Hippocampal Morphometry in Depressed Patients and Control Subjects: Relations to Anxiety Symptoms

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Background: *Although it has been hypothesized that glucocorticoid hypersecretion in depressed patients leads to neuronal atrophy in the hippocampus, magnetic resonance imaging (MRI)–based morphometry studies of the hippocampus to date have produced mixed results.*

Methods: *In our MRI study, hippocampal volumes were measured in 25 depressed patients (13 with melancholia and 12 without melancholia) and 15 control subjects.*

Results: *No significant differences in hippocampus volumes were found between any of the subject groups, although within subjects right hippocampal volumes were found to be significantly larger than left hippocampal volumes. Additionally, right and total (left + right) hippocampal volumes in control and depressed subjects were found to be positively correlated with trait anxiety as measured by the state/trait anxiety inventory.*

Conclusions: *Because our subject group is younger than those in studies reporting hippocampal atrophy, we conclude that longitudinal studies will be necessary for investigation of the lifelong course of hippocampal volumetry.* Biol Psychiatry 2001;50:960–964 © *2001 Society of Biological Psychiatry*

Key Words: MRI, hippocampus, depression, morphometry, volumetry

Introduction

There has been much discussion about possible neuronal damage in the human hippocampus associated with certain pathologies. It has been well documented that hippocampal cell death follows the hypersecretion of glucocorticoids in the brain (Sapolsky et al 1986). Although it is known that glucocorticoid hypersecretion is a physiologic symptom seen in some patients with major depression, especially those patients diagnosed with melancholic depression (Carroll 1982; Gold et al 1995), researchers using magnetic resonance imaging (MRI) to examine hippocampal volume in depressed patients have met with mixed results. Although our study was not designed to examine relations between cortisol and hippocampal volume, the search for possible hippocampal pathology in depressed patients was motivated by the basic research literature on the impact of glucocorticoid exposure on hippocampal neurons.

Some groups have reported no differences between hippocampal volumes of depressed patients and control subjects (Axelson et al 1993; Vakili et al 2000). One group has completed two studies in which smaller left and right hippocampal volumes were found in depressed patients; however, subjects from these studies were predominantly older women, with mean ages of 68 and 54 years, respectively (Sheline et al 1996, 1999). Two recent studies have found depressed subjects to have significantly reduced left, but not right, hippocampal volumes (Bremner et al 2000; Mervaala et al 2000). Given these varied results, it is difficult to draw firm conclusions about hippocampal atrophy in major depression. None of these studies have examined relations between hippocampal volume and specific aspects of depressive symptomatology.

We compared hippocampal volume in a group of younger depressed patients and control subjects and specifically contrasted melancholic and nonmelancholic patients. We also examined the relationship between hippocampal volume and self-reported affective symptoms in these subjects.

Methods and Materials

Subjects

Subjects were recruited via advertisements in local media. After the nature of the experimental procedures was explained, informed consent was obtained. Subjects were screened for psychopathology using the Structured Clinical Interview for DSM-IV (SCID; First et al 1995). Depressed subjects were required to meet criteria for DSM-IV major depressive disorder and had no history of mania or psychosis in themselves or in first-degree relatives. We also assessed DSM-IV criteria for melancholia. The depressed subjects (17-Item Hamilton Depres-

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sion Rating Scale score [$n = 23$]: M = 19.4, SD = 4.4; *Hamilton 1960*) did not meet Axis I criteria for any other current disorder, with the possible exception of specific phobia or dysthymia. Sixteen depressives reported definite or possible depressive symptomology in first-degree relatives. Control subjects had no past history of any Axis I disorders and no family history of Axis I disorders. All subjects were free of antidepressant medication for at least 4 weeks before testing. Subjects were right-handed as assessed by the Chapman Handedness Inventory (Chapman and Chapman 1987).

We tested 25 depressed subjects (14 women) and 15 nondepressed control subjects (9 women). The depressed group was further divided into a group of patients with melancholic depression ($n = 13$, 7 women) and a group of depressed patients without melancholia ($n = 12$, 7 women). No difference in age was found for depressed (M = 33.2 years; SD = 9.5) and control (M = 37.4 years; SD = 14.4) subjects, $t(38) = 1.11$, *ns*.

MRI Data Acquisition

Structural MRI scans were performed on a 1.5 Tesla GE Signa scanner (Milwaukee, WI). The MRI protocol consisted of an axial 3D SPGR, with 24 cm FOV, TE = 14, TR = 30, 256 × 192 matrix, NEX = 1, flip angle = 35°, and a 1.2-mm slice thickness, for a total of 124 slices.

