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Association of Depressive Symptoms with Hippocampal Volume in 1936 Adults

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Hippocampal atrophy is reported in major depressive disorder (MDD). However, sample sizes were generally modest, and participant characteristics, including age, differed between studies. This study used a community sample to examine relationships between current depressive symptom severity and hippocampal volume across the adult lifespan. A total of 1936 adults with magnetic resonance images of the brain and Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scores were included. Brain volumes were quantified using the FSL program. Multiple linear regressions were performed using left, right, and total hippocampal volume as criterion variables, and predictor variables of QIDS-SR total, total brain volume, age, gender, education, psychotropic medications, alcohol use, and race/ethnicity. *Post hoc* analyses were conducted in participants with QIDS-SR scores $\geqslant 11$ (moderate or greater depressive symptom severity) and <11, and older and younger adults. In the primary analysis (sample as a whole) QIDS-SR was inversely associated with total hippocampal volume ($b=-0.044$, $p=0.032$, (CI -0.019 to -0.001)) but not with left or right hippocampal volume evaluated individually. In participants with QIDS-SR scores of <11, hippocampal volumes were not associated with QIDS-SR scores. In those with QIDS-SR scores $\geqslant 11$ total, right, and left hippocampal volumes were modestly, but significantly, associated with QIDS-SR scores. The association between QIDS-SR scores and the hippocampal volume was much stronger in older persons. Findings suggest smaller hippocampal volumes among those with greater reported depressive symptom severity—an association that is strongest in people with at least moderate depressive symptom levels.

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INTRODUCTION

Smaller hippocampal volume in people with major depressive disorder (MDD), as compared with healthy controls, has been reported in some but not all studies (Arnone *et al*, 2012a; Campbell *et al*, 2004; Kempton *et al*, 2011; McKinnon *et al*, 2009; Videbech and Ravnkilde, 2004). Differences in population characteristics, including age, may have contributed to disparate outcomes. The inconsistent findings from prior studies have led some to question the strength of the evidence supporting hippocampal atrophy in MDD (Fink, 2011). Hippocampal volume reduction in MDD is a potentially important finding for several reasons. First, the hippocampus is involved in declarative memory processes (Eichenbaum *et al*, 1992). Declarative memory appears to be impaired, and associated with hippocampal volume, in patients with MDD (Clark *et al*, 2009; Turner and Lloyd, 2003). Second, the hippocampus is part of a larger neural circuit that includes limbic structures and the medial prefrontal cortex that may be central to the affective, emotional, and cognitive features of MDD (Clark *et al*, 2009; Drevets *et al*, 2008). Third, hippocampal volume may be associated with treatment response in MDD. Smaller hippocampal volume appears to be associated with a poorer response to antidepressants (Hsieh *et al*, 2002; Sheline *et al*, 2012; Vakili *et al*, 2000).

The etiology of hippocampal volume reduction in persons with MDD is not clear. Depressive episodes may cause hippocampal atrophy. In support of this idea are data suggesting a relationship between hippocampal volume and length of lifetime depression (Sheline *et al*, 1996). Cumulative stress and adversity are associated with changes in some brain regions (Ansell *et al*, 2012). Corticosteroid excess is associated with hippocampal atrophy in animal models and humans (Brown *et al*, 2004). Therefore, cortisol elevation during depressive episodes is a possible mechanism for hippocampal volume reduction in MDD. However, a report found that current cortisol levels did not significantly mediate the relationship between hippocampal volume and depression (Gerritsen *et al*, 2011). Glutamatergic pathways could also contribute to hippocampal changes in persons

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with MDD. Dysregulation of genes involved in glutamate-mediated neuronal and synaptic plasticity has been reported in postmortem hippocampal slices from depressed patients (Duric *et al*, 2013). Genetic factors may also have a role. Homozygosity for the L allele of the 5-HTTLPR biallelic polymorphism is associated with smaller hippocampal volume in patients with MDD but not controls (Frodl *et al*, 2004). Increased cellular density is another possible mechanism. A postmortem study found cellular changes including increased packing density of glia, pyramidal neurons, and granule cell neurons as well as differential shrinkage of frozen sections of the hippocampus, consistent with a reduction in water content, in patients with MDD (Stockmeier *et al*, 2004). Inflammation is an emerging area of interest in depression research (Eyre and Baune, 2012). Elevated levels of inflammatory biomarkers are associated with smaller hippocampal volumes in patients with MDD (Frodl *et al*, 2012).

Alternatively, rather than being a consequence of MDD, smaller hippocampal volume could potentially be a risk factor for the development of MDD. In support of this idea, reduced hippocampal volume has been reported in healthy girls at high risk for MDD based on family history (Chen *et al*, 2010). Some data suggest that small hippocampus may be a risk factor for post-traumatic stress disorder (Gilbertson *et al*, 2002), a stress-related disorder can co-occur with MDD.

