Gray Matter Differences Between Healthy and Depressed Adolescents: A Voxel-Based Morphometry Study

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Abstract

Background: Major depressive disorder (MDD) frequently begins during adolescence and is associated with significant morbidity and mortality. However, little is known about the neurobiology of adolescent depression. A better understanding of the neurobiology will be helpful in developing more effective preventive and treatment interventions for this highly disabling illness.

Methods: Using a voxel-based morphometric method, the study compared gray matter and white matter volumes in 22 adolescents with MDD and 22 age- and gender-matched normal controls.

Results: Compared with controls, depressed adolescents had smaller gray matter volume in the frontal lobe and caudate nucleus bilaterally and right superior and middle temporal gyri. However, the groups did not differ significantly on white matter volume.

Conclusions: These findings in depressed adolescents are consistent with the previous findings of gray matter abnormalities in frontolimbic areas and the striatum in depressed adults and suggest the presence of these structural changes at the onset of depressive illness.

Introduction

ADOLESCENCE IS A HIGHLY VULNERABLE PERIOD MARKED by developmental brain changes during which many psychiatric disorders become clinically visible. Thus, research during adolescence may provide a unique opportunity to investigate the developmental neurobiology of underlying psychiatric disorders. One of the most disabling and common psychiatric disorders diagnosed during adolescence is major depressive disorder (MDD; Kessler et al. 2001), with a point prevalence of 3% to 9% and a cumulative prevalence of 20% by the end of adolescent years (Whitaker et al. 1990; Garrison et al. 1992; Lewinsohn et al. 1993; Shaffer et al. 1996). The clinical significance of adolescent depression is underscored by its close association with significantly impaired social, academic, and family functioning (Birmaher et al. 1996a; Birmaher et al. 1996b; Fergusson and Woodward 2002; Rao and Chen 2009). Additionally, MDD in adolescents carries a higher risk for substance abuse and other psychiatric co-morbidities (Whitaker et al. 1990a; Garrison et al. 1992; Lewinsohn et al. 1993; Shaffer et al. 1996; Rao et al. 2009), and it has been linked with increased hospitalizations, recurrent depression, antisocial behaviors, and suicide (National Adolescent Health Information Center 2006; Rao et al. 1993; Shaffer et al. 1996b; Weissman et al. 1999; Aalto-Setälä et al. 2002; Rushton et al. 2002).

Despite the clinical significance of adolescent depression, there is limited understanding of its neurobiology. However, an in-

creasing number of neuroimaging studies are reporting neuroanatomical deficits in specific brain regions in adolescents with MDD. Some morphometric studies reported white matter deficits in the frontolimbic (Steingard et al. 2002) and temporal (Li et al. 2007) regions. Region of interest (ROI) analyses displayed gray matter deficits in the hippocampus (MacMaster and Kusumaker 2004; Caetano et al. 2007; Rao et al. 2010) and prefrontal cortex (PFC; Nolan et al. 2002) in depressed youngsters. Similarly, gray matter deficits in the hippocampus (Bremner et al. 2000; Ballmaier et al. 2004; Campbell et al. 2004; Vasic et al. 2008), orbitofrontal cortex (OFC; Lacerda et al. 2003; Vasic et al. 2008), dorsolateral prefrontal cortex (DLPFC; Vasic et al. 2008), and cingulate gyrus (Vasic et al. 2008; Zhou et al. 2010) have been observed in adult subjects with MDD.

Although hand-drawn ROI-based morphometry remains the standard approach for neuroanatomical localization, it is labor intensive, and subject to error from poor interrater reliability or drift from template standards (Soloff et al. 2008). As a result, studies using ROI-based approach are generally hypothesis-driven studies, which typically focus on a few predefined ROIs without addressing multiple regions (networks) that might be implicated in MDD. In contrast to this, voxel-based morphometry (VBM; Ashburner and Friston 2001) is a computer-based, automated, morphometric technique for voxel-wise comparisons between groups of subjects, which is relatively free of rater bias, interrater variability, and drift from template standards (Soloff et al. 2008). Additionally, VBM does not

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require *a priori* hypotheses or definitions of anatomical areas and is highly efficient for relatively large sample studies. However, normalization of images to a standard template in VBM may result in some deformation of the original brain structure and a possible error in detecting small volume differences (Soloff et al. 2008).

