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Amygdala volume in Major Depressive Disorder: A meta-analysis of magnetic resonance imaging studies

J. Paul Hamilton, Ph.D.,
Department of Psychology, Stanford University, Stanford, CA 94305, USA

Matthias Siemer, Ph.D., and
Department of Psychology, University of Miami, Coral Gables, FL 33146, USA

Ian H. Gotlib, Ph.D.
Department of Psychology, Stanford University, Stanford, CA 94305, USA

Abstract

Major Depressive Disorder has been associated with volumetric abnormality in the amygdala. In this meta-analysis we examine results from magnetic resonance imaging volumetry studies of the amygdala in depression in order to assess both the nature of the relationship between depression and amygdala volume as well as the influence of extra-experimental factors that may account for significant variability in reported findings. We searched PubMed and ISI Web of Knowledge databases for articles published from 1985 to 2008 that used the wildcard terms “Depress*” and “Amygdal*” in the title, keywords, or abstract. From the 13 studies that met inclusion criteria for our meta-analysis, we calculated aggregate effect size and heterogeneity estimates from amygdala volumetric data; we then used meta-regression to determine whether variability in specific extra-experimental factors accounted for variability in findings. The lack of a reliable difference in amygdala volume between depressed and never-depressed individuals was accounted for by a positive correlation between amygdala volume differences and the proportion of medicated depressed persons in study samples: whereas the aggregate effect size calculated from studies that included only medicated individuals indicated that amygdala volume was significantly *increased* in depressed relative to healthy persons, studies with only unmedicated depressed individuals showed a reliable *decrease* in amygdala volume in depression. These findings are consistent with a formulation in which an antidepressant-mediated increase in levels of brain derived neurotrophic factor promotes neurogenesis and protects against glucocorticoid toxicity in the amygdala in medicated but not in unmedicated depression.

Keywords

major depressive disorder; SSRI; SNRI; MRI volumetry; antidepressant; neurogenesis; BDNF; glucocorticoid; neurotoxicity

Introduction

Major Depressive Disorder (MDD) is characterized by a constellation of emotional and behavioral symptoms, and requires sustained sad mood or significantly diminished enjoyment of daily activities to yield a DSM-IV diagnosis of depression (1). Given that depression is, in important ways, a disorder of affective expression, experience, and regulation, attempts to

Correspondence regarding this manuscript should be addressed to: J. Paul Hamilton, Ph.D., email: paul.hamilton@stanford.edu, phone: 650-725-2458, fax: 650-725-5699.

understand the neural substrates of this disorder have focused primarily on structures implicated in the experience of emotion and the processing of affective information and stimuli (e.g., 2,3). Although anomalies in the structure and function of a number of limbic and paralimbic structures have been found to be associated with depression — most reliably the dorsolateral and ventral prefrontal cortex, hippocampus, and amygdala — the amygdala, a structure crucial to the perception of and memory for emotional material (e.g., 4,5–7), has, arguably, been the focus of the most extensive theoretical and empirical examination.

Studies using functional neuroimaging have found both elevated baseline activity in the amygdala (e.g., 8) and heightened amygdala responsivity to affective stimuli (e.g., 9) in depressed, compared with nondepressed, participants. Moreover, within depressed samples, elevated baseline amygdala activity has been found to be associated with symptom severity (8,10) and, further, to return to normal levels following successful pharmacotherapy (8).

In several structural neuroimaging studies, investigators have examined differences between depressed and nondepressed individuals in amygdala volume. These studies have yielded variable findings, with some reporting that depressed participants were characterized by smaller amygdala volume than were nondepressed participants (3,11–15), some finding greater amygdala volume in depressed than in nondepressed individuals (16–19), and others finding no difference in amygdala volume between depressed and nondepressed persons (17,20,21). It is not surprising, therefore, that a recent meta-analysis of six studies reported no aggregate difference in amygdala volume associated with depression (22).