A limitation of many studies of hippocampal volume in MDD has been small sample sizes. A solution to this problem has been to combine the data in meta-analyses. The meta-analyses reported, to date, have suggested that people with MDD have smaller mean hippocampal volume than non-depressed controls (Arnone *et al*, 2012a; Campbell *et al*, 2004; Kempton *et al*, 2011; McKinnon *et al*, 2009; Videbech and Ravnkilde, 2004). Meta-analysis helps achieve sufficient numbers for statistical significance but it does not address problems with selection bias inherent to case–control studies. Meta-analysis also depends on the ability to generalize findings from underlying heterogeneous studies. Differences in depression definition and method of assessment, magnetic resonance imaging (MRI) techniques, nature of control groups, age, gender, control for total brain volume or intracranial volume, and education levels of the participants have varied greatly between studies.

Inconsistent findings have been reported on age and genders effects on hippocampal volume in MDD. Frodl *et al* (2002) reported greater hippocampal volume reduction in men than in women with first episode MDD. However, a meta-analysis did not find a gender effect (Videbech and Ravnkilde, 2004). This same meta-analysis did not find an impact of age on hippocampal volume in MDD. However, a more recent meta-analysis reported greater hippocampal volume reduction in middle aged adults with MDD than in older or younger adults (McKinnon *et al*, 2009).

The current study examines the relationship between hippocampal volume and current depressive symptom severity in a population-based sample of 1936 adults participating in a large community-based research study. We hypothesized that current depressive symptom severity would be inversely associated with hippocampal volume. In addition, we used the large sample to explore age and gender effects.

MATERIALS AND METHODS

Participants and Assessments

The study population was obtained from the Dallas Heart Study (DHS), a multiethnic cohort of Dallas County English or Spanish speaking adult residents used to examine cardiovascular disease and collect data for future studies. The details of the participant selection process and the study design have been previously described (Neeland *et al*, 2012; Victor *et al*, 2004).

The DHS intentionally oversampled African–Americans to comprise $\sim$50% of the participants in order to explore cardiovascular disease risk factors in this subpopulation. All participants signed written informed consents approved by The University of Texas Southwestern Medical Center Institutional Review Board. The first phase of the study (DHS-1) did not assess either depressive symptoms or brain volumes. The data in the current report are from a second phase of the study (DHS-2). The DHS-2 sample had a slightly higher proportion of women and Caucasians than in the original DHS-1 population due to differences in attrition following DHS-1. The participants in DHS-2 included people who had participated in DHS-1as well as some family members and/or spouses of DHS-1 participants. DHS-2 was conducted from September 2007 to December 2009. For more information about DHS-2 please see these references (King *et al*, 2013; Kozlitina and Garcia, 2012; Lucarelli *et al*, 2013).

Extensive information, including demographic characteristics, was obtained as part of the study. Race and ethnicity were determined through self-identification and the categories included: African–American, Caucasian (non-Hispanic White), Hispanic, and Other (Native American, Alaska Native, Asian, Pacific Islander, and East Indian). DHS-2 collected MRI scans of the brain and other organ systems.

The 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) was also administered at DHS-2. The QIDS-SR is a 16-item, 0–3, patient-rated assessment of depressive symptom severity over the past 7 days (Rush *et al*, 2000; Rush *et al*, 2003; Trivedi *et al*, 2004). The QIDS-SR assesses the nine symptom domains that define MDD. The internal consistency of the QIDS-SR (Chronbach's alpha = 0.86) is comparable to that of the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) (Rush *et al*, 2003). Scores on the QIDS-SR correlate highly with those of the longer 30-item $IDS\text{-}SR_{30}$ ($r = 0.91$) and the $HAMD_{17}$ ($r = 0.85$) (Rush *et al*, 1996). QIDS-SR total score multiplied by 1.3 is approximately equivalent to the $HAMD_{17}$ total score (Rush *et al*, 2003). As in the National Comorbidity Survey Replication (Kessler *et al*, 2003), transformation rules were used to convert QIDS-SR scores into depressive symptom severity categories mapped to conventional HAMD ranges of none (0–5), mild (6–10), moderate (11–15), severe (16–20), and very severe (21 +) (Rush *et al*, 2003). For more information about the psychometric properties and use of the QIDS-SR see www.ids-qids.org.