To the best of our knowledge, there are no reported studies that examined gray matter differences in adolescents with depression using VBM methodology. In the current study, gray and white matter volumes were compared between adolescents diagnosed with MDD and normal controls using the VBM method to analyze magnetic resonance imaging (MRI) data (Good et al. 2001). Based on the findings from prior structural MRI studies, we hypothesized that adolescents with MDD will have smaller gray matter volume in the frontolimbic areas and striatum.

Methods

Participants

With approval from the Institutional Review Board, 22 depressed adolescents and 22 controls were recruited through local schools, mental health programs, and newspaper advertisements. The depressed adolescents met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text revision (DSM-IV-TR) criteria (American Psychiatric Association 2000) for MDD with a minimum duration of 4 weeks. Adolescents with a current or prior history of mania, hypomania, substance use disorder symptoms, schizophrenia, schizoaffective disorder, or autism were excluded from the study. Subjects also were excluded if there was a family history of bipolar disorder. Controls were free from any type of psychopathology in their lifetime and were not included if any first-degree relative had history of a major psychiatric disorder. Prior to performing the research procedures, all adolescents under 18 years signed a written assent form and parents (or subjects ≥ 18 years) signed an informed consent document. All participants were medically healthy and free from alcohol or illicit drug use, as determined by physical examination, full chemistry panel, thyroid function tests, electrocardiogram, and urine drug screens.

Of 22 depressed subjects, 18 were psychotropic naïve. The remaining four participants were free from any psychotropic agent for at least 8 weeks before the study. These four participants took short-acting selective serotonin reuptake inhibitors prior to the study, and one of them also used a stimulant in childhood.

Diagnostic evaluation

The diagnosis of MDD and other psychiatric disorders was based on a semistructured instrument, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997), designed to ascertain present and lifetime history of psychiatric illness according to the DSM-IV-TR criteria (American Psychiatric Association 2000). The K-SADS-PL was administered separately to the adolescent and parent, and both were reinterviewed to resolve discrepancies. Summary scores were tabulated from information obtained from both informants.

Other assessments

The Children's Depression Rating Scale-Revised Version (CDRS-R; Poznanski et al. 1985) and Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) were administered to assess the severity of depressive symptoms. The CDRS-R has established psychometric properties. Although HRSD is not normed for

younger children, we administered this instrument in order to compare adolescent and adult samples in our developmental studies. The Family History-Research Diagnostic Criteria (FH-RDC) was used for the evaluation of psychiatric disorders in the first-degree family members (Andreasen et al. 1977). The FH-RDC is sensitive for obtaining information from knowledgeable relatives (Thompson et al. 1982). Socioeconomic status (SES) was assessed with the Hollingshead Four Factor Index of Social Status (Hollingshead 1975). Intelligence Quotient (IQ) was estimated from vocabulary and block design scores using the Wechsler Intelligence Scale for Children (WISC IV; Wechsler 2003) for ages < 16 years and Wechsler Adult Intelligence Scale (WAIS III; Wechsler 1997) was employed for ages ≥ 16 years. The Tanner's scale was used to assess pubertal development (Marshall 1969, 1970).

The diagnostic and other assessments were performed by clinicians with a Bachelor's or Master's Degree in Psychology and a minimum of 3 months' training on the instruments. They achieved interrater reliability ≥ 0.85 with an expert rater (U.R.) on all symptom ratings and $\kappa \geq 0.95$ on diagnoses prior to conducting the semistructured interviews under the supervision of a trained interviewer. Independent interviews were conducted only after they were certified by the trained interviewer. All interviews were audio-taped, and a random set of assessments was independently coded by the expert rater ($\kappa = 1.00$).