The inconsistent results of these studies suggest that there is not a reliable association between depressive illness and amygdala volume. It is important to note, however, that the findings of these studies have not been examined systematically as an aggregate and, further, that there are several factors that distinguish studies of amygdala volume in depression that could account for the discrepant results obtained in these investigations. Indeed, some of these factors have been found in other studies to be associated with variation in volume in structures comprising the medial temporal lobes, including the use of antidepressant medication (23,24), the presence of chronic stress (25,26), and the age (27) and gender composition of samples studied (28, 29).

We conducted a meta-analysis of amygdala volume in depression to examine two questions: (1) whether there are reliable differences between depressed and healthy individuals in amygdala volume when the full body of available empirical work is considered systematically; and (2) whether there is significant heterogeneity in reported between-group amygdala volume differences and, if so, what factors account for this variability. Given the inconsistent findings in this literature, we predicted that there would not be a reliable difference between depressed and nondepressed individuals in amygdala volume, but that there would be significant heterogeneity across studies. Moreover, because depressed and nondepressed individuals in these studies differed with respect to antidepressant use and chronicity, or recurrence, of depressive illness, but not typically with respect to age and gender composition, we predicted further that variation in antidepressant use and chronicity of depressive illness, but not in age and gender composition, would predict significant variation in amygdala volume differences. More specifically, given evidence that antidepressant medication supports neurogenesis (24, 30) we predicted that average amygdala volume in depressed, relative to healthy, samples would increase with the proportion of medicated individuals in depressed samples. In addition, and consistent with studies showing volumetric decrease in the hippocampus associated with recurrence of depression (14,22,31), we predicted that amygdala volume in these samples would decrease relative to controls as a function of increasing chronicity of depression.

Methods

We used ISI Web of Knowledge (http://portal.isiknowledge.com) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) electronic databases to conduct our literature search. We conducted a subject search for articles published from 1985 to 2008 that used the wildcard terms "Depress*" and "Amygdal*" in either the title or abstract. Next, one of the authors (JPH) scanned the titles and, if necessary, the abstracts of the studies containing these search terms in order to identify those that conducted MRI-based volumetry of the amygdala with depressed participants. Several inclusion and exclusion criteria were applied by two of the authors (IHG and JPH) to the resultant set of studies. These criteria were: 1) diagnosis of depression was made using DSM-III, DSM-IV, or ICD-10 criteria; 2) individuals with current drug and/or alcohol dependency or neurological disorder were excluded from the study; 3) participants diagnosed with bipolar disorder were not included in the depressed group; 4) there was no report of unusual etiology of depressive illness in depressed samples; 5) the amygdala was defined and measured independent of the hippocampus; 6) the average estimated amygdala volume for both depressed and control groups was reported; 7) the average age of participants included in the study was between 20 and 60; and 8) depressed and control groups were equated for age and gender composition. Fourteen of the 1503 studies identified by the literature search met these criteria and were included in the meta-analysis presented here. Two of these 14 studies used overlapping participant samples: one was an assessment of volumetric abnormalities in the amygdala in recurrent depression (17), and the other was a one-year follow up to that study (32). In order to not violate assumptions of independence that underlie the statistical tests used in our meta-analysis, only data from the initial study (17) were analyzed, yielding a final sample of 13 studies.

Meta-analyses were conducted using a random-effects model (33) that weighted the contribution of each study inversely with the standard deviation of its mean in calculating a mean population effect size estimate, Cohen's *d* (34). We followed this by conducting a *Q* test in order to determine whether the degree of heterogeneity among studies exceeded chance levels. We then attempted to account for any sources of significant heterogeneity in results across studies by using a multi-level model approach to meta-analysis (35), also known as meta-regression. This statistical approach permitted an assessment of the independent impact of various study characteristics that might explain differences in the effect sizes obtained. In this approach, as in the random effects meta-analysis, studies were weighted by their precision (36). We used a restricted maximum likelihood estimation method to predict variation in effect size among studies with the following four factors: age (average age of the sample); gender (percent of female participants in each study); chronicity (the mean number of depressive episodes reported by MDD participants); and medication (percent of depressed participants in each study who were taking antidepressant drugs). All analyses were conducted with programs available in STATA (37). The criterion level for statistical significance of each of the analyses conducted here was set at $p = .01$.