Neuroimaging

Both MP-RAGE and FLAIR images were collected. All images were acquired on the same 3T MRI scanner

(Achieva, Philips Medical Systems, Best, the Netherlands). The images were taken in axial orientation from the vertex of the skull to the foramen magnum. The 3D MP-RAGE images were acquired with TR/TE = 9.6/5.8 msec, flip angle = 12 degrees, SENSE factor = 2, field of view (FOV) = 260 × 260 mm, 2 mm slices spaced at 1 mm centers, Rows × Cols × Slices = 288 × 288 × 140, and voxel size of 1 × 0.9 × 0.9 mm (Hulsey *et al*, 2012).

MRI quantification was performed using the freely available FMRIB software library, FSL (fsl.fmrib.ox.ac.uk). Volumes of the left and right hippocampus were derived from 3D-MP-RAGE sequences using the FSL tool FIRST (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) (Patenaude *et al*, 2011), which is a model-based segmentation and registration tool and which can segment subcortical structures, including the hippocampi, automatically. Total brain volume (gray matter plus white matter) was also obtained. Volumetric data were collected using the FSL routine called fslstats. Volumes of the left and right hippocampus, along with other cortical and subcortical structures not reported here, were derived from MP-RAGE sequences. For more information on the imaging methods in DHS see Hulsey *et al* (2012). Scans identified by an error code produced by the software or identified by review of outliers were inspected. Scans containing artifacts, encephalomalacia, or other abnormalities were excluded from the analysis. Individuals who were excluded from the MRI included people with a history of brain surgery, metal fragments, pacemakers, implantable cardiodefribrillators, cochlear implants, spinal cord stimulators, or other internal electrical devices. Individuals who were pregnant or had jobs that could have exposed them to metal fragments were also excluded from the MRIs. A total of 2082 participants underwent brain MR imaging. Thirty-seven were excluded for self-reported stroke. Images of outliers as found by Robust Minimum Covariance Distance analysis of brain segments (Lucarelli *et al*, 2013), individuals flagged for exclusion in previous DHS-2MR imaging brain studies, and individuals who had error flags generated during automated analysis were reviewed by a neuroradiologist (KSK). On MR imaging review, 70 individuals with 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) were excluded. In total, 107 individuals were excluded from subsequent analysis. The segmentation failure rate of the overall sample was 1.4%. In the current report, participants were also excluded if they had missing data for any of the other predictor or criterion variables tested resulting in 1936 participants used in these analyses.

Statistical Analysis

Multiple linear regressions were performed using SPSS version 20.0 (IBM SPSS Statistics) with left, right, and total hippocampal volume (ml) as criterion variables, and predictor variables of QIDS-SR total score, total brain volume (ml), age (years), gender (male, female), education (years), psychotropic medications (antidepressants, antipsychotics, anticonvulsants, anxiolytics, hypnotics, and stimulants), alcohol use (current drinking, recent abstainer, and lifetime abstainer), and race/ethnicity (Caucasian, African–American, Hispanic, and Other). In addition to the above analysis in the entire sample, *post hoc* linear regressions were performed, using the same criterion and predictor variables as above in participants with QIDS-SR scores of <11 and $\geqslant 11$ (moderate depressive symptom severity or greater). A QIDS-SR score of 11 is approximately equivalent to a $HAMD_{17}$ of about 14–15, which is potentially consistent with at least mild MDD (Rush *et al*, 2003). These QIDS-SR scores were used to define depression relapse in the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush *et al*, 2006a). Age × QIDS-SR and gender × QIDS-SR interactions were also explored in the entire sample and in those with QIDS-SR scores $\geqslant 11$.

RESULTS

The demographic characteristics of the participants are in Table 1. A total of 58.5% were women and 46.2% were African–American. The mean (± SD) age was 49.7 ± 10.6 years, and mean education level was 12.8 ± 2.3 years. Mean total QIDS-SR score was 5.1 ± 3.8 (range 0–24). A total of 9.9% of the entire sample and 20.3% of those with at least moderate depressive symptom severity (QIDS-SR $\geqslant 11$) were currently taking antidepressants. Participants with missing

Table 1 Demographic Features, $N = 1936$

Characteristics	N	%
Sex		
Male	804	41.5
Female	1132	58.5
Race		
Caucasian	702	37.2
Hispanic	276	14.3
African–American	895	46.2
Other	40	2.1
Concomitant medication		
Stimulants	33	1.7
Anticonvulsants	59	3.0
Antidepressants	192	9.9
Antipsychotics	28	1.4
Anxiolytics	90	4.6
Hypnotics	78	4.0
	Mean	SD
Age (years)	49.7	10.6
Education (years)	12.8	2.3
QIDS-SR score	5.1	3.8
Volumes (ml)		
Total brain	916.5	105.0
Total hippocampus	6.8	0.8
Left hippocampus	3.3	0.5
Right hippocampus	3.4	0.5

data and, therefore, not included in the analysis, were demographically similar (60.1% women, 56.4% African–American, 12.0% taking antidepressants, age 50.2 ± 11.9, and QIDS-SR 5.6 ± 4.2) to those included in the analysis.

