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Hippocampal volumes and depression subtypes

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Abstract

Studies of depression and hippocampal volume have yielded inconsistent results. This inconsistency could stem from the heterogeneity of depressive disorders. We conducted cross-sectional and longitudinal analyses of hippocampal volumes in atypical depressives, melancholic depressives, and controls. We found no effect of depression subtype on hippocampal volume or memory performance.

Keywords

depression; hippocampus; morphometry

1. Introduction

Many studies have investigated hippocampal atrophy in depression, but the results have been inconsistent. Some studies report left-sided atrophy, others report right-sided atrophy, others report bilateral atrophy, and still others report no significant atrophy at all (for reviews, see Campbell et al., 2004; Videbech and Ravnkilde, 2004; Sheline, 2003). This inconsistency could arise from the heterogeneity of the disorder, since there is some evidence that different depressive subtypes have different behavioral and neurochemical presentations. Patients with *melancholic depression* exhibit psychomotor retardation or agitation, sleep difficulties, and weight loss; they often have hypercortisolemia, which has sometimes been associated with hippocampal atrophy. Patients with *atypical depression*, however, exhibit leaden paralysis, hypersomnia, hyperphagia, and weight gain; they often have hypocortisolemia (Antonijevic, 2006; Gold and Chrousos, 2002). Hippocampal atrophy might therefore be associated with melancholic depression but not atypical depression. In turn, the results of a particular study might depend on the relative proportion of these subtypes in the sample.

To our knowledge, only one report has examined this question. It examined a small sample of younger adults and found no differences in hippocampal volumes across subtypes (Rusch et al., 2001). Differences might be more evident in an elderly sample, since depression and

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hypercortisolemia would have had more time to exert their effects (Campbell et al., 2004; Videbech and Ravnkilde, 2004). We therefore examined the relation between depression subtypes and hippocampal volumes in a large sample of elderly adults. We hypothesized that patients with melancholic depression would have smaller hippocampi than controls, while patients with atypical depression would not.

2. Methods

2.1. Participants

Participants were recruited from the Conte Center for the Neuroscience of Depression at Duke University. They were 60 or older and could speak and write English. Participants were excluded if they had histories of drug/alcohol dependence, primary neurologic illness, metal in the body, or major psychiatric illness aside from major depression. Most patients were receiving SSRIs at both baseline and followup; a few were receiving tricyclics. Medications were administered according to our guideline-based protocol; thus, different patients received different medications (or permutations of medications), and medications and doses were adjusted over the course of the study in accordance with the patients' needs.

Clinical assessments were conducted at baseline and repeated at regular intervals thereafter. Baseline assessments were performed at the beginning of treatment. At each assessment, participants received the Duke Depression Evaluation Schedule (DDES). The DDES is a structured psychiatric interview that includes the NIMH Diagnostic Interview Schedule depression subscale, the Cumulative Illness Rating Scale, and scales for measuring instrumental and self-maintenance activities of daily life. It includes questions about the patient's history of depression, the symptoms they have experienced (such as anxiety, sleep disturbances, and changes in weight or eating habits), and the age of their first, most severe, and most recent episode of depression. Previous reports have shown that the DDES has high reliability, with interrater reliabilities ranging from 0.83 to 1 (Krishnan et al., 1995). In addition to the DDES, participants received the Hamilton Rating Scale for Depression, which assesses depression severity (HAMD; Hamilton, 1960).

The results from the DDES questions were used to determine if participants met criteria for one of the subtypes of depression defined in the DSM-IV. Participants were divided into three groups based on DDES results and DSM-IV criteria. Controls ($n=83$) had no history of depression. The melancholic group ($n=56$) met criteria for melancholic depression. The atypical group ($n=68$) met criteria for atypical depression. Other patients ($n=51$) fell into neither category and were excluded. For unknown reasons, the prevalence of atypical depression was higher than in previous reports (38% vs. 15.5%; Benazzi, 2000).

2.2. Neuropsychological tests

Participants received the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) neuropsychological battery (Morris et al., 1989; Welsh et al., 1994). The CERAD includes tests of verbal learning and memory, consisting of immediate recall of 3 learning trials of a 10-item word list, delayed recall of the list, and recognition/discrimination of targets from foils. Participants also received the Logical Memory subtest of the Wechsler Memory Scale-Revised (Wechsler, 1987), which assesses immediate and delayed verbal memory.

