Posterior Hippocampal Volumes Are Associated with Remission Rates in Patients with Major Depressive Disorder

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Background: The hippocampus (HC) is smaller in patients with recurrent major depressive disorder (MDD), but few longitudinal studies have examined whether volume is associated with clinically meaningful outcomes such as response to treatment.

Methods: We compared regional (head and body/tail) HC volumes in 46 patients with MDD, 14 of whom remitted after 8 weeks of first treatment to HC volumes of 32 patients who were not in remission after 8 weeks.

Results: Patients who remitted had larger pretreatment hippocampal body/tail volumes bilaterally compared with those who were not in remission at 8 weeks. This difference was not apparent in either the right or left hippocampal head.

Conclusions: These findings extend a small number of previous reports, suggesting that regional brain volumes might be associated with rate and extent of clinical response to antidepressant medication.

Key Words: Depression, hippocampus, remission, response

Over thirty magnetic resonance imaging (MRI) studies have examined hippocampus (HC) volumes in patients with major depressive disorder (MDD); several meta-analyses have confirmed that, in the aggregate, people with MDD have HC volumes that are approximately 5% smaller than healthy comparison subjects (1–3). Cross sectional studies have reported that small HC volumes are associated with depression severity, age at onset, non-responsiveness to treatment, untreated days of illness, illness burden, history of childhood abuse, level of anxiety, and certain genetic polymorphisms (see [3] for a detailed review). There are, however, few prospective longitudinal studies that have examined whether HC volumes are associated with clinical outcome. We therefore examined HC volumes in a group of 46 subjects who had baseline MRI scans and then completed at least 8 weeks of first treatment for depressive symptoms. Hippocampal head (Hh; anterior HC) and hippocampal body/tail (Hbt; posterior HC) volumes of subjects who met criteria for clinical remission were compared with those of subjects who did not meet criteria for remission to determine whether there was an association with regional HC volumes and clinical response. We hypothesized that, on the basis of previous reports of associations with HC volume and outcome (4,5), patients who were in remission at 8 weeks of treatment would have larger hippocampal volumes than those who did not achieve remission.

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Received April 28, 2008; revised June 9, 2008; accepted June 29, 2008.

Methods and Materials

Fifty patients with a primary diagnosis of MDD were recruited from the Mood Disorders inpatient and outpatient clinics at St. Joseph's Healthcare Hamilton. Subjects were included only if they had < 21 days of lifetime exposure to psychotropic medication before MRI scanning; the mean number of days of lifetime exposure to medication in the sample was 5.2 days (SD = 6.8, range = 0–19 days). Hamilton Depression Rating Scale (HDRS) scores from 46 participants were available at baseline and at 8 weeks after baseline, and these subjects were included in the analyses. Subjects provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Boards of St. Joseph's Healthcare (Ontario, Canada).

The diagnosis of non-psychotic unipolar MDD was confirmed by the Structured Clinical Interview for DSM-IV (SCID) (6). Symptom severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS) (7) and the Global Assessment of Functioning Scale (GAF) (8). Exclusion criteria for patients and healthy control subjects were: 1) substance-use related disorder within the past 6 months as determined by the SCID; 2) lifetime history of substance dependence as measured by the SCID; 3) use of alcohol or illicit psychoactive substance within 48 hours of testing; 4) untreated medical illness; 5) history of head injury with loss of consciousness; 6) history of neurological disease; and 7) past treatment with pharmacotherapy (including stimulants in childhood), electroconvulsive therapy, transcranial magnetic stimulation, or psychotherapy.

Participants were treated naturalistically with a range of medications that are listed as first line medications in the Canadian guideline for the treatment of depression (9). Citalopram was the most commonly used antidepressant drug; 50% of patients who entered remission were treated with this medication, whereas 44% of patients who did not remit were treated with citalopram. Other patients were treated with standard doses of venlafaxine, bupropion, mirtazapine, sertraline, or fluvoxamine. One patient in each group had small doses of atypical antipsychotic medications (2.5 mg olanzapine, .5 mg risperidone) added over the 8 weeks of treatment, but no other augmentation or combination strategies were employed. Response was defined as a drop in HDRS scores of 50% from

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.06.027

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baseline scores, and remission was defined as HDRS scores ≤ 7 at 8 weeks (10).