Image Analysis

The MRI image data underwent the following preprocessing steps: 1) reformatting into a single three-dimensional volume (ANALYZE [R. Robb, Mayo Clinic] format); 2) psuedo-histogram rebinning to set the highest 0.1% of values to the 99.9 percentile level, enhancing the apparent contrast in the brain regions of interest; and 3) smoothing using a three-dimensional anisotropic annealing algorithm (Gerig et al 1992; Perona and Malik 1990), which preserves edges and small features while smoothing large homogeneous areas. The criterion for smoothing was that similar pixel clusters smaller than 2 to 4 pixels should be removed, but pixel clusters larger than 4 pixels should remain.

In-house software (SPAMALIZE) was used to define hippocampal, cerebellar, and whole brain regions of interest. This software displays axial, coronal, and sagittal views simultaneously and allows the user to draw in any of the views to quickly construct a three-dimensional volume-of-interest (VOI) with pixel-level precision. Volumes for the whole brain and the cerebellum were determined using automated segmentation techniques (Oakes et al 1999) followed by manual corrections if needed, whereas hippocampal VOIs were defined according to the following hippocampus boundary criteria.

Hippocampus Boundary Criteria

Hippocampus VOIs were traced and edited on both sagittal and coronal slices. Sagittal criteria were as follows: on the lateral-most slices, the hippocampus borders were defined superiorly by the fimbria, anteriorly by the alveus, posteriorly by the cerebrospinal fluid (CSF) of the lateral ventricle, and inferiorly by the white matter of the temporal lobe. On more medial slices, a white matter tract appearing posterior to the hippocampus was excluded. For most subjects, the amygdala could be readily distinguished from the hippocampus on sagittal slices by defining the alveus as the anterior border of the hippocampus. On the medial-most slices, the head and tail of the hippocampus are separated by thalamic nuclei. At this point, the tail was no longer traced sagittally because of an inability to exclude the gyrus fasciolaris and the fasciola cinera.

Coronal criteria were as follows: The posterior portion of the hippocampus was defined as being bordered laterally by the white matter of the fornix (or the CSF of the lateral ventricle in places where the fornix was indistinguishable), medially by CSF, inferiorly by white matter, and superiorly by the splenium of the corpus callosum (moving anteriorly, the superior border is defined by the gyrus fasciolaris and the fasciola cinera, and then by the fimbria). For the most anterior portions of the hippocampus, the amygdala delineated the superior edge of the hippocampus, the inferior border was defined by white matter, and the lateral and medial borders were defined by CSF; this resulted in the most superior portion of the subiculum being included in the hippocampal volume.

Volume Correction

To account for individual differences in overall brain size, the absolute hippocampus volumes were divided by whole brain volumes. These ratio scores will hereafter be referred to as corrected volumes. Because not all scans included the entire cerebellum, the cerebellum was excluded from whole brain measurements.

Affective Symptomatology

Potential correlations between corrected hippocampal volumes and various demographic and psychologic symptom variables were examined. These variables, which were taken within 3 months of the MRI session, included age, socioeconomic status, measures of depression severity such as the BDI (Beck Depression Inventory, Beck et al 1961), and the HAMD (Hamilton 1960), measures of state and trait affect (Positive and Negative Affect Schedule, Watson et al 1988) and measures of state and trait anxiety (Speilberger et al 1970). Some of these measures were implemented partway through the study. Therefore, the sample size was restricted for several calculated correlations. Because of cumulative Type I error associated with computing multiple correlations, an alpha level of 0.01 was used to reduce familywise error rate.

Computation of Reliability

For reliability purposes, percent overlap was determined for absolute left and right hippocampal VOIs drawn by two blind, independent raters. Image sets used in reliability calculations were chosen randomly ($n = 5$). Percent overlap was calculated by dividing the intersection of the absolute volume of each of the two raters' VOIs by the union of the absolute volume of the two VOIs. Additionally, intraclass correlation coefficients were computed.

Table 1. Hippocampal Volumes (± SD) in All Subjects with Depression (D), with (M) and without (NM) Melancholia, and Comparisons to Control Subjects (C)

	t	D	C	M	NM	*F*
Left hippocampus	−.40	2.17 ± .26	2.13 ± .27	2.20 ± .30	2.13 ± .20	.29
Right hippocampus	−1.00	2.29 ± .30	2.20 ± .24	2.36 ± .37	2.21 ± .20	1.36
Corrected left	−.25	$(1.77 \pm .23) * 10^{-3}$	$(1.76 \pm .25) * 10^{-3}$	$(1.77 \pm .17) * 10^{-3}$	$(1.78 \pm .28) * 10^{-3}$	.03
Corrected right	−.86	$(1.87 \pm .24) * 10^{-3}$	$(1.81 \pm .21) * 10^{-3}$	$(1.89 \pm .18) * 10^{-3}$	$(1.85 \pm .30) * 10^{-3}$	.51

Absolute left and right hippocampus values are in cubic centimeters. *t* values are generated from comparisons between all depressive and control subjects (df = 38). *F* values are generated from ANOVA comparisons between subjects with melancholia, without melancholia, and control subjects (df = 2,37).

