Hippocampal Volume in Primary Unipolar Major Depression: A Magnetic Resonance Imaging Study

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Background: Previous studies have shown that major depression is frequently accompanied by hypercortisolemia. There is some evidence suggesting that an increase in the glucocorticoid levels may make hippocampal cells more vulnerable to insults caused by hypoxia, hypoglycemia, or excitatory neurotransmitters. Using magnetic resonance imaging (MRI), the hippocampi of patients with major depression were measured and compared with values observed in control subjects.

Methods: Thirty-eight patients with primary unipolar major depression were recruited. Twenty control subjects were matched for age, gender, and years of education. The hippocampal volume was measured from coronal MRI scans in all of the subjects. Patients were also grouped and compared as responders and nonresponders to treatment with fluoxetine of 20 mg/day, for 8 weeks. Hamilton Depression Rating Scale (HDRS) was used to determine the severity of depression.

Results: No significant differences were observed between the hippocampal volumes of patients with major depression and control subjects; however, a significant correlation was observed between the left hippocampal volume of men and their HDRS baseline values. In addition, female responders had a statistically significant higher mean right hippocampal volume than nonresponders.

Conclusions: The results of our study indicate no reduction in the volume of the hippocampus in patients with major depression. Nonetheless, the results do suggest that the effects of disease severity, gender, and treatment response may influence hippocampal volume.

Key Words: Hippocampus, major depression, magnetic resonance imaging, gender

Introduction

Although there seems to be a consensus on the observed abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis in patients with major depression, changes in the volume of the hippocampus in depressed subjects is a topic of debate. It has been hypothesized that increased levels of glucocorticoids may lead to cognitive impairments related to the pathology of the hippocampus (Sapolsky et al 1986). Sapolsky (1992) discussed the proposed mechanisms by which high levels of glucocorticoids increase neuronal cell death in the hippocampus, which may lead to impairments of learning and memory. Based on this premise, one might expect a reduction in the volume of the hippocampus in those with hypercortisolemia, found in a group of patients with major depression.

Using magnetic resonance imaging, several groups have examined volumetric changes in the hippocampus of those with major depression. Some have found no difference between the hippocampal volume of nonpsychiatric control subjects and that of patients with major depression (Axelson et al 1993; Coffey et al 1993). On the other hand, Sheline et al (1996) reported smaller left and right hippocampal volumes in patients with major depression. In one study, the depressed group was divided into two subtypes based on the individual’s response to treatment (Pillay et al 1997). They analyzed volumetric changes in cerebral and cerebellar regions. Although they did not find significant differences when comparing depressed patients as a whole with control subjects, they did find significant results when depressed subjects were divided into groups of responders and nonresponders.

We therefore hypothesized a reduction in the volume of the hippocampus in subjects with major depression in comparison with control subjects and also examined whether differences existed between responders and nonresponders.
Methods and Materials

Human Subjects

After approval of the study by the Institutional Review Board of Massachusetts General Hospital, written informed consent was obtained from all subjects. Thirty-eight consecutively referred patients with primary unipolar major depression were recruited in the open phase of an NIMH-sponsored double-blind study of fluoxetine treatment, 20 mg/day, for 8 weeks. All depressed patients met the criteria for major depressive disorder, determined with the Structured Clinical Interview for Diagnosis (SCID), and had a baseline 17-item Hamilton Depression Rating Scale (HDRS) score of ≥16. Both of these instruments were administered by trained raters with an interrater reliability coefficient of >.80. Exclusion criteria for participation included any other Axis I diagnosis, a history of neurological illness, serious medical illness, active substance abuse within the past 6 months, or claustrophobia; age less than 18 or greater than 60; or the presence of a ferrous implant or pacemaker. Follow-up HDRS ratings were performed after 8 weeks of fluoxetine treatment or earlier in patients who dropped out of the study. A positive treatment response (responders) consisted of a decrease in initial HDRS rating of greater than 50%, and an end of trial HDRS less than 7 (n = 21). All subjects without a positive treatment response were considered nonresponders (n = 17). Patients were also administered the symptom questionnaire (Kellner 1987), which is a self-rating scale measuring anxiety, depression, somatic symptoms, and anger and hostility.

In addition, 20 comparison subjects were selected based on age, gender, and years of education. Comparison subjects were also screened with the SCID by the same interviewers. Exclusion criteria were the same as for depressed subjects, except that comparison subjects could not have any Axis I diagnosis. As a group, depressed patients had a mean (± SD) age of 38.5 ± 10.0 years and the comparison subjects had an mean age of 40.3 ± 10.4 years [F(1,56) = 0.412, p = .52; analysis of variance (ANOVA)]. In the depressed group, 21 of the 38 patients were women, compared with 11 out the 20 female subjects in the comparison group [χ²(1) = 0.0004, p > .99]. All but one of the depressed patients and all of the comparison subjects were strongly right-handed.