2.3. MRI methods

Every 2 years, participants were scanned with a 1.5-Tesla whole-body MRI system (Signa, Milwaukee, WI, USA) using the standard head radiofrequency coil (see Steffens et al., 2000, for imaging parameters). We obtained 2 sets of dual-echo fast-spin-echo acquisitions with 3-

mm thickness: an axial series for morphometry of the intracranial volume (ICV), and a coronal-oblique series perpendicular to the AC-PC line for hippocampal measurement.

Hippocampal volumes were determined using the in-house GRID program (Steffens et al., 2000). On each scan, we began with the most posterior coronal slice and then moved anteriorly. We began measuring the hippocampus when the pulvinar nucleus of the thalamus obscured the crura fornicis; if the crus was only obscured on one side, we only measured that side. The fimbria, which extends from the superior surface of the hippocampus across the CSF into the white matter above, was transected at its narrowest point. Along the medial border of the hippocampus, the thin strip of gray matter was cut at its narrowest point, and tracing then continued around the hippocampal body to the starting point. The amygdala-hippocampal transition zone appeared as a diffuse area of gray matter between the anterior portion of the hippocampus and the posterior portion of the amygdala; as with the fimbria, this area was transected at its narrowest point, which was usually found between the inferior lateral ventricles and the cistern. Continuing anteriorly, the inferior lateral ventricles gradually shift from a vertical to a horizontal orientation but remain superior to the hippocampus. We defined the anterior border of the hippocampus as the slice on which the inferior lateral ventricles appeared horizontally without any body of gray matter visible below them.

ICV measurements used a modified version of MrX Software (GE Corporate Research and Development, Schenectady, NY, USA; Brigham and Women's Hospital, Boston, MA, USA). The segmentation protocol has been previously described (Payne et al., 2002). Reliability was 0.8 for left hippocampus, 0.9 for right hippocampus, and 0.99 for ICV.

2.4. Statistical methods

Analyses were conducted using SAS 9.1 for PCs (Cary, NC, USA). We conducted power analyses (Cohen and Cohen, 1988) with power levels set at 0.8. For our main cross-sectional analyses, we calculated that we could detect an increment of 0.03 to the overall R^2 ; for our main longitudinal analyses, we could detect an increment of 0.01. Based on regression diagnostics, we dropped 1 participant with a studentized residual of 3.04, leverage of 0.09, and Cook's D of 0.14; no other participant met all these criteria for influential observations. No substantial heteroscedasticity or deviations from normality were observed in residual plots. All tolerance values were above 0.58.

3. Results

3.1. Cross-sectional analyses

Table 1 presents demographic information. The gender composition of our groups did not significantly differ ($\chi^2=1.63$, $P=0.44$), nor did the age ($F(2,204)=0.58$, $P=0.56$). The groups did differ significantly in years of education ($F(2,204)=11.80$, $P=0.0001$, $\omega^2=0.10$). Specifically, both groups of depressed patients differed from controls (controls vs. melancholic, $t(137)=4.44$, $P<0.0001$, $\omega^2=0.14$; controls vs. atypical, $t(149)=3.90$, $P=0.0002$, $\omega^2=0.09$), but did not differ from each other ($t(122)=0.45$, $P=0.66$).

Duration and frequency of depression may influence hippocampal atrophy (Campbell et al., 2004; Videbech and Ravnkilde, 2004). These variables were log-transformed to reduce negative skew. Significant differences were found in age of onset ($t(117)=2.56$, $P=0.011$, $\omega^2=0.04$) and number of depressive episodes ($t(122)=-2.96$, $P=0.004$, $\omega^2=0.06$). We did not find differences between patient groups in depression severity as measured by the HAMD ($t(69)=-0.59$; $P=0.56$).

Cross-sectional analyses were conducted using multiple regression. Two effects-coded variables represented patient groups (Cohen and Cohen, 1988). Separate models were

constructed for left and right hippocampus. The ICV, age, education, and sex variables were entered first, followed by transformed variables for age of onset and number of depressive episodes. Then the set of effects-coded variables was entered, and the increment to R^2 was tested for statistical significance. We found no statistically significant effect of participant group on left hippocampus ($F(2,200)=1.35$, $P=0.25$, $sr^2=0.006$) or right hippocampus ($F(2,200)=0.85$, $P=0.36$, $sr^2=0.003$). We then removed the covariates in a stepwise fashion; the pattern of results did not change, even when all covariates were removed and one-tailed t tests were conducted between the control group and each patient group. We found no correlation between depression severity and hippocampal volume for either patient group (both $|r| < 0.10$; both $P > 0.50$).