Results

Table 1 presents participant information and results for the 13 studies that met criteria for inclusion in the meta-analysis presented here. An initial random effects meta-analysis yielded a weighted mean effect across all 13 studies of $d = -.208$ that did not differ significantly from an effect size of zero ($z = -0.722$, $p = .47$). A test for heterogeneity of the effects across studies, however, yielded a highly significant result ($Q = 117.98$, $p \ll .01$), indicating that the variation in volume differences across the 13 studies exceeds chance levels. We then examined whether variation in the characteristics of studies could explain this heterogeneity. This analysis, conducted with those studies that included all four variables of interest in our meta-regression — age, chronicity, gender and medication — indicated that only medication explained a

significant amount of the variation in amygdala volume difference across studies. Specifically, as the proportion of depressed individuals taking antidepressant medication increased across studies, so did amygdala volume in the depressed relative to the control participants. Regression fit coefficients and their corresponding z-scores and probabilities under the null hypothesis for each of the four variables of interest are presented in Table 2.

Given that we found the proportion of medicated depressed persons in a study to predict the magnitude of the difference in amygdala volume between depressed and control participants, we conducted a follow-up analysis to explore further how the inclusion of medicated participants in studies might affect conclusions drawn from the literature examining amygdala volume in depression. We calculated weighted mean effect sizes for two types of studies comparing amygdala volume in depressed and nondepressed samples: those using depressed samples composed entirely of unmedicated individuals and those using samples in which all of the depressed participants were medicated. These calculations indicate that whereas for studies that included only unmedicated depressed participants amygdala volume is significantly lower in depressed than in control groups ($d = -1.238$, $z = -2.416$, $p = .01$), studies in which all depressed participants were medicated show the opposite effect, with amygdala volume significantly *increased* in depressed relative to control participants ($d = .938$, $z = 3.243$, $p < .01$). These results are presented in Figure 1.

Discussion

The meta-analysis presented here showed that while there was no aggregate-level difference between depressed and nondepressed individuals in amygdala volume, there was significant inter-study variability in the difference between depressed and nondepressed groups in amygdala volume. Further, among four factors considered in studies of amygdala volume in depression – proportion of medicated depressed participants, chronicity of depressive illness, age, and gender composition of samples – the proportion of medicated depressed persons included in the studies predicted significant unique variation in group differences in amygdala volume. More specifically, the greater the proportion of medicated individuals in a depressed sample, the larger the difference between depressed and nondepressed participants in amygdala volume. Follow-up meta-analyses indicated that amygdala volume was significantly *decreased* in depression in studies that included unmedicated depressed participants, and significantly *increased* in depression when considering only studies with samples composed entirely of medicated depressed persons.

These results are important for several reasons. First, they are consistent with an account of the inconsistencies in the literature relating depression to amygdala volume in which confounding of depression with antidepressant usage biases estimates of amygdala volume in depression. Second, these findings support the formulation that depression, as an unmedicated disorder, is associated with decreased amygdala volume. Finally, these results provide evidence that antidepressant pharmacotherapy can facilitate neuro- or gliogenesis in the human amygdala.

Our finding that unmedicated depression is associated with decreased amygdala volume is consistent with a literature demonstrating decreased hippocampal volume in depression (14, 22,31,38). Stress-induced glucocorticoid excitotoxicity, which has been postulated to underlie hippocampal atrophy in psychiatric illness (e.g., 39), stands as a potential moderator of amygdalar volume loss in depression. This is a reasonable hypothesis given that the amygdala, like the hippocampus, is dense with glucocorticoid receptors (e.g., 40). However, if cumulative effects of glucocorticoid exposure account for volumetric decrease of the amygdala in depression then we would also expect a negative correlation between amygdala volume and recurrence or chronicity of depression, as has been shown in studies of hippocampal volume