Results of multiple linear regression analyses, using hippocampal volume as the criterion variable, are presented in Table 2. After controlling for demographic features and total brain volume, total hippocampal volume was inversely associated with total QIDS-SR score ($b = -0.044$, $p = 0.032$ (CI −0.019 to 0.001)). Left ($b = -0.036$, $p = 0.085$ (CI −0.009 to 0.001)) and right ($b = -0.029$, $p = 0.167$ (CI −0.009 to 0.002)) hippocampal volumes when evaluated individually did not reach statistical significance. Total brain volume and race/ethnicity were also significantly related to hippocampal volume in these analyses. Gender was significantly related to right and total, but not left, hippocampal volume. An independent association of age with hippocampal volume only reached significance on the right. The variance inflation factor (VIF) a measure of multicollinearity ranged from 1.049 to 1.651 for the predictor variables, including 1.129 for the predictor variable of interest (QIDS-SR scores). Because these values were modest (Pan and Jackson, 2008), predictor variables were not removed or centered to manage high intercorrelation. To examine age and gender effects on the relationship between depression and hippocampal volume, we explored age × QIDS-SR ($b = 0.41$, $p = 0.674$) and gender × QIDS-SR ($b = -0.031$, $p = 0.705$) interactions both of which were nonsignificant.

Given the relatively modest associations between the severity of current depressive symptoms and hippocampal volume in this sample, and in light of the many studies suggesting a reduction in hippocampal volume in people with a diagnosis of MDD, *post hoc* analyses (including the same predictor variables as in the primary analysis) in those with QIDS-SR scores $\geqslant 11$ and < 11 were conducted to see whether stronger associations were observed in those with at least moderate levels of depressive symptom severity that might be consistent with current MDD (Table 3). Scatter plots of hippocampal volumes *vs* QIDS-SR scores are in Figure 1. In those with QIDS-SR scores < 11 no significant relationships between hippocampal volumes and QIDS-SR scores were observed. However, in those with QIDS-SR scores $\geqslant 11$ total ($b = -0.184$, $p = 0.005$, (CI −0.092 to 0.016), left ($b = -0.135$, $p = 0.042$ (CI −0.042 to 0.001)), and right ($b = -0.134$, $p = 0.049$ (CI −0.044 to 0.000)) hippocampal volumes were significantly related to QIDS-SR scores. Other predictor variables such as race/ethnicity, gender, and age were no longer significantly associated with hippocampal volume in the group with higher levels of depressive symptom severity.

We examined age × QIDS-SR and gender × QIDS-SR interaction terms in the regression model of total hippocampal volume in those with QIDS-SR scores $\geqslant 11$. Gender × QIDS-SR interaction was nonsignificant ($p = 0.058$). However, a significant age × QIDS-SR interaction was observed ($p = 0.032$). Based on a meta-analysis that found greater hippocampal volume reduction in older and younger adults than middle aged adults with MDD (McKinnon *et al*, 2009), we conducted linear regressions in ages < 40, 40–59, and 60 years and above, in those with QIDS-SR scores $\geqslant 11$ using total hippocampal volume as the criterion variable and the same predictor variables as in the other analyses. The standardized coefficients and significance for the QIDS-SR increased with age (age < 40, $n = 36$, $b = -0.129$, $p = 0.268$; age 40–59, $n = 122$, $b = -0.173$, $p = 0.480$; age 60+, $n = 25$, $b = -0.651$, $p < 0.001$).

DISCUSSION

The findings suggest that current depressive symptom severity is negatively associated with total hippocampal volume in a population-based sample. Prior research has generally used an MDD diagnosis when assessing hippocampal volume. This study suggests a relationship between the level of current depressive symptom severity and size of the hippocampus in a sample that includes participants with and without symptom severity that typifies a major depressive episode. However, it is important to note that the observed inverse relationship between QIDS-SR scores and hippocampal volume was modest and only reached significance for total hippocampal volume, not left, or right volumes.