These analyses included all depressed patients who met our criteria, but other studies have shown that early-onset and late-onset depression might have different clinical courses and outcomes. To examine this factor, we conducted a subanalysis limited to patients who reported early-onset depression (i.e., onset before age 60). We found no effect of participant group (left hippocampus, $F(2,169)=1.46$, $P=0.23$, $sr^2=0.007$; right hippocampus, $F(2,169)=0.39$, $P=0.54$, $sr^2=0.002$). The sample size for late-onset depression was too small to permit subanalysis.

Our sample is naturalistic, which increases external validity but raises the possibility that within-group heterogeneity could obscure significant differences. To address this possibility, we conducted another subanalysis using groups that were more homogeneous. We eliminated participants who were not strongly right-handed and matched patients to controls based on age and years of education. We then conducted an analysis of covariance on the resulting groups. The dependent variables were the left and right hippocampal volumes. ICV and sex were entered as covariates, and hemisphere was treated as a repeated measure. These analyses did not reveal any effect of participant group ($F = 3.67$, $P = 0.06$, $\omega^2=0.04$).

The failure to find significant results may raise questions about the sensitivity and validity of our method of hippocampal measurement. We therefore attempted to detect the commonly-reported association between hippocampal volumes and age in a cross-sectional sample. We conducted multiple regression analyses with hippocampal volumes as dependent variables. Cerebral volume, years of education, and sex were entered as covariates, and age was entered as the independent variable of interest. We found significant associations for both the left and right hippocampi (left hippocampus, $t(202)=-3.10$, $P=0.0022$, $sr^2=0.04$; right hippocampus, $t(202)=-3.01$, $P=0.0029$, $sr^2=0.04$). We found no age-sex interactions (both $|t| < 1.15$, both $P > 0.25$), a result in accordance with previous reports (Greenberg et al., in press).

3.2. Longitudinal analyses

This analysis only included participants who had participated at baseline, year 2, and year 4 (see Table 2 for demographics). Participant groups did not significantly differ in age ($F(2,137)=1.95$, $P=0.15$, $\omega^2=0.01$) but did differ in education ($F(2,137)=4.07$, $P=0.02$, $\omega^2=0.04$). The melancholic group differed from the control group ($t(93)=2.91$, $P=0.045$, $\omega^2=0.07$), but the atypical group did not ($t(109)=1.71$, $P=0.09$, $\omega^2=0.02$). We did not find a significant difference in education between patient groups ($t(72)=1.11$, $P=0.27$). We did not find a significant difference in log-transformed age of onset ($t(92)=-1.74$, $P=0.09$, $\omega^2=0.03$) but log-transformed number of depressive episodes was just at the level of statistical significance ($t(71)=1.99$, $P=0.0501$, $\omega^2=0.04$). Kruskal-Wallis tests did not reveal any differences in depression severity at any of the three time points (all $\chi^2 < 0.6$; all $P > 0.46$).

We conducted mixed-models analyses using SAS's PROC MIXED with the REPEATED option. Separate models were constructed for left and right hippocampal volumes. Participant number, patient group, and time of measurement were entered as class variables. Patient group, time, and the patient group $\times$ time interaction were entered as independent variables. Based on

examination of the R correlation matrix, we selected an autoregressive variance structure. We found no significant effects of patient group, time, or the patient group $\times$ time interaction for either the right or the left hippocampus (all $F < 1.08$, all $P > 0.32$). One-tailed t tests between controls and each depressed group did not yield significant results at any time point (all $|t| < 0.7$, all $P > 0.46$).

Some studies have indicated that depression severity may be associated with hippocampal atrophy (e.g. Frodl et al., 2004). We conducted correlational analyses between hippocampal volume at each time point and HAMD score at each time point. We found no significant correlations (all $|r| < 0.3$, all $P > 0.06$). In addition, we compared hippocampal volumes of responders (defined here as a HAMD score less than 10) to nonresponders (those with scores above 10). We found no significant differences between these groups (all $|t| < 1.4$, all $P > 0.16$).