Results

Interrater Reliability of Hippocampus Volumes

Average scores for percent overlap of left and right hippocampal volumes were 81.8 and 81.3, respectively. Intraclass correlations indicated reliable tracing of both the left ($IC = .97$, $p = .007$) and right ($IC = .80$, $p = .10$) hippocampi.

Patient Group Differences in Measured Volumes

Independent *t* tests comparing corrected hippocampal volumes of patients and control subjects revealed no statistically significant differences between groups. See Table 1 and Figure 1. Repeated measures ANOVA analysis revealed that right corrected hippocampal volumes were significantly larger than left corrected hippocampal volumes $F(1,38) = 17.28$, $p = .0002$; however, no significant hemisphere by group interaction was found. No difference in whole brain size (cerebellum excluded) was detected between the two groups.

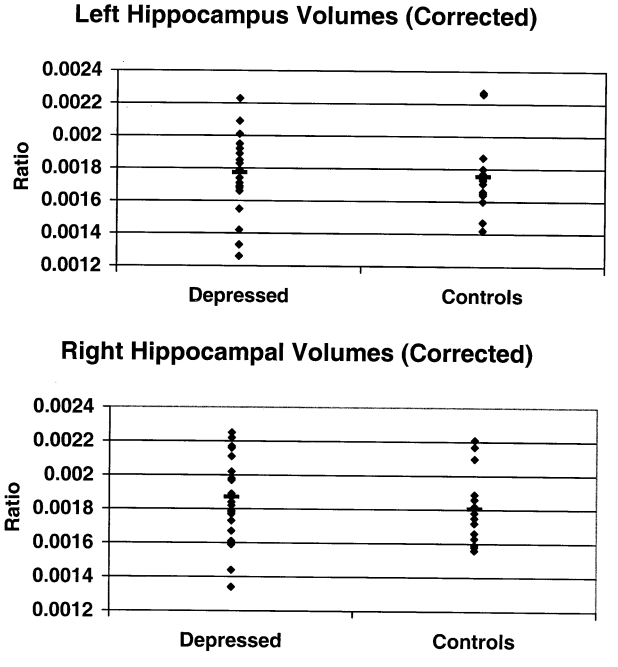


Figure 1. Comparison of corrected hippocampal volumes between patients and control subjects. Horizontal bars indicate mean corrected hippocampal volumes.

One-way analyses of variance (ANOVAs) were used to separately compare the left and right corrected hippocampal volumes of the two depressed subgroups (with and without melancholia) with the control group; these analyses revealed no significant differences between the groups; see Table 1.

Gender Differences in Measured Volumes

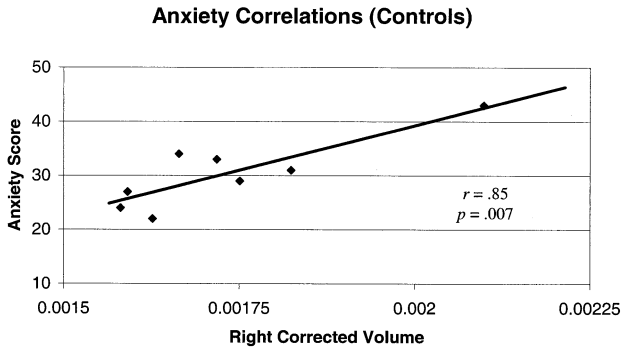
Men were found to have significantly larger absolute left hippocampal volumes (M = 2.25 cm^3, SD = .29) than women (M = 2.08 cm^3, SD = .21), $t(38) = 2.12$, $p = .04$, significantly larger absolute right hippocampal volumes (M = 2.38 cm^3, SD = .34) than women (M = 2.15 cm^3, SD = .18), $t(38) = 2.69$, $p = .01$, and significantly larger absolute total (left + right) hippocampal volumes (M = 4.63 cm^3, SD = .61) than women (M = 4.24 cm^3, SD = .37), $t(38) = 2.51$, $p = .02$. No significant gender difference in corrected hippocampal volumes was found. Men were also found to have significantly larger cerebellum-excluded whole brain volumes (M = 1339.3 cm^3, SD = 126.10) than women (M = 1146.7 cm^3, SD = 98.1), $t(38) = 5.44$, $p < .0001$.

Affective Symptomatology and Hippocampal Volume

Right and total (left + right) corrected hippocampal volumes in both control[1] (Figure 2) and depressed (Figure 3) subjects were found to be positively correlated with trait anxiety scores as measured by the state/trait anxiety inventory (Speilberger et al 1970). No other correlations were found between hippocampal volumes and the demographic and psychological symptom variables.