Unlike the current study, most prior studies examining the relationship between hippocampal volume and depression have used participants with a diagnosis of syndromal MDD based on clinical criteria and a non-depressed control group. Therefore, we conducted a *post hoc* analysis to determine whether the relationship between hippocampal volume and depressive symptom severity was stronger in those with at least a moderate level of depressive symptom severity based on the QIDS-SR. In participants with lower levels of depressive symptom severity, no significant relationships between QIDS-SR scores and hippocampal volumes were observed. However, in participants with more clinically significant levels of depressive symptoms, the relationships between QIDS-SR scores and total, right, and left hippocampal volume were significant. The standardized coefficients (a measure of SD change in a criterion variable based on SD change in the predictor variable) were approximately nine times larger in the group with higher QIDS-SR scores as compared with those with lower QIDS-SR scores (Table 3), and four times larger than in the sample as a whole (Table 2). In addition, other independent variables, with the exception of total brain volume, lost significance in the group with higher QIDS-SR scores. These data are potentially consistent with the idea of a threshold level of depression at which hippocampal volume is related to the levels of depression severity. Furthermore, the data suggest that relatively mild depressive symptoms are not associated with hippocampal volume differences. A recent report by Spalletta *et al*, (2013) examined the relationship between hippocampal volume and Beck Depression Inventory (BDI) scores in 102 participant free of psychiatric illness. BDI scores were consistent with minimal to mild depression. A significant correlation was observed between hippocampal volume and BDI score in men but not in women. These findings differ from findings in our participants with lower QIDS-SR scores (Table 3). The differences could be due to different participant characteristics, differences in measurement of brain volumes, or differences in the depression scales.

Before the current report, few large studies have examined the relationship between depression and

Table 2 Linear Regression Analyses of Total, Left, and Right Hippocampal Volume ($n = 1936$)

Predictor variable	b (Standardized coefficient)	*P*	95% CI	
			Lower bound	Upper bound
Total hippocampal volume ($R^2 = 0.287$)				
QIDS-SR (depressive symptoms)	−0.044	**0.032**	−0.019	−0.001
Total brain volume	0.450	<**0.001**	0.003	0.004
Gender	−0.055	**0.020**	−0.178	−0.015
Age	0.005	0.788	−0.003	0.004
Drinking status	−0.032	0.102	−0.098	0.009
Stimulants	−0.022	0.263	−0.406	0.111
Anticonvulsants	−0.013	0.500	−0.263	0.128
Antidepressants	0.000	0.981	−0.116	0.119
Antipsychotics	−0.018	0.364	−0.409	0.150
Anxiolytics	0.026	0.198	−0.055	0.263
Hypnotics	−0.002	0.931	−0.177	0.162
Education	0.013	0.516	−0.010	0.020
Race/ethnicity	0.130	<**0.001**	0.099	0.185
Left hippocampal volume ($R^2 = 0.236$)				
QIDS-SR	−0.036	0.085	−0.009	0.001
Total brain volume	0.429	<**0.001**	0.002	0.002
Gender	−0.028	0.250	−0.071	0.018
Age	−0.033	0.111	−0.003	0.000
Drinking status	−0.031	0.124	−0.052	0.006
Stimulants	−0.015	0.475	−0.193	0.090
Anticonvulsants	−0.023	0.261	−0.169	0.046
Antidepressants	0.018	0.393	−0.037	0.093
Antipsychotics	0.013	0.523	−0.105	0.206
Anxiolytics	0.020	0.335	−0.045	0.131
Hypnotics	−0.012	0.562	−0.121	0.066
Education	0.005	0.792	−0.007	0.009
Race/ethnicity	0.101	<**0.001**	0.035	0.082
Right hippocampal volume ($R^2 = 0.243$)				
QIDS-SR	−0.029	0.167	−0.009	0.002
Total brain volume	0.397	<**0.001**	0.002	0.002
Gender	−0.075	**0.002**	−0.119	−0.027
Age	0.049	**0.018**	0.000	0.004
Drinking status	−0.029	0.144	−0.053	0.008
Stimulants	−0.019	0.356	−0.216	0.078
Anticonvulsants	−0.017	0.405	−0.159	0.064
Antidepressants	−0.015	0.471	−0.092	0.043
Antipsychotics	−0.018	0.373	−0.235	0.088
Anxiolytics	0.009	0.672	−0.071	0.111
Hypnotics	−0.003	0.893	−0.103	0.090
Education	0.027	0.193	−0.003	0.014
Race/ethnicity	0.154	<**0.001**	0.069	0.118

Bold values denote statistical significance.

hippocampal volume. In one such study, Gerritsen *et al* (2011) examined depression and hippocampal volume in people with atherosclerosis ($N = 636$). They reported that a lifetime history of depression and current depression were associated with approximately a 1.7% ($p < 0.05$ on left but not right) and 2.3% ($p =$ NS) smaller hippocampal volume, respectively. However, current depressive symptom severity, as assessed by the Patient Health Questionnaire

Table 3 Linear Regression Analyses of Total, Left, and Right Hippocampal Volume By QIDS-SR score <11 *vs* $\geqslant 11$