Magnetic resonance imaging

Structural images of the brain were obtained using a 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a transmit/receive quadrature RF head coil. To avoid large motions, the head was immobilized with tightly-fitting foam padding and a strap was fastened across the forehead. High-resolution T1 images of the entire brain were acquired in the sagittal plane (3D SPGR pulse sequence: TR = 19 ms; TE = 4.6 ms; flip angle = 30° ; matrix = 192×256 ; FOV = 230 mm; slice thickness = 1.2 mm).

VBM preprocessing. The data were analyzed by VBM methodology using Statistical Parametric Mapping, Version 5 (SPM5; Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk) running on MATLAB 7.9 (www.mathworks.com) on windows vista platform. No data were excluded from analysis because of excessive head motion (more than 3 mm in each direction). We used the VBM 5 toolbox (<http://dbm.neuro.uni-jena.de>) for image preprocessing, which included the following steps: normalization, segmentation, smoothing, and modulation. The VBM5 toolbox uses a new tissue-segmentation method implemented in SPM5. The details of the segmentation process performed in VBM5 toolbox have been described elsewhere (<http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/manual/>). To preserve the potential volume changes, the segmented images were modulated by the Jacobian determinants obtained from the spatial normalization procedure (Good et al. 2001). The analysis of the modulated gray and white matter segmented images can detect regional differences in the volumes of gray and white matter, respectively. Finally, the modulated gray matter images were smoothed with an isotropic Gaussian kernel with 8-mm full width-half maximum (FWHM) and analyzed statistically.

Statistical analysis

For group comparisons of demographic and clinical variables, the chi-square was used to analyze categorical variables and the Student's *t*-test for independent samples was employed for

continuous measures. For gray and white matter volumes, the following analyses were performed: (1) group comparison of gray and white matter volumes in controls > depressed adolescents; (2) group comparison of gray and white matter volumes in depressed adolescents > controls. The analysis included grand mean scaling and absolute threshold masking (0.1). Subtraction analyses were employed to compare gray and white matter density in the two groups on a voxel-by-voxel basis using the two-sample *t*-test with SPM5. Significant group differences were estimated by the theory of random Gaussian fields, and alpha was set at 0.05 (family-wise error corrected), while the cluster size was set at > 100 voxels displayed as statistical parametric maps into standard anatomical space (Zhou et al. 2009). In addition, an SPM5 regression analysis was conducted to examine the effect of SES and depression severity (based on total scores from HRSD/CDRS-R) on gray matter volume within each group separately as well as in the full sample. Furthermore, SES was employed as a covariate to examine its impact on gray matter differences between the two groups using SPM5 two-sample *t*-test.

Results

Sample characteristics

Demographic and clinical characteristics of the sample are provided in Table 1. The groups did not differ significantly on any sociodemographic characteristics with the exception of SES (healthy adolescents had higher SES scores than depressed youth). As expected, depressed adolescents scored significantly higher on depression severity than controls. Out of 22 depressed adolescents, 2 met criteria for anxiety disorder and 3 for attention-deficit/hyperactivity disorder (ADHD). Based on FH-RDC, 52% of the depressed adolescents had family history of depression in their first-degree relatives. However, depressed adolescents with a family history of bipolar disorder in the first-degree relatives were excluded from the study. In addition, the healthy controls did not have any history of psychiatric illness in their first-degree relatives. No data were collected for the second-degree relatives for either group.