3.3. Neuropsychological results

We did not find any significant differences in hippocampal volumes among groups; however, patients may suffer from functional impairment even when structural abnormalities are absent. We therefore examined scores on the memory tests described above. The melancholic group scored lower on all tests than the atypical group, but this difference was never statistically significant (Table 3). We also calculated correlations between neuropsychological test scores and hippocampal volumes. Significant differences were seen in the melancholic group, where left hippocampal volume correlated with scores for the Logical Memory I ($r = 0.63$, $P = 0.0006$) and Logical Memory II ($r = 0.66$, $P = 0.0003$) subtests. All other correlations did not meet the threshold for statistical significance.

4. Discussion

Depression is a behaviorally and neurochemically heterogeneous disorder. Based on prior reports, it seemed possible that hippocampal atrophy would be associated with melancholic depression but not atypical depression. We tested this hypothesis in a large sample of elderly adults that provided us with the power to detect small differences. We did not find any significant differences in hippocampal volume across groups. Furthermore, we did not find any significant differences in neuropsychological test scores, suggesting that if differences in volumes did exist, they are not of great clinical significance.

Our results are consistent with those of Rusch and colleagues (2001), who also failed to find differences in hippocampal volumes between groups of depressed participants. They are inconsistent with the idea of glucocorticoid-induced hippocampal atrophy. In addition, they do not support the hypothesis that hippocampal atrophy is a risk factor rather than a consequence of psychiatric disease (Gilbertson et al., 2002; Lupien et al., 2007).

The limitations of this study mostly arise from our classification scheme. First, the subtypes we examined are not completely distinct: Participants in the melancholic group had some symptoms of atypical depression and vice versa. In principle, this problem could be avoided by limiting analyses to patients who had all the symptoms of one group but no symptoms of the other. This strategy proved impossible in this study, however, because fewer than 10 patients met these stringent criteria. Second, we based our classifications on participants' retrospective reports, but these are not always reliable (Schraedly, Turner, & Gotlib, 2002).

Third, we excluded participants with histories of substance abuse or cardiovascular disease, yet these may be the very patients who are most vulnerable to stress-induced hippocampal pathology. Including these patients would introduce other confounds, however, since alcoholism (Bleich et al., 2003) and cardiovascular disease (Koschack and Irle, 2005) are associated with hippocampal atrophy. Fourth, our control group may include participants with

some form of preclinical neurodegenerative disorder; if so, then they might have some degree of hippocampal volume loss, which would have reduced our ability to detect atrophy in the groups of depressed participants. It seems likely that neurodegenerative disease would have affected the patient groups as well, however, given that performance on memory tests did not differ across groups. Fifth, genetic risk factors for hippocampal atrophy (e.g. the BDNF Val66Met polymorphism, Frodl et al., 2007) could have been distributed unequally across patient groups, potentially obscuring a significant effect of depression subtype. Finally, childhood traumas could have been unequally distributed across groups, which might also obscure the effect of depression subtype (Vythilingam et al., 2002).

In the longitudinal analysis, we observed a slight increase in hippocampal volumes, particularly in the group of patients with atypical depression, but this difference was never statistically significant. This result could be attributable to measurement error, which could arise in part from the slice thickness of 3 mm. Current studies tend to use higher-resolution scans; however, since our study is longitudinal, we wanted to use the same measurement method for all scans and thus chose to retain the 3-mm slice thickness that was used on the scans of our original participants. Nevertheless, if the observed increase reflects a limitation of our method, then we could have missed a decrease in volume of similar magnitude. Alternatively, the measured increase could reflect a real increase in hippocampal volume as a result of antidepressant treatment, as has been shown in PTSD (Vermetten et al., 2003). Given the absence of a statistically significant difference, we cannot make any definitive statements about this possibility.

As noted above, there are several reasons to expect differences in hippocampal atrophy across depression subtypes. Nevertheless, this study and one other (Rusch et al., 2001) have failed to find such differences. A prospective longitudinal study that examined cortisol levels, symptoms, and hippocampal volumes across multiple syndromes and subsyndromes would help clarify the issue.

