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Relationship between depressive symptom severity and amygdala volume in a large community-based sample

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ABSTRACT

Amygdala is an affective processing center that regulates and assigns valence to different emotions and has been implicated in the pathophysiology of mood disorders. This population-based study employed a community sample of 1747 adults to examine relationships between amygdala volume and depressive symptom severity. Neuroimaging data from participants in the Dallas Heart Study were used. Magnetic resonance images of right, left, and total amygdala volume were used as response variables in multiple regressions. Predictor variables included Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scores, intracranial volume, age, gender, race/ethnicity, body mass index, self-reported alcohol use, years of education, and psychotropic medication use. In the overall sample, QIDS-SR scores were not significantly related to left, right or total amygdala volume. A significant QIDS-SR by age interaction was observed, thus a follow-up subgroup analysis was conducted in age groups 18–39, 40–59, and ≥ 960. A significant negative relationship was observed between QIDS-SR scores and right and total, but not left, amygdala volume in the 18–39 age group but not in other age groups. Significant relationship between QIDS-SR scores and amygdala volume in young adults suggests possible biological differences in depressive symptoms in people of this age group.

1. Introduction

Depression is a serious mood disorder that affects nearly 25 million individuals per year in the United States (Keller, 1994). The annual economic cost of depressive disorder averages over 40 billion dollars based on broad measures such as treatment costs, work absenteeism, worker productivity decline, and other factors (Antonuccio et al., 1997).

The amygdala plays a key role in emotional regulation and affective processing, and, thus, has been hypothesized to be of importance in the pathophysiology of mood and anxiety disorders (Drevets et al., 2008). Amygdala shares multiple projections with cortical and subcortical regions implicated in depression, including the hippocampus, anterior cingulate cortex, medial prefrontal and orbitofrontal cortices (Drevets et al., 2008). Studies show that these anatomical regions share a role in the emotionally salient event processing, with amygdala, in particular, playing a major role in assigning valence to positively and negatively charged emotional events and integrating reward information (Murray, 2007, Sergerie et al., 2008). Thus, the amygdala is a brain region that may be highly pertinent to the pathophysiology of depression and other mood disorders. A meta-analysis of 94 healthy control functional magnetic resonance imaging (MRI) studies showed that bilateral amygdala had the highest level of functional connectivity with regions involved in affective processing during the exposure to negative visual stimuli. In particular, the authors noted that the younger (age 17–31), but not the older (age 59–84) participants, had the highest level of activation in the left amygdala region (Garcia-Garcia et al., 2016).

Some evidence suggests that depression is associated with amygdala volume; however, the direction of difference in amygdala volume between depressed and non-depressed people is complex (Drevets et al., 2008). Previous reports on amygdala volume in depression reveal mixed findings, including larger (Weniger et al., 2006, Frodl et al., 2002), smaller (Caetano et al., 2004, Coffey et al., 1993), or no difference (Munn et al., 2007) in amygdala volume in patients with depression versus healthy controls. These findings, however, also suffer from small sample sizes or samples limited to only females. Structural imaging findings on amygdala volume and depression may also be confounded by having the sample limited to patients receiving antidepressant treatment at the time of their scan (Weniger et al., 2006,

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Frodl et al., 2002, Bremner et al., 2000), as well as by a significant variation in severity of depressive symptoms (Mervaala et al., 2000) and the number of depressive episodes in the patient sample (Frodl et al., 2002). A meta-analysis of 13 studies reported a "lack of a reliable difference in amygdala volume between depressed and never-depressed individuals" that appeared to be related to medication effects (Hamilton et al., 2008). Due to these mixed findings in the existing literature, significant controversy exists concerning whether amygdala volume increases or decreases in people with depression. As a result of prolonged stress exposure, such as the extensive processing of fearful or negative responses (Vyas et al., 2002, Hölzel et al., 2010), the amygdala could potentially increase in size in depressed people, much as the hippocampus increases in size with increased use of spatial memory processing (Maguire et al., 2006). On the other hand, the effects of depression on the brain (e.g. cortisol elevations that lead to brain region atrophy), could cause amygdala volume, like hippocampal volume (Geerlings and Gerritsen, 2017, Brown et al., 2014), to be smaller in depressed people than controls. Thus, the mixed findings regarding the relationship between amygdala volume and depression present a conundrum. Due to the mixed findings on the relationship between amygdala volume and depressive symptoms, as well as lack of consistent findings regarding the demographic variables that influence this relationship, we used the large sample size of the Dallas Heart Study (DHS) study to examine the relationship between depressive symptom severity and amygdala volume. Specifically, we wanted to assess the direction of the relationship between amygdala volume and depressive symptom severity in a large, multi-ethnic, population-based cohort of English or Spanish-speaking adults, and explore whether demographic characteristics influence the findings.