Predictor variable	QIDS-SR <11 ($n=1753$)				QIDS-SR $\geqslant 11$ ($n=183$)			
	b	*p*	95% CI		b	*p*	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Total hippocampal volume								
QIDS-SR	−0.021	0.319	−0.021	0.007	−0.184	**0.005**	−0.092	−0.016
Total brain volume	0.442	**<0.001**	0.003	0.004	0.488	**<0.001**	0.003	0.006
Gender	−0.064	**0.011**	−0.197	−0.026	0.002	0.982	−0.268	0.275
Age	−0.002	0.926	−0.004	0.003	0.072	0.283	−0.005	0.018
Stimulants	−0.012	0.545	−0.371	0.196	−0.085	0.246	−1.064	0.275
Drinking status	−0.038	0.069	−0.109	0.004	0.031	0.653	−0.130	0.207
Anticonvulsants	−0.012	0.556	−0.299	0.161	−0.001	0.986	−0.408	0.401
Antidepressants	0.006	0.792	−0.110	0.145	−0.082	0.323	−0.503	0.167
Antipsychotics	−0.016	0.452	−0.451	0.201	−0.028	0.710	−0.711	0.485
Anxiolytics	0.020	0.327	−0.088	0.264	0.062	0.392	−0.224	0.568
Hypnotics	−0.012	0.569	−0.243	0.133	0.082	0.241	−0.163	0.643
Education	0.021	0.309	−0.008	0.024	−0.048	0.495	−0.063	0.030
Race/ethnicity	0.134	**<0.001**	0.102	0.193	0.090	0.184	−0.044	0.228
Left hippocampal volume								
QIDS-SR	−0.015	0.483	−0.010	0.005	−0.135	**0.042**	−0.042	−0.001
Total brain volume	0.417	**<0.001**	0.002	0.002	0.495	**<0.001**	0.002	0.003
Gender	−0.035	0.175	−0.080	0.015	−0.007	0.922	−0.155	0.140
Age	−0.040	0.066	−0.004	0.000	0.053	0.435	−0.004	0.009
Stimulants	−0.005	0.826	−0.173	0.138	−0.082	0.268	−0.564	0.158
Drinking status	−0.027	0.201	−0.051	0.011	−0.066	0.344	−0.135	0.047
Anticonvulsants	−0.022	0.302	−0.195	0.060	−0.011	0.884	−0.234	0.202
Antidepressants	0.026	0.241	−0.028	0.112	−0.071	0.398	−0.258	0.103
Antipsychotics	0.019	0.379	−0.101	0.266	0.003	0.970	−0.316	0.328
Anxiolytics	0.017	0.436	−0.059	0.136	0.036	0.623	−0.160	0.266
Hypnotics	−0.025	0.247	−0.165	0.042	0.091	0.197	−0.075	0.360
Education	0.016	0.470	−0.005	0.012	−0.089	0.209	−0.041	0.009
Race/ethnicity	0.110	**<0.001**	0.039	0.089	0.012	0.860	−0.067	0.080
Right hippocampal volume								
QIDS-SR	−0.015	0.497	−0.011	0.005	−0.134	**0.049**	−0.044	0.000
Total brain volume	0.388	**<0.001**	0.002	0.002	0.436	**<0.001**	0.001	0.003
Gender	−0.082	**0.001**	−0.128	−0.031	−0.051	0.476	−0.211	0.099
Age	0.038	0.079	0.000	0.004	0.136	0.052	0.000	0.013
Stimulants	−0.011	0.590	−0.206	0.117	−0.081	0.281	−0.586	0.171
Drinking status	−0.041	0.053	−0.064	0.000	0.085	0.231	−0.037	0.154
Anticonvulsants	−0.026	0.233	−0.213	0.052	0.021	0.784	−0.197	0.260
Antidepressants	−0.015	0.484	−0.099	0.047	−0.069	0.419	−0.267	0.112
Antipsychotics	−0.012	0.584	−0.244	0.137	−0.052	0.501	−0.454	0.222
Anxiolytics	−0.004	0.839	−0.112	0.091	0.087	0.246	−0.092	0.356
Hypnotics	−0.011	0.589	−0.137	0.078	0.064	0.374	−0.125	0.331
Education	0.033	0.131	−0.002	0.016	0.000	0.995	−0.026	0.026
Race/ethnicity	0.158	**<0.001**	0.070	0.122	0.121	0.083	−0.009	0.145

Bold values denote statistical significance.