and depression (14,22,31,38). It is noteworthy, then, that we did not find that chronicity of depression predicted variability in group differences in amygdala volume across studies. One likely reason for this is that, perhaps not unexpectedly, in the studies included in the present meta-analysis, there was a near-significant negative correlation between chronicity of depression and proportion of medicated depressed participants in a given sample [$r(7) = -.63$, $p = .07$]. After this association was accounted for in our meta-regression, the medication variable continued to predict significant variation in differences in amygdala volume, while the chronicity variable did not. Excluding the medication factor in a meta-regression (i.e., including only age, gender, and chronicity variables), we found chronicity, but not age or gender, to account for significant variation in group differences in average amygdala volume (regression coefficient = −.67, $p < .01$). It will be important in future research to distinguish and separate medication status and chronicity of depression in order to assess the independent contribution of these of these factors and their interaction in affecting amygdala volume in depression.

Our finding that amygdala volume is significantly increased in samples of medicated depressed participants is consistent with, and extends, a growing body of evidence that antidepressant treatment facilitates growth of new neurons and glia. In studies with both rodents (24,30) and nonhuman primates (41), administration of antidepressant medication has been found to lead to neurogenesis in the hippocampus. Adding to this, there is evidence that neurogenesis also takes place in the amygdala (42–44), and that gliogenesis in the amygdala can occur following induced electroconvulsive seizures (45), a common and effective intervention for intractable depression. It is possible that increased production of brain-derived neurotrophic factor (BDNF), which has been demonstrated to facilitate neurogenesis and protect against excitotoxicity in both the hippocampus (46–48) and striatum (49,50), mediates the increase in amygdala volume in samples of medicated depressed individuals. This is a viable hypothesis given both that administration of antidepressant medication has been found to increase BDNF expression in the hippocampi of rodents (51) and humans (52), and that BDNF and its receptor, tyrosine kinase B, are present in the amygdala and are centrally involved in amygdala-dependent learning (53,54).

One variable that was not investigated in the present meta-analysis was the way in which, across the various studies, the amygdala was defined for purposes of volume estimation. This is an important variable to consider in light of work by Sheline et al. (3) showing a significant decrease in core amygdala nuclei (basal, accessory basal, and lateral) but *not* in total amygdala volume in depression. While we were careful to include only studies in which the amygdala was defined independent of the hippocampus, the definitions of amygdala volume reported in the larger literature were highly variable and not easily quantifiable and were, thus, not included in our meta-analysis. Future meta-analyses that will be able to incorporate a larger number of studies will be important in examining the impact of variation in amygdala boundary definitions on estimated amygdala volumetric differences between depressed and healthy individuals.

The present findings raise several questions to be addressed in future research. While investigators have found smaller amygdala volume in depression to be associated with *increased* responsivity to affective stimuli (55), the functional implications of increases in amygdala volume in depression – potentially instigated by antidepressant treatment – have not been adequately explored. It is likely that the cellular composition of any increase in amygdala volume will determine the nature of its functional consequences. Work by Wennstrom, Hellsten, and Tingstrom (45), for example, suggests that generation of oligodendrocytes in the amygdala is responsible for the antidepressant-related volumetric increase in this structure. These investigators found that inducing electroconvulsive seizures in rats facilitated generation of amygdalar oligodendrocytes, cells shown both to be reduced in the amygdala of depressed individuals (56) and to be implicated in uptake of extracellular glutamate (57), a

neurotransmitter which, when present in excess in the extracellular environment, promotes excitotoxic neural degeneration (39). It will be important in future research to examine whether pharmacological antidepressant therapy similarly influences oligodendrocyte proliferation in humans.

To the extent that the current findings show that a volumetric decrease in the amygdala is associated with unmedicated depression, they also raise questions concerning *how* this volumetric decrease relates to depressive pathology. Does abnormally low amygdala volume precede and function as a potential risk factor for depression, or might it be a symptom or consequence of a depressive episode? Research with never-depressed populations at high risk for depression, and with identical twins discordant for depressive illness, will be instrumental in addressing these issues concerning the temporal and causal relation between amygdala abnormality and depression.