2. Methods

2.1. Participants

The DHS was designed to examine cardiovascular disease risk factors and collect data for future studies. The initial study (DHS-1) consisted of an epidemiologic sample of Dallas County adults, except for intentional over-sampling of African Americans (approximately 50%) to examine cardiovascular risk factors in this subpopulation. DHS-1 collected socioeconomic, biomarker, and a variety of other data from participants. Both monolingual (English only, Spanish only) and bilingual (English and Spanish, English and other language) participants were included in the study. Although the focus of the study was cardiovascular risk factors, participants were not selected based on pre-existing or increased risk for cardiovascular disease. The participant sample was selected to be representative of Dallas County and was not a clinical population selected for the presence or absence of clinical symptoms, including depressive symptoms. The second phase (DHS-2) included both participants from DHS-1, who could be contacted and agreed to participate, as well as new participants (e.g. family members and spouses of DHS-1 participants) for a total sample of $N = 3401$. The DHS-2 sample had a slightly higher proportion of women and Caucasians than DHS-1 due to differential attrition following DHS-1. For DHS-2, additional blood sample collections, structural MRI, depressive symptom assessment symptoms and other phenotypes were collected. The data used in this study were obtained from DHS-2. All participants signed written informed consents approved by The University of Texas Southwestern Medical Center Institutional Review Board. DHS-1 and 2 designs, participant selection methods, assessments, laboratory tests, and imaging methods have been described previously in detail (Victor et al., 2004, Lucarelli et al., 2013, Gupta et al., 2015).

The DHS-2 data in the current report were collected from September 2007 through December 2009. Extensive information regarding subject social and biological variables were obtained as part of the study. Demographic characteristics included in this current study consist of gender, race/ethnicity (African American, Caucasian, Hispanic, and other), body mass index (BMI), age (all adults over the age of 18), education years, and self-reported alcohol use. The DHS-2 collected MRI scans of the brain and other organ systems. Individuals with a history of brain surgery, metal fragments, pacemakers, implantable cardio-defibrillators, cochlear implants, spinal cord stimulators, or other internal electrical devices, or who were pregnant or had jobs that could have exposed them to metal fragments were also excluded from the MRIs. Thirty-seven ($n = 37$) participants were excluded from subsequent neuroimaging analysis for self-reported stroke. Seventy ($n = 70$) additional individuals were excluded during MRI review due to major structural defects (such as corpus callosum agenesis, imaging evidence of stroke, and hydrocephalus) or image-acquisition errors (such as metal and motion artifacts and other noise). In total, 107 individuals were excluded from the subsequent analysis.

Images of outliers, as determined by Robust Minimum Covariance Distance analysis of brain segments (A Jackson and Chen, 2004), individuals flagged for exclusion in previous DHS-2 MRI brain studies, and individuals who had error flags generated during automated analysis were reviewed by a neuroradiologist. The participants with a Talairach atlas registration had the atlas manually realigned and the images reanalyzed. The images with minor analysis errors and timeout errors were also manually reviewed and reanalyzed (Lucarelli et al., 2013).