We have previously reported the details of scanning and the protocol used to measure hippocampal volumes (11), which are also available at: http://physics.stjosham.on.ca/~kaan/HippoProtocol.pdf. We used a 1.5-T Sigma GE Genesis-based Echo-Speed scanner (General Electric Medical Systems, Milwaukee, Wisconsin) and a 3-T Sigma GE Genesis scanner (General Electric Medical Systems). We performed preliminary analyses on this patient group and on a larger group of patients and healthy control subjects scanned on the 1.5-T compared with the 3-T. There were no differences in HC volumes between groups scanned on either machine, and we therefore treated the images acquired in our study at 1.5-T (66% of patients) and 3-T (34% of the sample) as a single data set.

Hippocampal head (Hh) and hippocampal body/tail (Hbt) volumes were assessed in addition to right and left total HC volumes. The most posterior slice for the Hh on the coronal view was the last slice where gyrus intralimbicus was observed (12). The gyrus intralimbicus is a small structure located on the medial portion of the posterior part of the Hh and is defined easily (12). The presence of the alveus in the sagittal plane also helped to delineate Hh from the Hbt (see Figure 1).

We compared demographic variables and total and regional HC volumes between patients who were and were not in remission after 8 weeks of treatment with univariate analyses of covariance and independent sample *t* tests. Analyses of covariance were conducted with total lifetime exposure to medication, measured in days of treatment, as a covariate to determine whether this influenced the pattern of results. We also conducted the analyses with total cerebral volume as a covariate and with age as a covariate. We used analyses of variance to determine whether the effect was restricted to either gender; previous investigators have reported that HC volume was associated with outcome in women but not men (5) and in men but not women (13).

Pearson's *r* was used to examine for significant correlations between baseline HDRS scores and HC volumes and past number of untreated depressions and regional HC volumes.

Results

Fourteen subjects (30%) met criteria for remission at 8 weeks of treatment. Baseline HDRS scores did not differ significantly between remitters and non-remitters nor did past number of untreated episodes (see Table 1). There were no correlations between baseline HDRS scores and any measures of HC volume. Past number of untreated depressive episodes did not predict any measure of HC volume, but the likelihood of detecting such relations was limited by the fact that most patients were in a first or second episode of illness.

Baseline right HC volumes were larger in patients who achieved remission ($t = 2.7$, $p = .009$). Baseline left HC volumes were also larger in remitted patients ($t = 2.3$, $p = .03$; see Table 2). Both left and right baseline Hbt volumes were larger in patients who remitted ($t = 2.7$, $p = .01$, $t = 2.9$, $p = .006$, respectively; see Table 2), but there was no evidence of a similar difference in either left Hh ($t = .27$, $p > .05$) or right Hh ($t = .86$, $p > .05$). Co-varying for total cerebral volume did not alter the pattern of results.

A similar pattern of results was apparent when clinical response was examined in the overall group, defined by a 50% reduction in HDRS scores. Right ($p = .005$) and left ($p = .04$) total HC volumes were larger in responders compared with non-responders. Left Hbt ($p = .01$) and right ($p = .006$) were larger in responders, whereas there were no differences in left or right Hh scores for responders compared with non-responders (p values $> .05$).

Patients in the group who remitted had an average of 6.1 (SD = 7.2, range = 0–18) days of lifetime exposure to psychotropic medication at the time of MRI scanning, whereas patients who did not remit had an average of 4.8 (SD = 6.7, range = 0–19) days of exposure to medication. Although we limited the sample to only patients with < 21 days' lifetime exposure to psychotropic medication, we performed correlational analyses with number of days of exposure to medication to examine in a preliminary way whether there was any evidence that early exposure to medication could predict regional hippocampal volumes. We found no significant correlations between lifetime

Table 1. Demographic and Clinical Characteristic of Patients Who Did or Did Not Achieve Remission Over 8 Weeks of First Treatment

	Remission ($n = 14$)	No Remission ($n = 32$)	p
Men/Women	8/6	15/17	ns
Age	30.5 (9.5)	27.6 (10.5)	>.05
Baseline HDRS	17.0 (7.7)	18.0 (5.5)	>.05
Baseline GAF	59 (8.6)	57 (7.2)	>.05
# Past Untreated Episodes	3.1 (2.9)	2.8 (3.0)	>.05
Lifetime Days Exposure to Medication at Scan	6.1 (7.2)	4.8 (6.7)	>.05

HDRS, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning Scale.