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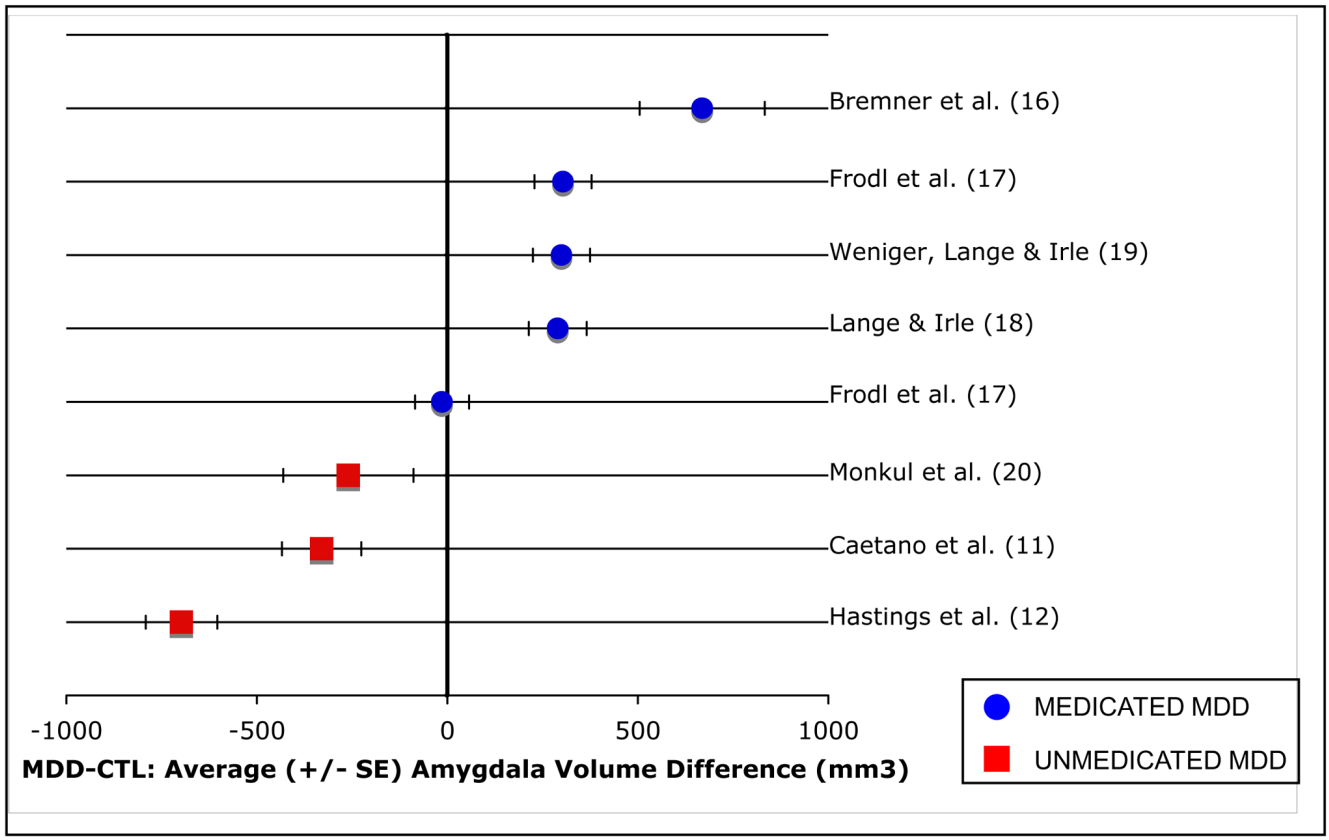

Figure 1.
Average (+/− SE) amygdala volume difference between depressed and nondepressed samples for studies in which all depressed participants were medicated and for studies using unmedicated depressed samples.

