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Amygdala Volume in Late-Life Depression: Relationship with Age of Onset

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Abstract

Objectives—Depression is common in the elderly population. Although numerous neuroimaging studies have examined depressed elders, there is limited research examining how amygdala volume may be related to depression.

Design—A cross-sectional examination of amygdala volume comparing elders with and without a diagnosis of major depressive disorder, and between depressed subjects with early and later initial depression onset.

Setting—An academic medical center.

Participants—Ninety-one elderly patients meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for major depression (54 early-onset depressed and 37 late-onset depressed) and 31 elderly subjects without any psychiatric diagnoses.

Measurements—Amygdala and cerebral volumes were measured using reliable manual tracing methods.

Results—In models controlling for age, sex, and cerebral volume, there was a significant difference between diagnostic cohorts in amygdala volume bilaterally (left: $F_{[2, 116]} = 16.28$, $p < 0.0001$; right: $F_{[2, 116]} = 16.28$, $p < 0.0001$). Using least squares mean group analyses, both early- and late-onset depressed subjects exhibited smaller bilateral amygdala volumes than did the nondepressed cohort (all comparisons $p < 0.0001$), but the two depressed cohorts did not exhibit a statistically significant difference.

Limitations—Limitations include missing antidepressant treatment data, recall bias, inability to establish a causal relationship between amygdala size and depression given the cross-sectional nature of the design.

Conclusions—Depression in later life is associated with smaller amygdala volumes, regardless of age of initial onset of depression.

Keywords

age of onset; amygdala; depression; geriatrics; MRI

Neuroimaging has been widely used to elucidate anatomic differences related to major depressive disorder (MDD), many of which have focused on components of frontostriatal or frontolimbic neural circuits. Volumetric studies in adult MDD and geriatric late-life

depression (LLD) have reported smaller frontal lobe volumes,^{1,2} including smaller orbital frontal cortex volumes,³ as well as increases in age-related subcortical hyperintensities.^{2,4} Similarly, meta-analyses of neuroimaging studies in depression show consistent changes in the prefrontal cortex, hippocampus, and striatum, but the findings with regard to the amygdala have been less consistent. Despite differences in potential contributors to vulnerability to depression, such as observations of a significant association between LLD and medical comorbidity, there may be a common neural substrate across age groups in brain dysfunction related to depression. As classic symptoms of depression suggest dysfunctional emotive behavior and stress responses,⁵ the amygdala is of particular interest in MDD, and this region has not been extensively studied in LLD.

The amygdala plays a role in both the fear response and in processing emotional facial expressions, including sadness⁶ and fear.⁷ Functional neuroimaging studies support an association between amygdala function and depression, demonstrating that resting cerebral blood flow and glucose metabolism in the amygdala is positively correlated with depression severity.^{5,8} Interestingly, amygdala metabolism is found to decrease with treatment response, whereas persistent elevation is associated with depressive relapse.⁹ Furthermore, an asymmetrically response is observed in MDD patients who were shown fearful¹⁰ and sad faces,¹¹ a finding which resolved with antidepressant therapy.

Given the amygdala's role in modulating emotional behavior and stress responses, dysfunction of neural circuits involving the amygdala may play a role in the pathogenesis of depression.⁵ Previous studies in adult MDD have had conflicting results, showing evidence of increased amygdala volumes,^{12,13} which may be unilateral,¹⁴ reduced amygdala volumes,^{15,16} and asymmetrically reduced amygdala volumes (right smaller than left) in depressed individuals.¹⁷ Other studies suggest a relationship between antidepressant medication use¹⁸ and gender¹⁹ on amygdala volume in depressed patients. None of the aforementioned studies examined the geriatric population. One study did examine the amygdala in LLD,²⁰ but no significant volumetric differences were observed between depressed and nondepressed groups. However, the authors reported statistically significant contractions in the anterior amygdala of individuals with LLD, a region associated with the basolateral nucleus, which plays a key role in emotion regulation.

Given these past discrepancies and relative paucity of studies examining the amygdala in LLD, we explored this relationship further. We hypothesized that there is a relationship between LLD and amygdala volume. We also sought to determine whether amygdala volumetric differences were related to age of onset of MDD in an older cohort.