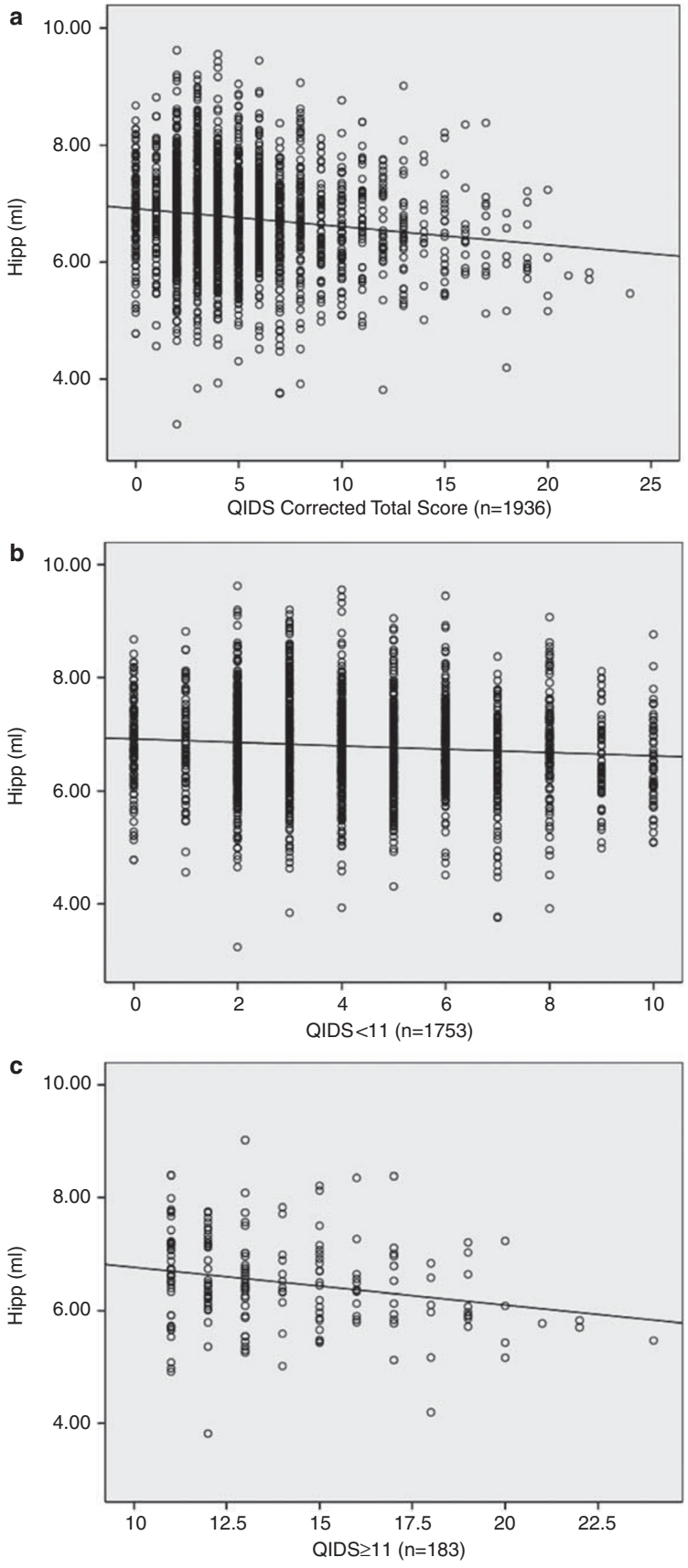

Figure 1 Scatterplots of total hippocampal volume *vs* Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scores in (a) the total sample, (b) participants with QIDS-SR scores <11 and (c) participants with QIDS-SR scores $\geqslant 11$.

(PHQ-9) (Kroenke *et al*, 2001), was not significantly associated with the hippocampal volume. Thus, our current report found a more robust association between depressive symptom severity and hippocampal volume than the report by Gerritsen *et al* (2011). This difference may be due to the larger sample size in the current report and greater representation of women (58 *vs* <20%). Some reports suggest a greater decline in hippocampal volume with age in men than in women (Pruessner *et al*, 2001). Therefore, a sample primarily consisting of men could show greater age-related hippocampal atrophy in general, and, therefore, less difference with depression. Because depression is more common in women than in men, a sample consisting of mostly men might also have fewer participants with elevated depressive symptoms scores. By design, the DHS was racially and ethnically diverse and oversampled for African–Americans. To our knowledge, one large study ($N>600$) in an ethnically diverse sample has been previously reported. Geerlings *et al* (2012) examined hippocampal volume in a community sample ($N=630$, 29% Caucasian, 34% African–American, 36% Hispanic, and 2% Other) of older persons (mean age 80 years). They reported that participants with current depression, defined as a Center for Epidemiologic Studies-Depression Scale score $\geqslant 4$ or current antidepressant use, had smaller hippocampal volumes.