Table 1

Participant Information and Results from MRI Studies of Amygdala Volume in Major Depression

Study	n	Avg. MDD Age	% Female	% MDDs on Antidepressant Meds	Avg. Number of Episodes	Avg. MDD Bilateral Volume (SD) in mm^3	Avg. CTRL Bilateral Volume (SD) in mm^3	Avg. Volume Difference (mm^3)	Additional information
Hastings, Parsey, Oquendo, Arango and Mann (12)	18 MDD 18 CTRL	40	55%	0%	4.7	2865 (280)	3563 (282)	−698*	Right amygdala significantly smaller and left marginally smaller (p = .08) in MDD. Effect driven by female participants..
von Gunten, Fox, Cipolotti and Ron (15)	14 MDD 14 CTRL	57	57%	79%	NA	3247 (271)	3758 (245)	−511*	Left amygdala significantly smaller and right marginally smaller in MDD.
Caetano et al. (11)	31 MDD 31 CTRL	38	77%	0%	5	3870 (430)	4200 (385)	−330*	Both currently and remitted depressed included. Left amygdala marginally smaller in MDD.
Hickie et al. (13)	45 MDD 16 CTRL	52	66%	64%	6.9	3100 (699)	3400 (500)	−300*	Total amygdala volume reported; significaantly smaller in MDD.
Monkul et al. (20)	10 MDD 17 CTRL	36	100%	0%	3.9	3810 (445)	4070 (410)	−260	Neither left nor right amygdala volumes differed significantly between groups.
Sheline, Sanghavi, Mintun and Gado (14)	24 MDD 24 CTRL	53	100%	67%	4.8	3273 (207)	3437 (178)	−164*	Volume of core nuclei but not whole amygdala was significantly decreased in MDD, bilaterally.
Sheline, Gado and Price (3)	20 MDD 20 CTRL	54	100%	70%	NA	3374 (307)	3534 (296)	−160*	Volume of core nuclei but not whole amygdala was significantly decreased in MDD, bilaterally.
Frodl et al. (17)	27 MDD 27 CTRL	49	48%	100%	NA	3542 (242)	3556 (280)	−14	Neither left nor right amygdala volumes differed significantly between groups.
Munn et al. (21)	26 MDD 18 CTRL	21	100%	8%	NA	3617 (225)	3572 (221)	45	Neither left nor right amygdala volumes differed significantly between groups.

Study	n	Avg. MDD Age	% Female	% MDDs on Antidepressant Meds	Avg. Number of Episodes	Avg. MDD Bilateral Volume (SD) in mm^3	Avg. CTRL Bilateral Volume (SD) in mm^3	Avg. Volume Difference (mm^3)	Additional information
Lange and Irle (18)	17 MDD 17 CTRL	34	100%	100%	2	2550 (260)	2260 (185)	290*	Left and right amygdala volume together, but not individually, was significantly greater in
Weniger, Lange & Irle (19)	21 MDD 23 CTRL	34	100%	100%	1.4	2600 (300)	2300 (200)	300*	Both left and right amygdala significantly larger in MDD.
Frodl et al. (17)	30 MDD 27 CTRL	40	56%	100%	1	3895 (277)	3591 (286)	304*	Left amygdala significantly larger in MDD.
Bremner et al. (16)	16 MDD 16 CTRL	43	38%	100%	2	3351 (474)	2682 (449)	669*	Left and right amygdalae marginally larger in MDD.

Note. CTRL, control participants; MDD, particpants with major depressive disorder; NA, information not available;

* significant ($p < .05$) or marginally significant ($.10 > p > .05$) difference between MDD and CTRL in left, right or total amygdala volume.

Table 2

Results of a Meta-Regression of Amygdala Volume Differences Against Percentage of Female Participants, Proportion of Medicated Depressed, Age of Sample, and Number of Episodes for MDD Study Participants.

	Regression Coefficient	*SE*	*z*	*p*
Medication	2.47	0.92	2.67	< 0.01
Chronicity	0.03	0.27	0.09	0.93
Age	−0.07	0.06	−1.17	0.24
Gender	−0.23	1.02	−0.22	0.82

Note. SE, standard error.