METHODS

Sample

All participants were 60 years or older and took part in the National Institute of Mental Health--sponsored Conte Center for the Neuroscience of Depression at Duke University Medical Center. Depressed participants met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for MDD on the basis of the National Institute of Mental Health Diagnostic Interview Schedule and by clinical interview with a geriatric psychiatrist. Exclusion criteria were (1) another major psychiatric illness; (2) history of substance abuse or dependence; (3) primary neurologic illness, including dementia; and (4) Magnetic resonance imaging (MRI) contraindications, such as implanted metal. Participants were recruited primarily through clinical referrals and also through limited advertising. Comparison participants were community-dwelling patients recruited from Duke's Aging Center Subject Registry. Eligible comparison participants met study entry criteria but had neither a self-report of neurologic or psychiatric illness nor evidence of a psychiatric

diagnosis on the basis of the diagnostic interview schedule and no contraindication to MRI. The study was approved by the Duke University Medical Center institutional review board, and all participants provided written informed consent.

MRI Acquisition and Image Analysis

MRI of the brain was performed on a 1.5T system (Signa, GE Medical Systems, Milwaukee, WI). Details of imaging procedures have been described elsewhere.²¹ An axial T1-weighted IR-prepped spoiled gradient echo 3D series was used for measuring the amygdala, with pulse sequence parameters of TE = 5, TI = 300 ms, TR = 16, full bandwidth = 32 KHz, a 256 × 256 matrix, 1.25-mm section thickness, 1 excitation and 25-cm field of view.

The MR images were transferred to the Duke Neuropsychiatric Imaging Research Laboratory, where all image analyses were performed. Images were initially resliced to a common geometry of 1 × 1 × 1.5 mm voxels. An automated 4-channel lesion segmentation, which takes advantage of FLAIR images for lesion detection, was performed to assess gray matter, white matter, cerebrospinal fluid, and white matter lesions. The algorithm used was a variation on the fully automated Expectation Maximization Segmentation method,^{22–24} which was optimized for vascular lesion assessment in elderly subjects. The software assigns a probability that a given pixel should be classified as gray matter, white matter, cerebrospinal fluid, lesion or nonbrain. First, images are aligned to a set of tissue probability images by using the mutual information registration tool.²⁵ The probability atlas provides spatial priors for each tissue that are used to initialize the tissue intensity histograms for the segmentation algorithm. The tissue probabilities are then derived in an iterative process using the intensity distributions of the different tissues for each of the input image contrasts. The process also evaluates and compensates for spatial distributions of intensity that could be due to various MRI artifacts such as radiofrequency inhomogeneity (bias correction). Lesions are detected as “outliers” to the normal tissue distributions. The method is capable of distinguishing and classifying lesions and other brain tissues simultaneously. The cerebrum, including both cerebral hemispheres (gray matter, white matter, lesions, and CSF), was measured as proxy for total brain volume and did not include the brain stem or cerebellum.

Amygdala processing was completed separately from this segmentation process. It used the Neuropsychiatric Imaging Research Laboratory software program GRID, using anatomic boundaries, which have been described previously.^{21,26} The GRID program allows for viewing and tracing in any of three orthogonal planes, regardless of acquisition. Volumes are calculated by multiplying the traced area on each slice-by-slice thickness and then summing the volumes. Briefly, the hippocampal-amygdala border is first outlined in the sagittal plane and then viewed in the coronal plane, where the amygdala is traced. Next, the hippocampal-amygdala transition area is identified in the axial plane, and its border is projected to the coronal plane. Third, the anterior amygdaloid area is recognized by using the optic chiasm as a landmark to identify the most anterior slice to be processed.²¹

Reliability was established by blinded raters who conducted two repeated measurements on 10 scans with at least 7 days between measurements. Analysts had to demonstrate good reliability before they were approved to process study data. Intraclass correlation coefficients were the following: total cerebrum = 0.997, left amygdala = 0.9, and right amygdala = 0.8.

Statistical Analyses

All statistical analyses were conducted using SAS 9.2 (Cary, NC). Subjects were classified in three cohorts: nondepressed, early-onset depressed, or late-onset depressed. Early- and

late-onset cohorts were defined as initial onset of depression before or at age 50 years, or after age 50 years.²⁷

Analysis of covariance was used to examine differences between the three cohorts in continuous variables. χ^2 tests were used to examine group differences in categorical variables, such as sex or race (dichotomized as Caucasian and non-Caucasian). General linear models (e.g., PROC GLM) were created to examine differences in amygdala volume in each hemisphere by cohort, where age, sex, and total cerebral volume were independent variables. Least square means analyses were used to test for differences between the three diagnostic cohorts, when the primary effect in the overall model reached statistical significance. Similar models were also created wherein the sample was dichotomized into depressed or nondepressed cohorts and not further subdivided on the basis of age of onset.