2.2. DHS-2 missing data excluded from the analysis

The initial DHS-2 sample consisted of $n = 3401$ participants. Participants were excluded from the analysis if they were missing an MRI scan ($n = 1396$) and/or missing a Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) score ($n = 375$), and/or alcohol use ($n = 128$), and/or education years ($n = 96$), and/or BMI ($n = 27$), resulting in the final analyzed sample of $n = 1797$ and excluded sample of $n = 1604$. The excluded participants were demographically similar to those included in the analysis except there was a higher proportion of Caucasian individuals (37.6% versus 25.7%) and fewer African American individuals (46.3% versus 56.0%) in the included data.

2.3. Neuroimaging acquisition and analysis

All Magnetization Prepared Rapid Acquisition GRE (3D Inversion Recovery) (MP-RAGE) images were collected on a single 3T MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands). Axial images were obtained from the vertex of the skull to foramen magnum. The 3D MP-RAGE images were acquired with TR (repetition time)/TE (echo time) = 9.6/5.8 msec, flip angle = 12°, sensitivity encoding (SENSE) factor = 2, field of view (FOV) = 260 × 260 mm, 2 mm slices spaced at 1 mm centers, Rows x Cols x Slices = 288 × 288 × 140, and voxel size of 1 × 0.9 × 0.9 mm (Hulsey et al., 2012).

As part of DHS-2 data analysis, MRI quantification was performed using FreeSurfer image analysis (Version 4.4, available from http://surfer.nmr.mgh.harvard.edu) previously described elsewhere (Gupta et al., 2015). The FreeSurfer based segmentation protocol has been found comparable in its performance relative to the manual segmentation (Grimm et al., 2015). FreeSurfer was used for the structural MRI data. The neuroimaging data were recorded by the DHS using gray-white matter segmentation, cortical surface models, and statistical analysis of morphometry differences (Desikan et al., 2006, Fischl et al., 2002). The fully automated analysis was performed at the Texas Advanced Computing Center at The University of Texas at Austin. Volumes of the left and right amygdala, as well as other cortical and subcortical structures not reported here, were derived from MPRAGE sequences.

2.4. Assessments

The QIDS-SR is a 16-item, self-rated assessment of depressive symptom severity over the prior seven days (Rush et al., 2000, 2003, Trivedi et al., 2004). This assessment was completed in either English or Spanish, depending on the language preference indicated by each participant via self-report. Bilingual participants completed the QIDS-SR in their preferred language. The QIDS-SR assesses the nine symptom domains of the major depressive disorder (MDD), with the total score ranging from zero to 27. The symptom severity can be interpreted based on the following categories: "no symptoms" (0–5), "mild" (Garcia-Garcia et al., 2016, Weniger et al., 2006, Frodl et al., 2002, Caetano et al., 2004, Coffey et al., 1993), "moderate" (Munn et al., 2007, Bremner et al., 2000, Mervaala et al., 2000, Hamilton et al., 2008, Vyas et al., 2002), "severe" (Hölzel et al., 2010, Maguire et al., 2006, Geerlings and Gerritsen, 2017, Brown et al., 2014, Victor et al., 2004), and "very severe" (Lucarelli et al., 2013, Gupta et al., 2015, A Jackson and Chen, 2004, Hulsey et al., 2012, Grimm et al., 2015, Desikan et al., 2006, Fischl et al., 2002, Rush et al., 2003). The internal consistency of the QIDS-SR (Cronbach's alpha = .86) is comparable to that of the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) (Rush et al., 2003). QIDS-SR has shown robust reliability and validity across a variety of races (Lamoureux et al., 2010, Sung et al., 2013), ages (Bernstein et al., 2010, Doraiswamy et al., 2010), and languages (Trujols et al., 2014). Scores on the QIDS-SR correlate highly with those of the longer 30-item Inventory of Depressive Symptomatology Self-Report ($IDS\text{-}SR_{30}$) (r = .83) and $HAMD_{17}$ (r = .86) (Trivedi et al., 2004).