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Table 1

Cross-Sectional Demographics

	Controls	Melancholic Depression	Atypical Depression
<i>n</i>	83	56	68
Age (mean ± SD)	69±7	71±7	70±8
Years of education (mean ± SD)	15±2	13±3	14±3
Females (<i>n</i> , %)	63 (75%)	37 (66%)	48 (71%)
Age of depression onset (mean ± SD)	n/a	49±20	40±20
Number of depressive episodes (mean ± SD)	n/a	3±4	8±16
Depression severity (mean ± SD)	n/a	21±6	21±7
Strongly right-handed (laterality >60; <i>n</i> , %)	71 (85%)	47 (84%)	57 (84%)
Race/ethnicity (<i>n</i>)			
Asian	2	1	2
African-American	8	3	7
Caucasian	71	50	57
Unknown/other/refused	2	2	2
Left HPC volume (mean ± SD)	2.95 ± 0.45	2.91 ± 0.45	2.99 ± 0.48
Right HPC volume (mean ± SD)	3.13 ± 0.44	3.13 ± 0.36	3.07 ± 0.46
Left HPC volume ratio (mean ± SD)	0.003 ± 0.001	0.003 ± 0.001	0.003 ± 0.001
Right HPC volume ratio (mean ± SD)	0.004 ± 0.001	0.004 ± 0.001	0.004 ± 0.001

Note: SD = standard deviation, HPC = hippocampus, n/a = not applicable.

Table 2

Longitudinal Demographics

	Controls	Melancholic Depression	Atypical Depression
<i>n</i>	66	29	45
Age (mean $\pm$ SD)	68 $\pm$ 5	67 $\pm$ 5	66 $\pm$ 6
Years of education(mean $\pm$ SD)	15 $\pm$ 2	14 $\pm$ 2	15 $\pm$ 2
Females (<i>n</i> , %)	39 (59%)	19 (65%)	32 (71%)
Age of depression onset (mean $\pm$ SD)	n/a	44 $\pm$ 19	35 $\pm$ 18
Number of depressive episodes (mean $\pm$ SD)	n/a	12 $\pm$ 22	5 $\pm$ 5
Depression severity, baseline (mean $\pm$ SD)	n/a	22 $\pm$ 8	22 $\pm$ 4
Depression severity, year 2 (mean $\pm$ SD)	n/a	7 $\pm$ 8	6 $\pm$ 6
Depression severity, year 4 (mean $\pm$ SD)	n/a	7 $\pm$ 8	6 $\pm$ 5
Strongly right-handed(laterality > 60; <i>n</i> , %)	60 (91%)	26 (90%)	37 (82%)
Race/ethnicity (<i>n</i>):			
Asian	0	0	1
African-American	7	0	3
Caucasian	52	26	38
Unknown/other/refused	2	0	1
Left hippocampal volume, baseline(mean $\pm$ SD)	2.96 $\pm$ 0.46	2.88 $\pm$ 0.49	2.97 $\pm$ 0.46
Left hippocampal volume, year 2 (mean $\pm$ SD)	2.92 $\pm$ 0.47	2.88 $\pm$ 0.45	2.92 $\pm$ 0.43
Left hippocampal volume, year 4 (mean $\pm$ SD)	3.00 $\pm$ 0.47	2.96 $\pm$ 0.56	3.04 $\pm$ 0.46
Right hippocampal volume, baseline (mean $\pm$ SD)	3.15 $\pm$ 0.45	3.13 $\pm$ 0.36	3.06 $\pm$ 0.46
Right hippocampal volume, year 2 (mean $\pm$ SD)	3.09 $\pm$ 0.46	3.04 $\pm$ 0.42	3.08 $\pm$ 0.47
Right hippocampal volume, year 4 (mean $\pm$ SD)	3.09 $\pm$ 0.46	3.06 $\pm$ 0.55	3.16 $\pm$ 0.57

Note: SD=standard deviation. n/a = not applicable.

Table 3

Neuropsychological Test Scores by Participant Group

	Controls (mean ± SD)	Melancholic (mean ± SD)	Atypical (mean ± SD)	Atypical vs. Melancholic		
				B (SE)	t	p
Word List Memory	8.3±1.5	6.2±2.0	7.1±1.5	-0.6 (0.5)	-1.23	0.23
Word List Memory, Delayed	7.4±1.8	4.7±2.7	5.7±2.2	-0.5 (0.7)	-0.72	0.48
Logical Memory I	27.7±7.9	18.7±8.9	22.9±9.5	-1.8 (2.2)	-0.80	0.43
Logical Memory II	24.0±8.8	13.6±9.8	19.9±11.3	-3.4 (2.4)	-1.44	0.16

Note. SD=standard deviation; B=unstandardized regression weight; SE=standard error; t =t-statistic; r^2 =squared semipartial correlation coefficient.