RESULTS

This study examined 91 elderly subjects with major depression and 31 elderly nondepressed comparison subjects. Fifty-four of the depressed subjects had an early-onset depression (EOD) and 37 had late-onset depression (LOD). Of note, 14 depressed subjects completed study procedures but could not conclusively identify an initial age of depression onset. These subjects were not included in the primary analyses but were included in secondary analyses examining the depressed and nondepressed cohorts, which did not dichotomize subjects by age of onset.

There were statistically significant group differences in age, education, and Mini-Mental State Exam (MMSE) score but not other demographic measures (Table 1). Using least squares means analyses, EOD subjects were significantly younger than LOD subjects ($p = 0.0066$), but there were no significant differences in comparisons with the nondepressed cohort. The LOD cohort also reported less education ($p = 0.0052$) and significantly lower MMSE scores ($p = 0.0066$) than the nondepressed cohort, but there were no significant group differences with the EOD cohort. Based on mean Montgomery-Asberg Depression Rating Scale (MADRS) scores, the majority of depressed subjects were symptomatic (Table 1); all LOD subjects exhibited a MADRS of 11 or greater, whereas only two EOD subjects exhibited a MADRS score less than 11.

In univariate analyses of MRI measures, significant group differences were noted in bilateral amygdala measures (Table 1). In these unadjusted comparisons, the nondepressed cohort exhibited significantly larger left and right amygdala volumes than both the EOD and LOD groups (all comparisons $p < 0.0001$). Comparing amygdala volumes between the EOD and LOD cohorts, left amygdala volume did not differ significantly ($p = 0.0522$), but the EOD cohort did exhibit significantly larger right amygdala volume than the LOD cohort ($p = 0.0423$).

Initial multivariate models included not only age, sex, and cerebral volume but also education and MMSE score, as these variables differed between some cohorts. Neither education nor MMSE was significantly associated with amygdala volume, so were removed from the models. In parsimonious models controlling for age, sex, and cerebral volume, cohort continued to be significantly associated with amygdala volume bilaterally (left: $F_{[2, 116]} = 16.28$, $p < 0.0001$; right: $F_{[2, 116]} = 16.28$, $p < 0.0001$). Using least squares means analyses, both depressed cohorts exhibited significantly smaller amygdala volumes bilaterally than did the nondepressed cohort (all comparisons $p < 0.0001$). However, the two EOD and LOD cohorts did not differ significantly (left: $p = 0.0997$; right: $p = 0.1115$). In these models, neither age nor sex was significantly associated with amygdala volume in

either hemisphere; however, total cerebral volume exhibited a significant positive association with amygdala volume bilaterally (data not shown).

We also tested for differences between depressed and nondepressed cohorts, without dividing the depressed cohort on the basis of age of onset. For these analyses, we included the 14 subjects who did not have definitive ages of initial depression onset, resulting in a comparison of 105 elderly depressed subjects and 31 elderly nondepressed subjects. After controlling for age, sex, and total cerebral volume, the presence of depression continued to be significantly associated with smaller volume of both the left amygdala ($F_{[1, 131]} = 27.15$, $p < 0.0001$) and the right amygdala ($F_{[1, 131]} = 29.71$, $p < 0.0001$).

DISCUSSION

The primary finding in this study is that when compared with elderly nondepressed subjects, both early-onset and late-onset depressed individuals exhibit significantly smaller amygdala volumes bilaterally. Although initial univariate comparisons found a difference in right amygdala volume between early- and late-onset depressed cohorts, this difference was no longer statistically significant in models controlling for age, sex, and cerebral volume, so we conclude that there is no difference between depressed cohorts based on age of depression onset.

This study supports previous findings indicating smaller amygdala volumes in depressed individuals.^{17,29,30} Although most prior studies examined general adult populations, our study expands this concept to older patients. In addition, previous studies have suggested differences in amygdala size in depressed versus remitted patients,^{9–11} but we were unable to replicate those findings in this elderly cohort, as our subjects were symptomatic.