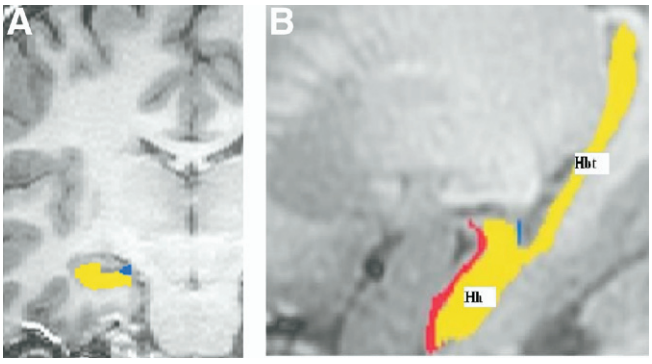

Figure 1. (A) The last slice of right Hh (hippocampal head) is shown on the coronal plane. Gyrus intralimbicus traced on the medial portion of the Hh is in blue. **(B)** Right hippocampus on the sagittal plane showing Hh and Hbt. Red: alveus, blue: gyrus intralimbicus (the corresponding tracings made on the coronal plane).

Table 2. Total and Regional Hippocampal Volumes for Patients Who Were or Were Not in Remission After 8 Weeks of Treatment

		Remission Mean (SD)	Non-Remission Mean (SD)	p
Total Hippocampus	Right	2637 (271)	2415 (247)	.009
Hippocampus	Left	2580 (293)	2379 (265)	.027
Hippocampus	Right	1406 (178)	1239 (183)	.006
Body/Tail	Left	1448 (196)	1263 (220)	.01
Hippocampus	Right	1230 (184)	1176 (198)	.39
Head	Left	1132 (210)	1115 (190)	.79

Volumes are in mm^3.

days of medication exposure and HC volume when we examined the overall group (remitters and those who did not remit, all p values $> .05$).

Although number of days of medication was not a significant predictor of HC volume overall, we re-ran the analyses with days of medication exposure as a co-variate and found that there was no change in the pattern of results, because both the right [$F(1,43) = 6.9$, $p = .01$] and left [$F(1,43) = 5.1$, $p = .03$] total HC volumes were significantly larger in patients who entered remission. This effect continued to be accounted for by significant differences in right [$F(1,43) = 8.0$, $p = .007$] and left Hbt [$F(1,43) = 7.8$, $p = .008$], whereas no differences emerged in either the left or right Hh.

Finally, we examined whether there was any evidence of an effect of gender on the observed pattern of results. Despite previous reports of the associations between outcome and HC volume being restricted to women (5) or men (13), we did not observe a gender-specific effect. Our overall sample consisted of 50% men and women. There were 8 of 14 (57%) men in the group that remitted, and 15 of 32 (47%) in the group that did not remit. Although the sample was limited by very small sample size when we examined men and women separately, there was no evidence that the relations between outcome and hippocampal volumes were restricted to either gender.

Discussion

The key finding of this study is that patients who met criteria for clinical remission at 8 weeks of treatment had larger pre-treatment total HC volumes bilaterally than non-remitters. This finding was accounted for by differences in the Hbt bilaterally and did not extend to the Hh. The main strength of this study is that the results were not confounded by past treatment effects, because patients averaged < 1 week of lifetime exposure to medication at the time that the MRI scans were obtained. The differences in HC volume between remitters and non-remitters were not related to severity of mood symptoms at baseline, duration of untreated illness, or differences in patient age between remitters and non-remitters. To our knowledge, this is the first study to examine regional HC volumes in patients differentiated by response to first treatment for depressive symptoms.

The current study has several limitations, however, including the small sample size. Medications were naturalistically prescribed, and therefore patients received a variety of medications at different dosages over the 8 weeks of treatment. Despite this, we had detailed treatment records for each patient and could find no evidence of a differential intensity of treatment in either group. Furthermore, because MRI scans were obtained before or shortly after first treatment was initiated, it is unlikely that treatment intensity could have systematically influenced the differences observed in baseline HC volumes between patients who did and did not remit.