Studies in both living depressed patients (Sheline *et al*, 2003) and postmortem analyses (Boldrini *et al*, 2013) suggest that antidepressants may modify the association between hippocampal volume and depression. However, in the current report none of the analyses suggested a relationship between hippocampal volume and antidepressant, or other psychotropic medication use. This difference may potentially be explained by two factors. First, antidepressant use was not common. Thus, we may not have the power to detect effects of the antidepressants on hippocampal volume. Second, given the design of the study, we do not know how long participants had been taking an antidepressant. If antidepressant treatment was initiated shortly before the MRI was obtained then one might expect little effect of the antidepressant on the hippocampal volume.

Our findings suggest that the relationship between depressive symptom severity and hippocampal volume may increase in older adults. The standardized coefficient was five times greater in those age 60 years and over as compared with those under age 40. These findings differ somewhat from the findings of a meta-analysis that reported the greatest reduction in hippocampal volume was observed in middle age adults (McKinnon *et al*, 2009). These differences may be explained by differences in the study methods and design. Our analysis examined relationships between current depressive symptom severity and hippocampal volume in different age groups rather than examining differences in volume compared with controls in participants with MDD. In addition, the age of onset of depression and illness duration varied among the studies in the meta-analysis and is not known in our study. Thus, the participant characteristics may be quite different. Because the hippocampus is involved in memory, our findings are potentially consistent with the greater deficits in memory performance in older *vs* younger persons with MDD (Thomas *et al*, 2009).

Strengths of the study include the large population-based sample and racial/ethnic diversity, which increase the generalizability of the findings. The size of the sample allowed for an analysis of the impact of depressive symptom severity as well as gender and age. Our analyses controlled for total brain volume (white matter plus gray matter) minimizing the effects of more generalized brain atrophy beyond the hippocampus. Although the total sample size was very large, the subgroups that were analyzed were much smaller which may increase the risk of type II errors. In addition, the study controlled for medication use, alcohol use, education, and other variables that might influence the relationship between depression and hippocampal volume. Another potential strength is the use of an automated method to derive hippocampal volumes that results in excellent reproducibility (Lucarelli *et al*, 2012; Nugent *et al*, 2012) and avoids a left-right bias that may be inherent with manual segmentation (Maltbie *et al*, 2012).

The study has several limitations. The QIDS-SR is a self-rated instrument that assesses current depressive symptom severity. A strength of the QIDS-SR is its ability to assess current depressive symptoms. The QIDS-SR assesses core symptoms of MDD in the DSM-IV-TR and is strongly associated with scores on clinician-rated depression instruments (Rush *et al*, 2003) and structured diagnostic interviews (Bernstein *et al*, 2009; Doraiswamy *et al*, 2010), and has been used in large clinical studies (Kessler *et al*, 2003; Rush *et al*, 2006b; Trivedi *et al*, 2006). However, if the hippocampal volume changes occur over long periods then the study is limited by only comparing a slowly changing brain change with a current measure of depression. Because of the study design, limited information was available on the neurological histories of the participants. However, we were able to exclude participants with a known history of stroke, a condition that might directly impact brain volumes. Although the findings are somewhat mixed in terms of laterality, studies generally suggest that severe alcohol dependence is associated with reduced hippocampal volume (Beresford *et al*, 2006; Laakso *et al*, 2000; Le Berre *et al*, 2012; Ozsoy *et al*, 2013). To our knowledge, the degree of reversibility of hippocampal volume changes with alcohol dependence has not been investigated. The current report controlled for current alcohol use but lifetime alcohol use patterns were not available. Thus, we cannot rule out the possibility that past heavy alcohol use may have influenced the findings.

Given the cross-sectional nature of the study, it cannot address mechanisms, causality, or reversibility. As discussed in the introduction, numerous mechanisms might potentially result in hippocampal changes with depression. Changes in the hippocampus could either be a result of biological changes with depression or be a pre-existing risk factor for the development or chronicity of depression. Data are mixed on whether hippocampal volume changes in depression are reversible. The smaller hippocampal volumes in older patients with past, but not current, MDD in the report by Sheline *et al* (1996) might suggest that volume reduction is either irreversible or resolves very slowly . However, a recent report by Arnone *et al* (2012b) observed hippocampal gray matter reduction in patients with current, but not remitted depression, as compared with controls. These findings are potentially consistent with a reversible process.

In summary, elevated QIDS-SR scores were associated with decreased total hippocampal volumes in a population-based sample of 1936 participants. The relationship between depressive symptom severity and hippocampal volume was much stronger in those with at least moderate levels of depressive symptoms. In those participants with at least moderate depressive symptom severity the strength of the relationship between depressive symptom severity and hippocampal volume increased with age.

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