81</sup>

We have hypothesized that hypercortisolemia, acting through the hippocampus (a major target area for glucocorticoids), mediates verbal memory deficits associated with depressive episodes.<sup>86</sup> Evidence to support the hypothesis that the pattern of verbal declarative memory deficits seen in depression is secondary to hippocampal dysfunction comes from studies of patients with epilepsy undergoing surgical treatment of their disorder. In these patients, there was a correlation between deficits on the types of measures used in studies of depression, including delayed paragraph recall and word-list learning, and decreased neuronal number in the CA3 region of the left hippocampus.<sup>84</sup> In summary, hypercortisolemia seen in depressive episodes is associated with reversible deficits in

verbal declarative memory function, and these effects are likely mediated through hippocampal dysfunction.

The reversibility of memory deficits following successful treatment of depression with SSRIs has implications for hypotheses regarding hippocampal dysfunction in depression.<sup>79</sup> Antidepressant treatment has been shown to increase dendritic branching in the hippocampus and promote neurogenesis. It is possible that antidepressants improve memory function in depressed patients by acting directly on the hippocampus. Reductions in cortisol levels with treatment of depression could reverse hippocampal atrophy and lead to an improvement in memory function. Since the effects of cortisol on cognition are seen in normal individuals and are rapidly reversible, it is also possible that memory deficits in depression are not related to long-standing hippocampal damage, but are merely related to elevated levels of ambient cortisol during depressive episodes.

However, in a substantial percentage of depressed patients, memory deficits associated with depressive episodes are not reversible with treatment. Resistance to reversibility of cognitive deficits might be related to chronicity and the interaction of normal aging with the cumulative effect of depressive episodes.<sup>84,85</sup> Repeated episodes of hypercortisolemia seen during depressive episodes interact with the aging process to cause progressive hippocampal damage with associated cognitive deficits.<sup>86,87</sup> We found a 0.44 correlation between number of hospitalizations and left hippocampal volume reduction in depression,<sup>11</sup> while other groups found a correlation between lifetime duration of depression and smaller hippocampal volume.<sup>34,35</sup> These findings are consistent with the idea that chronicity of depression, possibly acting through repeated episodes of hypercortisolemia, is related to lasting hippocampal volume reduction.

### **CONCLUSION**

This paper has reviewed structural changes in the brain in patients with depression. Studies have implicated white matter lesions in elderly patients with depression, which are thought to be related to microinfarcts and to disrupt circuits connecting the frontal cortex to areas such as the hippocampus, amygdala, and thalamus, leading to neurologically based symptoms of depression. Some studies, but not all, have found reduction of volume of the hippocampus. Factors that might influence hippocampal volume reduction in patients with depression include exposure to stress, disease recurrence, and chronicity. An unexpected finding is increased volume of the amygdala, which requires further replication and an expanded understanding of its significance. There are emerging findings implicating abnormalities in areas of the medial prefrontal cortex, both from imaging and postmortem studies, including the orbitofrontal cortex and subgenual cortex, which might underlie symptoms of depression. These findings are consistent with the hypothesis that a circuit including the amygdala, hippocampus, caudate, thalamus, and various subregions of the medial prefrontal cortex

underlie symptoms of depression, and that disruptions of this circuit lead to symptoms of depression. Understanding the neural circuitry of depression will go a long way to developing new treatments for this disorder. **CNS**

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