2.5. Statistical analysis

Multiple linear regressions were performed using SPSS Statistical Software version 25. Left, right, and total amygdala volumes (mL) were used as the response variable, while the predictor variables included age (years), gender (male, female), race/ethnicity (Caucasian, African-American, Hispanic, Other), psychotropic medications (yes, no), intracranial volume (mL), BMI (kg/m^2), alcohol use (current drinker versus lifetime or recent abstainer), years of education, and QIDS-SR total score. Both intracranial volume and BMI were used in the analysis, as the variables did not appear to have a meaningful correlation ($r = -.19$). The total amygdala volume was calculated by adding the left and right amygdala volumes together. Psychotropic medications in the dataset included attention deficit hyperactivity disorder (ADHD), anticonvulsant, antidepressant, antidepressant/antipsychotics, antipsychotics, anxiolytics, and hypnotic medications. The original analyses included language as a covariate due to the bilingual nature of the sample. However, the variable did not appear to have a statistically significant moderating effect on the results and was, thus, removed from the final models. In addition to the linear regressions, exploratory analyses on the interactions between QIDS-SR scores and significant covariates were conducted. To create the interaction terms, continuous variables were mean-centered and multiplied together.

The follow-up age subgroup analysis was conducted by splitting the dataset into three age group (18–39, 40–59, ≥ 60) and using multiple linear regression to examine the relationship between the predictor and response variables within each group. Statistical significance was defined by a p value < .05.

3. Results

3.1. Demographics

The demographic features of the participants are summarized in Table 1. There was a greater proportion of women (59.6%) than men (40.4%) in this study. A total of 46.3% were African American, 37.6% were Caucasian, 13.70% were Hispanic, 2.1% were other, and the remaining 0.3% were of unknown racial or ethnic groups. The dataset was primarily composed of English-only speakers (85.9%). Individuals who were not on psychotropic medications comprised of 82% of the sample. The participant age ranged from 19 to 85 (M = 49.86, SD = 10.60), and the QIDS-SR score was between zero and 24 (M = 5.27, SD = 3.77, which is at the boundary between none and mild depressive symptom severity).

Table 1
Sample demographic characteristics (N = 1797).

	Mean	SD	Range
Age (years)	49.86	10.60	19–85
Years of education	12.87	2.14	0–16
BMI	29.72	5.66	17.9–53.7
QIDS-SR	5.27	3.77	0–24
Total amygdala volume (mL)	3050.46	412.17	1008–4645
Left amygdala volume (mL)	1457.68	210.76	490–2229
Right amygdala volume (mL)	1592.78	227.19	518–2457
Total intracranial volume (mL)	1.1×10^6	2.4×10^5	6.2×10^5–1.9×10^6
	n	%	
Sex			
Male	726	40.4	
Female	1071	59.6	
Race/Ethnicity			
Caucasian	676	37.6	
Hispanic	247	13.7	
African American	832	46.3	
Other	37	2.1	
Unknown	5	0.3	
Language			
English only	1544	85.9	
English and spanish	148	8.2	
Spanish only	72	4.0	
English and other	27	1.5	
Unknown	6	0.3	
Psychotropic medications			
Yes	320	17.8	
No	1477	82.2	
Alcohol use			
Current drinker	1310	72.9	
Lifetime/recent abstainer	487	27.1	

Note: BMI – Body Mass Index; QIDS-SR – Quick Inventory of Depressive Symptomatology Self-Report; SD – Standard Deviation. Alcohol use was measured via self-report.

3.2. Primary analysis

The results of multiple linear regressions with amygdala volume as the outcome variable are displayed in Table 2. After controlling for demographic features and intracranial volume, QIDS-SR scores were not significantly related to left (p = .650), right (p = .440) or total (p = .505) amygdala volumes in the overall sample.

The total amygdala volume was significantly predicted by age (p < .001), gender (p < .001), ethnicity (p = .013), BMI (p < .001), years of education (p = .006), and psychotropic medication use (p = .015). The right amygdala volume was significantly related to age (p < .001), gender (p = .001), BMI (p < .001), and years of education (p = .013), while the left amygdala volume was significantly related to age (p < .001), gender (p < .001), ethnicity (p = .004), BMI (p < .001), years of education (p = .007), and psychotropic medication use (p = .005).