These data are consistent with results from a study of patients with geriatric depression in which patients with smaller right HC volumes in the lowest quartile of the sample were less likely to achieve remission compared with those with HC volumes in the highest quartile (4) and with another study reporting that women who responded to 8 weeks of fluoxetine had larger right HC volumes than non-responders (5). Frodl *et al.* (14) reported that depressed patients who were not remitted from an episode of depression 1 year after discharge had smaller left and right HC volumes at baseline scan. Kronmuller *et al.* (13) recently reported associations between left and right HC volumes and 2-year outcome, although the associations between larger HC volume and good outcome were restricted to men. Bilaterally smaller HC volumes have also been reported in currently depressed patients compared with those of remitted patients (15), and decreases in hippocampal activation after treatment with fluoxetine have been noted (16).

None of the studies examining the association with HC volume and treatment outcome have focused on patients who had minimal prior treatment, and none examined variation in sub-regions of the HC, although these regions are likely functionally distinct. Relatively few volumetric studies of patients with MDD have differentiated the anterior and posterior HC; small posterior HC volumes have been reported in unmedicated remitted patients (17) and in treatment-resistant patients with MDD (18). There is a large pre-clinical literature that implicates the HC as a key target of antidepressant medication (19), and specific serotonin reuptake inhibitor effects have been linked to regional changes in the HC in several animal studies (20–23). Further clinical and preclinical studies are required, however, to determine whether relative treatment resistance might be in some measure associated with structural changes in the posterior HC that influence responsiveness to medication.

In addition to studies examining associations between HC volume and treatment outcome, a recent study reported that greater grey matter volume in pregenual anterior cingulate cortex predicted faster rates of symptom improvement after 8 weeks of treatment with fluoxetine in 17 patients with MDD (24). The HC is part of an extensive network that regulates mood (25), including regions of the anterior cingulate cortex that also correlated with antidepressant response at 8 weeks (24). Future studies are required to confirm whether assessment of key components of fronto-temporal networks might have utility for identifying patients who are particularly likely or unlikely to respond to pharmacotherapy and whether similar relations hold for other therapy modalities. The capacity to identify patients who are likely to respond to various treatment modalities could eventually have relevance to clinical practice; in the shorter term, such methods might be more readily applied to reducing the sample sizes required in clinical trials by identifying and excluding patients who are unlikely to respond to certain treatment modalities.

This study was supported by a Canadian Institutes of Health Research (CIHR) grant to GMM. Dr. MacQueen has received honoraria, consulting fees, or research support from: Wyeth, AstraZeneca, Janssen, Lilly, Novartis, GSK, Boerbinger, Oryx, Lundbeck, CIHR, the Ontario Mental Health Foundation (OMHF), the National Institutes of Mental Health, National Alliance for Research on Schizophrenia and Depression (NARSAD), the Stanley Medical Research Foundation, the Scottish Rite Foundation, and AllerGen. Dr. Taylor has received grants from: NARSAD; CIHR; OMHF; Society of American Gastrointestinal and Endoscopic Surgeons; Community Health, Education, and Research Fund; Regional Medical Association; Center for Minimally Invasive Surgery; Sanofi-Aventis (Canada); Novartis (Canada); and Eli Lilly Neurosciences Foundation (Canada). Dr. Taylor has worked as a consultant for Sanofi-Aventis (International). She is a member of Speakers' Bureau for AstraZeneca (Canada); Allergan (Canada); Sanofi-Aventis (International). Dr. Joffe reports no biomedical financial interests or potential conflicts of interest. Dr. Yucel received the Etherden/Sluzas Fellowship for Studies in Mood Disorders from St. Joseph's

Healthcare Foundation. Dr. Macdonald has received consulting fees from Astra-Zenca.

We are grateful to the patients and their families for their assistance. We thank Cathy Preete and Anthony Nazarov for their assistance in preparation of this manuscript and Laura Garrick, Helen Begin, Cindy D'Amico, Scott Simmons, and Tana Pati for assistance with patient scheduling and testing. We are also grateful to Geoff Hall and Andrea Milne for assistance in running the brain imaging protocol.

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