Previous studies have shown that lesions to the amygdala change emotional responses, especially recognition of facial expression.³¹ Electrical stimulation of the amygdala induces strong emotional responses, and increased cortisol secretion; furthermore, there is greater amygdala activity in depressed individuals.⁹ Other studies have suggested that increased amygdala activity may contribute to elevation of corticotrophin releasing hormone secretion seen in MDD.³² These findings support the impact of amygdala dysregulation on major depression, which also applies to the pathophysiology of LLD.

LLD is heterogeneous; however, this study demonstrates that there may be common neuroanatomic differences observed in LLD even when age of onset suggests different contributing etiologies. Subjects with a later-life onset of depression often exhibit greater age-related changes on MRI^{33–37} and greater cognitive impairment^{38,39} than do individuals with earlier age of depression onset. Moreover, genetic/familial associations differ at age of depression onset.⁴⁰ However, despite these clinical differences, which may represent different etiologic vulnerabilities, EOD and LOD cohorts exhibited no difference in amygdala volumes.

Limitations of this study include a lack of antidepressant treatment data. Some studies have suggested a relationship between antidepressant medication and amygdala volume,¹⁸ so our imaging results may have been influenced by antidepressant use. Given the cross-sectional design of our study, we are unable to establish a causal relationship between amygdala size and depression. It is not clear if amygdala atrophy occurs due to depression and so may be a state marker, or if smaller amygdala volume is a trait marker and may represent a vulnerability factor for developing depression. Another limitation of our study is the impact of recall bias on age of onset data. Uncertainty of initial age of onset likely contributed to missing data for this variable, although exact age of onset may not be critical, as our dichotomous classification of this variable minimizes risk of inaccuracies. Finally, the

relationship between amygdala structure and function has not been determined. Although many studies have suggested that depressed individuals have smaller or larger amygdala volumes, there is no definitive evidence that smaller amygdala volumes result in impaired function. This limitation may be broadly applied to many structural imaging studies.

Although the results of this study are generalizable only to older populations, similar findings have been found in younger adult populations. We believe that our results have not only successfully replicated previous findings of smaller amygdala size in adult populations to the elderly population, but our findings improve our understanding of the neuroanatomic basis of depression in this elderly population. Future examination of this subject and understanding of the relationship between amygdala structure and function may lead to advancements in the clinical treatment of MDD, specifically LOD.

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Table 1

Demographics and Statistical Analyses

	EOD subjects (n = 54)	LOD subjects (N= 37)	Non- Depressed subjects (n = 31)	df	Test Value	P-value
Age, y	66.1 (6.0)	70.1 (6.6)	68.8 (6.0)	2, 119	F = 4.95	0.0086
Sex, % female,(n)	63.0% (34)	51.4% (19)	67.7 (21)	2	$\chi^2 = 2.12$	0.3473
Ethnicity, % Caucasian, (n)	85.2% (46)	91.9% (34)	87.1 (27)	-	Fisher's Exact Test	0.6853
Education, y*	14.4 (2.6)	13.8(2.6)	15.4 (1.6)	2, 118	F = 4.10	0.0189
MMSE*	28.3 (1.8)	27.6 (2.2)	28.9(1.3)	2,114	F = 3.83	0.0245
MADRS*	23.15(5.85)	24.4 (6.94)	-	88	t = 0.86	0.3572
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Amygdala volume (ml)						
Right	2.05 (0.38)	1.89 (0.27)	2.40 (0.40)	2, 119	F = 17.55	<0.0001
Left	2.06 (0.41)	1.91 (0.38)	2.43 (0.30)	2, 119	F = 17.05	<0.0001
Cerebrum volume (ml)	1144.5 (150.1)	1155.0 (108.4)	1173.4 (102.9)	2, 119	F = 0.50	0.6059

Continuous variables presented as mean (standard deviation). Comparison of sex differences utilized the chi-square test, while the ethnicity analysis used the Fisher's exact test. Continuous variables were compared using ANCOVA, except for the MADRS comparison, which used a pooled, two-tailed t-test. EOD = Early onset depression; LOD = Late onset depression; MADRS = Montgomery-Asberg Depression Rating Scale; MMSE = Mini-Mental State Exam.

* There were missing data for some variables: education (1 LOD subject), MMSE (3 LOD, 2 EOD), and MADRS (1EOD)