3.3. Exploratory and follow-up analyses

The influence of significant predictor variables on the relationship between QIDS-SR and amygdala volume, controlling for other covariates, was examined using the following interaction terms: age*QIDS-SR, gender*QIDS-SR, ethnicity*QIDS-SR, BMI*QIDS-SR, years of education*QIDS-SR, and psychotropic medication use*QIDS-SR. The

Table 2
Linear regression analyses of left, right, and total amygdala volume (N = 1797).

Predictor variable	*B* (Coefficient)	*p*-value	95% CI lower bound	95% CI Upper Bound
Left amygdala volume (R^2 = .172)				
QIDS-SR	−0.58	.650	−3.08	1.92
Age	−4.29	.000	−5.15	−3.44
Gender	46.09	.000	22.01	70.17
Ethnicity	17.41	.004	5.611	29.21
BMI	4.01	.000	2.39	5.64
Years of education	6.02	.007	1.64	10.41
Alcohol use	15.00	.152	-5.53	35.53
Psychotropic medications	−34.40	.005	−58.56	−10.24
Intracranial volume	0.00	.000	0.00	0.00
Right amygdala volume (R^2 = .132)				
QIDS-SR	−1.09	.440	−3.84	1.67
Age	−4.71	.000	−5.65	−3.76
Gender	45.90	.001	19.32	72.48
Ethnicity	11.77	.077	−1.26	24.79
BMI	5.25	.000	3.45	7.04
Years of education	6.14	.013	1.30	10.98
Alcohol use	10.01	.386	−12.65	32.67
Psychotropic medications	−24.18	.076	−50.84	2.49
Intracranial volume	0.00	.000	0.00	0.00
Total amygdala volume (R^2 = .132)				
QIDS-SR	−1.66	.505	−6.56	3.23
Age	−9.00	.000	−10.68	−7.32
Gender	91.99	.000	44.80	139.17
Ethnicity	29.18	.013	6.06	52.29
BMI	9.26	.000	6.07	12.44
Years of education	12.16	.006	3.57	20.75
Alcohol use	25.01	.223	−15.21	65.24
Psychotropic medications	−58.58	.015	−105.92	−11.24
Intracranial volume	0.00	.000	0.00	0.00

Note: QIDS-SR – Quick Inventory of Depressive symptomatology Self-Report; BMI – Body Mass Index; CI – Confidence Interval.

age*QIDS-SR interaction term was the only significant interaction observed for the total ($p < .001$), left ($p = .001$), and right ($p < .001$) amygdala volumes. Therefore, a follow-up subgroup analysis divided by age (18–39–young adults, 40–59–middle-aged adults, ≥ 60–older persons) was conducted (Table 3). Those between the ages of 18 to 39 years, but not middle-aged to older age groups, displayed a significant, negative relationship between QIDS-SR scores and total ($p = .048$) and right ($p = .044$) amygdala volumes. However, this finding in younger adults did not withstand correction for multiple comparisons (.05/3 = .017).

4. Discussion

The current study results suggest that depressive symptom severity is not significantly associated with amygdala volume in a sample of 1747 participants. The findings suggest that any relationship between amygdala volume and depressive symptoms may be relatively modest (e.g. $B = -10.42$, $p = .048$ for the total amygdala volume in those between the ages of 18 and 39), which may explain the mixed findings in prior, smaller studies.