Magnetic Resonance Imaging

All subjects underwent brain magnetic resonance imaging using a 1.5-T (Signa; General Electric, Milwaukee, WI) whole body imaging device. Sagittal localized images were obtained first, followed by 3-mm spoiled gradient-recalled acquisition (SPGR) T1-weighted coronal images through the whole brain. Acquisition parameters included repetition time = 35 msec, echo time = 5 msec with one repetition, flip angle = 45° with a 256 × 256 matrix. Voxel dimensions were 0.976 × 0.976 × 3 mm.

Image Analysis

Analysis of images was performed off-line using a SUN Microsystems (Mountainview, CA) Sparc2 workstation and a semiautomated computerized software package (MRX; Kikinis et al. 1992). Operator input involved restoring the image from the scanner and using the MRX software to manually trace the hippocampal region in the appropriate coronal slices. The volume was then automatically calculated by summing the traced areas. The hippocampal boundaries that were used followed the methods of Sheline et al. (1996). The actual volumes measured in cubic centimeters are referred to as absolute volumes. A ratio of the absolute hippocampal volume to the total cerebral volume, including the cerebrospinal fluid volume (TCV) is used for comparison purposes.

Statistical Tests

Statistical tests included ANOVA and all reported correlations are Fisher’s r to z test. All significance levels are two-tailed, defined at the p < .05 level. An intrarater reliability coefficient was calculated for various brain regions as r = .90.

Results

Analysis of variance comparing left and right hippocampal volumes of the major depressed patients to the left and right hippocampal volumes of the control subjects revealed no statistically significant differences (Table 1). Repeated measures ANOVAs revealed no statistically significant differences between the volumes of the left and right hippocampus in both the 20 control subjects and the 38 patients with major depression. In addition, no significant difference was observed when the ratios of the hippocampus volume to the cerebral volumes were used for comparison.

Independent ANOVA analysis by gender was not statistically significant for either gender; however, relatively greater differences were obtained among females subjects (absolute left hipp. p = .06; LH/TCV, p = .08) in the two diagnostic groups (control and depressed subjects) than

Table 1. Comparison of Hippocampal Volumes between Control Subjects and Depressed Patients

<table>
<thead>
<tr>
<th></th>
<th>Depressed patients</th>
<th>Control subjects</th>
<th>F value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute left hipp. vol.</td>
<td>2.64 ± 0.55</td>
<td>2.46 ± 0.38</td>
<td>1.7</td>
<td>.20</td>
</tr>
<tr>
<td>Absolute right hipp. vol.</td>
<td>2.61 ± 0.58</td>
<td>2.60 ± 0.51</td>
<td>0.003</td>
<td>.95</td>
</tr>
<tr>
<td>Left hipp./total cerebral vol.</td>
<td>0.208 ± 0.041</td>
<td>0.20 ± 0.03</td>
<td>1.2</td>
<td>.27</td>
</tr>
<tr>
<td>Right hipp./total cerebral vol.</td>
<td>0.206 ± 0.045</td>
<td>0.21 ± 0.04</td>
<td>0.04</td>
<td>.85</td>
</tr>
</tbody>
</table>

Tissue volumes are in mL.
Table 2. Correlation between Hippocampal Volumes and Hamilton Depression Rating Scale Scores

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p value</td>
</tr>
<tr>
<td>Absolute left hipp. vol.</td>
<td>-.767</td>
<td>.002</td>
</tr>
<tr>
<td>Absolute right hipp. vol.</td>
<td>-.688</td>
<td>.011</td>
</tr>
<tr>
<td>Left hipp./total cerebral vol.</td>
<td>-.739</td>
<td>.004</td>
</tr>
<tr>
<td>Right hipp./total cerebral vol.</td>
<td>-.656</td>
<td>.019</td>
</tr>
</tbody>
</table>

among male subjects (absolute left hipp., \( p = .9 \); LH/TCV, \( p = .8 \)) in the two groups.

A Fisher’s \( r \) to \( z \) test was used to examine a possible correlation between the absolute hippocampal volumes of the patients with major depression and HDRS scores. A significant negative correlation was observed with the left hippocampal volume \( (r = -.4, p = .02) \), and a trend was observed for right hippocampal volume \( (r = -.3, p = .08) \) when considering the depressed group as a whole. When this correlation was examined independently in men and women, a more statistically significant correlation was found in males \( (p = .002) \); no significant correlation was observed with regard to the female subjects (Table 2).

After comparing the responders and nonresponders, no significant difference in the mean volume of either the right or the left hippocampus was observed. When the groups were considered independently based on gender, however, the mean difference between the right hippocampal volumes of female responders and nonresponders showed the greatest degree of significance (Table 3). Significant negative correlations were observed between the absolute hippocampal volumes and HDRS scores (absolute left hipp., \( r = -.54, p = .03 \); absolute right hipp., \( r = -.55, p = .02 \)).

Discussion

The comparison of absolute hippocampal volumes or the comparison of the ratios of hippocampal volumes to cerebral volumes between the 20 control subjects and the 38 patients with major depression revealed no statistically significant differences (Table 1).