Because of the significant relations discovered between

[1] The correlations of anxiety scores with right and total hippocampal volumes of control subjects included a potential outlier. When this point is removed, the correlations between right corrected volumes and trait anxiety scores and between total corrected volumes and trait anxiety scores become $r = .58$ and $r = .67$, respectively.



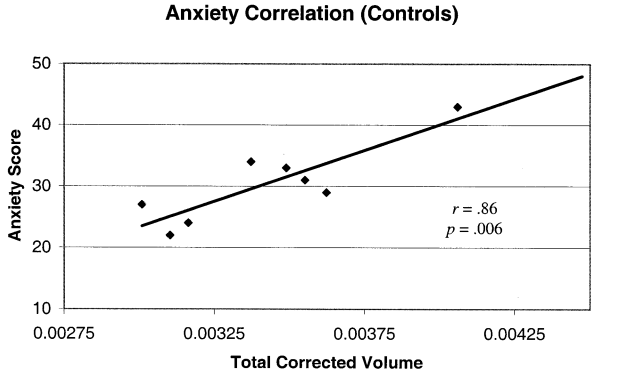
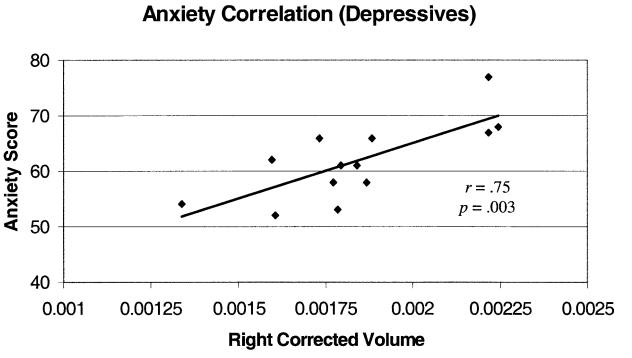


Figure 2. Scatterplots of significant correlations between trait anxiety scores and corrected hippocampal volumes in control subjects ($n = 8$).



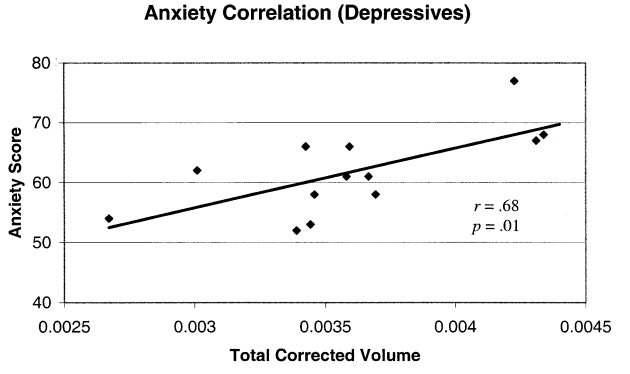


Figure 3. Scatterplots of significant correlations between trait anxiety scores and corrected hippocampal volumes in depressed subjects ($n = 13$).

hippocampal volumes and anxiety scores, several post hoc analyses involving the anxiety scores were performed. Correlations were performed between trait anxiety scores and depression severity as measured by the HAMD ($n = 11$); however, no significant correlations between these scales were discovered among the depressed patients, $r = .18$, *ns*. Additionally, a comparison of anxiety scores by gender failed to yield a significant result, $t(19) = .17$, *ns*.

Discussion

Our study failed to find any significant differences in left or right corrected hippocampal volumes between depressed patients and control subjects. Additionally, no difference in hippocampal volumes was found when control subjects were compared with depressed individuals with and without melancholia. Consistent with other recent reports (Mervaala et al 2000; Pruessner et al 2000), right corrected hippocampal volumes were found to be significantly larger than left corrected hippocampal volumes.

Although congruent with other reports of null results (Axelson et al 1993; Vakili et al 2000), our study fails to replicate previous findings of reduced hippocampal volumes in depressed subjects. One potential explanation for this discrepancy could be the relatively young age of the subjects in this study. It is probable that atrophy of the hippocampus is a chronic process and that measurable volumetric changes are not noticeable until later in life. A longitudinal study of hippocampal volumes in depressed patients will be needed to address this issue.

The discovery of a positive correlation between trait anxiety and right and total corrected hippocampal volumes is an intriguing one. Animal studies have suggested a role for the hippocampus as part of a coping system for stressful situations, with the dentate gyrus (Belzung 1992; Henke 1990) and ventral subiculum (Herman et al 1998) being specifically implicated. Furthermore, it has been hypothesized that hippocampal hyperactivity may be a potential cause of generalized anxiety (McNaughton 1997). The functional consequences of this association require study in future research.

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