Given the large and diverse sample in the current study, subgroup analyses were explored. Gender, ethnicity, years of education, BMI, and psychotropic medication use did not appear to moderate the relationship between depressive symptom severity and amygdala volume in this sample. A prior meta-analysis reported that amygdala volume is smaller in unmedicated, depressed people and larger in medicated, depressed people than in controls (Hamilton et al., 2008). Psychotropic medication use was related to the left amygdala volume in the current report (Table 2); however, the QIDS-SR by psychotropic medication interaction was not significant suggesting that psychotropic medication use did not moderate the relationship between QIDS-SR scores and amygdala volume in the current sample. Although prior research on the relationship between the depressive symptoms, psychotropic medication use, and amygdala volume are limited; some research exists on the amygdala activation in response to psychotropic treatment with selective serotonin reuptake inhibitors (SSRIs) in depression. For example, a 7-day treatment with escitalopram in sample of depressed patients

Table 3
Linear regression analyses of left, right, and total amygdala volume by age group.

	18–39 Years (n = 335)			40–59 Years (n = 1091)			≥ 60 Years (n = 371)		
Left amygdala volume	***B* (Coefficient)**	***p*-value**	***t***	***B* (Coefficient)**	***p***	***t***	***B* (Coefficient)**	***p***	***t***
QIDS-SR	−4.20	.105	−1.63	0.26	.871	0.16	1.31	.695	0.39
Gender	44.98	.112	1.60	50.70	.001	3.20	31.90	.238	1.18
Ethnicity	53.58	.000	4.96	1.87	.814	0.24	18.71	.240	1.18
BMI	7.30	.000	4.56	2.88	.008	2.65	2.77	.173	1.37
Years of education	3.68	.464	0.73	5.22	.065	1.85	7.16	.183	1.34
Alcohol use	38.95	.088	1.71	4.06	.768	0.30	36.75	.106	1.62
Psychotropic medications	−48.07	.130	−1.52	−18.09	.259	−1.13	−76.93	.002	−3.09
Intracranial volume	0.00	.000	5.09	0.00	.000	6.68	0.00	.037	2.10
Right amygdala volume									
QIDS-SR	−6.23	.044*	−2.03	0.10	.956	0.06	2.89	.424	0.80
Gender	41.99	.212	1.25	50.44	.004	2.91	35.37	.227	1.21
Ethnicity	36.05	.005	2.80	0.38	.965	0.04	17.84	.301	1.04
BMI	8.19	.000	4.29	4.48	.000	3.78	2.60	.238	1.18
Years of education	9.12	.129	1.52	5.76	.063	1.86	2.12	.715	0.37
Alcohol use	19.03	.483	0.70	−0.484	.974	−0.03	41.15	.095	1.68
Psychotropic medications	−97.37	.010	−2.58	−15.35	.381	−0.88	-30.74	.255	−1.14
Intracranial volume	0.00	.000	3.62	0.00	.000	5.61	3.45	.587	0.54
Total amygdala volume									
QIDS-SR	−10.42	.048*	−1.99	0.36	.909	0.11	4.20	.517	0.65
Gender	86.96	.130	1.52	101.14	.001	3.27	67.27	.200	1.28
Ethnicity	89.62	.000	4.09	2.25	.885	0.15	36.55	.237	1.18
BMI	15.50	.000	4.76	7.36	.001	3.47	5.37	.174	1.36
Years of education	12.80	.211	1.25	10.98	.047	1.99	9.28	.374	0.89
Alcohol use	57.97	.210	1.26	3.57	.894	0.13	77.90	.078	1.77
Psychotropic medications	−145.43	.024	−2.26	−33.45	.285	−1.07	−107.67	.027	−2.23
Intracranial volume	0.00	.000	4.63	0.00	.000	6.56	0.00	.168	1.38

Note: QIDS-SR – Quick Inventory of Depressive symptomatology Self-Report; BMI – Body Mass Index; CI – Confidence Interval.

reduced amygdala hyperactivity in response to negative stimuli and normalized it to the healthy control level (Godlewska et al., 2012). Similar findings were observed by Victor et al. who suggested that an 8-week sertraline course was associated with an increased amygdala response to happy faces and a simultaneous decrease in response to sad faces (Victor et al., 2010). These findings suggest that, in a clinical population, psychotropic medication use may play a role in structural brain changes and subsequent functional activity. Although the current study utilized a community sample and not a clinical sample, it is possible that psychotropic medications may influence the structural and functional brain changes regardless of the severity of depressive symptoms; however, additional research is needed to better understand these relationships.