The results presented here do not replicate the findings (Sheline et al 1996) of a reduction in the hippocampal volume of patients with major depression. These results are in accordance with findings of Coffey et al (1993) and Axelson et al (1993). Sheline et al (1996) did observe hippocampal atrophy in patients with recurrent major depression. One major difference between that study and the current study is the age of the study subjects. The depressed subjects in this study had a mean \( (\pm SD) \) age of 38.5 \( \pm 10.0 \) and the control subjects a mean age of 40.3 \( \pm 10.4 \) years, whereas Sheline et al (1996) studied subjects with a mean \( (\pm SD) \) of 68.5 \( \pm 10.4 \) years. The Sheline study included only 10 control subjects and 10 depressed subjects, and all were women. This study had a greater number of subjects and also included men. The factors just stated, especially the age difference between the subjects in the two studies, could lead to the differences in results between this study and that of Sheline et al (1996).

Previously, Coffey et al (1993) and Axelson et al (1993) had studied subjects with mean ages of 62 \( \pm 16.4 \) and 46.7 \( \pm 20.4 \), respectively. Despite the higher age range, they did not find any reduction in the volume of the hippocampus. The study being presented here, with a lower age range than the studies mentioned above, suggests that hippocampal atrophy may not be characteristic of all patients with major depression.

Although no significant differences were observed between the mean volumes of the control subjects and the depressed patients, some interesting trends within the depressed group and its clinical subtypes were observed. Male patients had a significant degree of correlation between the left hippocampal volume and HDRS scores. This was true not only for the hippocampal to total cerebral volume ratio, but also for the absolute hippocampal volume. Nonresponders also showed a correlation between the absolute hippocampal volumes and the HDRS. This may be attributable to the fact that nonresponders have had a more severe course of depressive

Table 3. Comparison of Responders with Nonresponders of Hippocampal Volumes, Divided by Gender

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F value</td>
<td>p value</td>
</tr>
<tr>
<td>Absolute left hipp. vol.</td>
<td>2.26 ± .67</td>
<td>2.90 ± .56</td>
</tr>
<tr>
<td>Absolute right hipp. vol.</td>
<td>2.76 ± .57</td>
<td>2.83 ± .59</td>
</tr>
<tr>
<td>Left hipp./total cerebral vol.</td>
<td>1.9 ± .05</td>
<td>2.01 ± .03</td>
</tr>
<tr>
<td>Right hipp./total cerebral vol.</td>
<td>2.01 ± .05</td>
<td>2.02 ± .04</td>
</tr>
</tbody>
</table>

Tissue volumes are in mL.
R. responder; NR. nonresponder.
illness than had the responders, judging from their reduced response to treatment.

The hippocampus, along with other areas of the brain, is part of the serotonergic pathway that is implicated in the pathophysiology of depression as evidenced by the positive response of depressed patients to selective serotonin reuptake inhibitors. Duman et al (1997) proposed a cellular and molecular model for the effects of antidepressants and stress on the survival of hippocampal neurons. They proposed that a depletion in serotonin and norepinephrine may lead to decreased levels of brain-derived neurotrophic factor (BDNF), which may be decreased even further by glucocorticoids, eventually leading to neuronal cell death. Their model suggests that antidepressants may prevent the down-regulation of BDNF in response to stress. The hypothalamic-pituitary-adrenal axis has been well established in the physiological response to stress, and the hippocampus has been suggested as a suprahypothalamic regulator involved in the negative-feedback control of cortisol (Jacobson and Sapolsky 1991). Therefore, any insult to the hippocampus causing a dysfunction in its inhibitory regulation of the hypothalamic-pituitary-adrenal axis may result in hypercortisolemia. Higher levels of cortisol may induce neuronal damage in the hippocampus (Sapolsky 1985) because of the high levels of glucocorticoid receptors in the hippocampus (Reul and De Kloet 1986). Hippocampal atrophy may then result from a long-term exposure to higher levels of glucocorticoids. Sheline et al (1996) presented evidence supporting this fact when they found a correlation between lifetime duration of illness and hippocampal volume loss. Such comparisons could not be made in our study because the data on the duration of illness of the patients was not available.

The proposed cellular and molecular mechanisms involved in the pathogenesis of depression point to the possibility of neuronal cell loss in the hippocampus of untreated patients. Over time, this may lead to hippocampal atrophy, which may be detected by magnetic resonance imaging. In our study, gross hippocampal atrophy was not observed in the depressed subjects. As mentioned earlier, this may be a result of the age factor. Advancing age along with longer exposure to corticosteroids, may result in some atrophy of the hippocampus as seen in the Sheline study. The hippocampus may indeed be implicated in the pathogenesis of depression, but its pathology may be at a cellular level and studied best through methods that will detect chemical and minute physical changes. A study by Krishnan et al (1991) found shorter hippocampal T1 relaxation times in the depressed patients compared to control subjects. Changes in relaxation times may be attributable to changes in water or tissue contents of the considered region. These initial changes, not detectable by gross examination using structural MRI of the hippocampus, may be important in defining the early role and involvement of the hippocampus in depression.

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References