The age by QIDS-SR interaction term was significant. A subgroup analysis revealed that QIDS-SR scores were negatively related to amygdala volume in individuals among the 18–39 age group (young adults) but not in the middle-aged to older age groups. This finding is, to our knowledge, relatively novel. Age has not been extensively explored as a factor in the relationship between amygdala volume and depressive symptoms. However, one study reported greater amygdala gray matter volume in young women (M = 20.26 years, SD = 0.89) with subthreshold depression as compared to controls (Li et al., 2015). The current findings suggest the opposite; a greater depressive symptom severity is associated with smaller amygdala volume in younger people. A small sample (N = 12) of adolescents (M = 14.95 years, SD = 1.60) showed greater right amygdala activation during encoding of positive stimuli compared to adults; however, this finding is limited to a non-clinical sample (Vasa et al., 2011). These studies differ in populations studied (undergraduate women in China versus a community sample of ages 18–39 years in Dallas, Texas versus a sample of adolescents), depressive symptom assessment (subthreshold depressive symptomatology versus non-depressed controls using Beck Depression Inventory cutoffs versus continuous QIDS-SR scores versus healthy controls), and imaging analysis (gray matter quantification using SPM8 versus volumetric analysis with FreeSurfer versus fMRI). Due to the limitations of the current dataset, depression course and history is not known. However, all of the younger participants in the DHS were, by definition, experiencing depressive symptoms at a relatively young age, while, presumably, the onset was more variable in older age groups. A recent study suggests a larger left amygdala gray matter volume in patients with later MDD onset compared to patients with longer disease progression (Zavorotnyy et al., 2018). Thus, the relationship between depressive symptom severity and amygdala volume may be due to pathophysiological differences in the nature (e.g. higher genetic load), severity, age of symptom onset, or persistence of depressive symptoms in younger people (Verduijn et al., 2017). The findings in this report, are consistent with findings from a recently published study that investigated the subcortical volumetric differences to find that the right amygdala volume was significantly smaller in clinically depressed young people (18–25 years) compared to healthy controls (Eggins et al., 2018). Another recent study reported significantly smaller amygdala volume among patients with MDD than healthy controls (Chen et al., 2016). Both of these reports, however, used a clinical adult sample compared a community-based sample of the current study, thus the similarities between the findings should be interpreted with caution.

The study has several limitations. Data are not available on the onset or course of depression. The QIDS-SR is designed to assess depressive symptom severity, not for obtaining a DSM-*5* MDD diagnosis. However, the use of a continuous, rather than a dichotomous measure such the presence or absence of MDD outcome measure, increased the statistical power of the analysis (Altman and Royston, 2006). Information about other psychiatric disorders is not available. Thus, the depressive symptoms could be the result of MDD, another depressive disorder such as dysthymic disorder, symptoms of subsyndromal depression, or depressive symptoms that accompany an anxiety disorder, bipolar disorder or some other psychiatric illness. Similar to the observations in the current study, a recent study found females diagnosed with MDD and comorbid anxiety showed smaller amygdala volume and reduced functional connectivity between amygdala and cortico-striatal circuitry compared to healthy controls (Yang et al., 2017). It is possible that anxiety may be an important predictor of the relationship between depressive symptoms and amygdala volume; however, the data available from the DHS do not allow for a determination of the comorbid anxiety diagnosis, or the context or duration of any anxious symptoms. Finally, it is possible that the age results may be skewed due to the group membership definitions used in our analysis. Strengths of the study include the large and diverse community sample and extensive demographic information. To our knowledge, this is the largest study to date to examine the relationship between depressive symptoms and amygdala volume.

In summary, amygdala volume was not significantly associated with depressive symptom severity in the overall sample. However, a subgroup analysis revealed a negative relationship between amygdala volume and depressive symptom severity in younger people.

Conflicts of Interests

Dr. Brown has a research grant from Otsuka. All other authors have no conflicts of interest to disclose.

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