Gray matter volume

As shown in Table 2 and Figure 1, the VBM data illustrated that depressed adolescents had lower gray matter volume in bilateral dorsolateral prefrontal cortex (DLPFC) [including parts of right and left inferior and middle frontal gyri (MFG)], right OFC (BA 11), right frontopolar cortex (BA 10), right middle temporal gyrus

(MTG), right superior temporal gyrus (STG), bilateral caudate, bilateral thalamus (pulvinar), and bilateral cerebellum (uvula and tonsil) than controls. In contrast to this, the controls had lower gray matter volume in the lentiform nucleus, globus pallidus, subgyral temporal lobe, and midbrain than the depressed group. The observed gray matter differences between the two groups lost statistical significance after covarying for SES. In addition, the gray matter volume did not correlate significantly with SES, CDRS-R, or HRSD scores. It is important to note that SES scores were missing for five controls and eight depressed adolescents, and exclusion of these subjects resulted in a reduced sample size for these analyses. One volunteer in the control group had an estimated IQ score of < 70 but this subject had no evidence of mental retardation based on clinical evaluation, academic achievement scores, and psychosocial functioning. Exclusion of this participant from the analysis did not alter the results. There were no significant group differences in the white matter.

Discussion

This study demonstrated significantly lower gray matter volume in the frontolimbic areas and caudate in depressed adolescents than controls. These brain regions are similar to those implicated in the psychopathology of MDD in both adolescents and adults in a number of prior neuroimaging studies (Merriam et al. 1999; Botteron et al. 2002; Bremner 2002; Frodl et al. 2004; Rajkowska et al. 2007; Steele et al. 2007; Drevets et al. 2008; Grimm et al. 2008; Zou et al. 2010; Peng et al. 2011). Although some of these studies used VBM to assess gray matter deficits in the prefrontal and limbic system in depressed adults (Frodl et al. 2004; Zou et al. 2010; Peng et al. 2011), to the best of our knowledge, the current study is the first VBM study to observe reduced gray matter volume in both prefrontal and limbic regions in adolescent depression.

The findings from this study should be interpreted with caution due to the modest sample sizes, which, along with missing SES data, could explain loss of significance in gray matter differences between the two groups after covarying for SES. Similar explanation can be given for lack of correlation between SES scores and gray matter volume in depressed adolescents in this study. It is worth mentioning that several investigations in animals and some human studies have demonstrated that adverse environmental conditions (which frequently coincide with low SES) can potentially induce structural and functional brain changes in youngsters and adults (Teicher et al. 2006). A subgroup of depressed adolescents had co-morbid anxiety disorders ($n=2$) and ADHD ($n=3$). Anxiety disorders and ADHD

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE HEALTHY AND DEPRESSED ADOLESCENTS

	Healthy controls (n=22)	Depressed (n=22)	Statistics
Age (years)	16.0 ± 2.1 (range = 12–20)	15.0 ± 2.1 (range = 12–20)	$t = 1.03$ $p = 0.31$
Gender	females = 10 (45%), males = 12 (55%)	females = 11 (50%), males = 11 (50%)	$\chi^2 = 0.09$ $p = 0.76$
Ethnicity	Caucasian = 16 (72.7%), non-Caucasian = 6 (27.3%)	Caucasian = 16 (72.7%), non-Caucasian = 6 (27.3%)	$\chi^2 = 0.00$ $p = 1.00$
Hollingshead SES score	50.4 ± 7.9 (range = 38–66)	39.6 ± 11.0 (range = 14–55)	$t = -3.19$ $p = 0.003$
Full-scale IQ score	109 ± 22.3 (range = 62–141) ^a	102 ± 14.0 (range = 78–129)	$t = -1.19$ $p = 0.24$
HAMD	1.09 ± 1.27 (0–4)	25.67 ± 6.26 (16–38)	$t = 18.05$ $p \leq 0.001$
CDRS-R	18.7 ± 1.6 (17–22)	53.1 ± 7.0 (39–76)	$t = 22.60$ $p \leq 0.001$

Data are presented as means and standard deviations along with ranges, or as raw numbers and proportions.

^aAlthough one participant from the control group had an estimated IQ score < 70 based on brief The Wechsler Intelligence Scale for Children, this participant had no evidence of mental retardation based on clinical evaluation, academic achievement scores, and psychosocial function. Hence, this participant was included in the study. Analysis of data excluding this participant did not change the results.

HAMD = Hamilton Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; IQ = Intelligence Quotient.

TABLE 2. WHOLE-BRAIN GROUP STATISTICS FOR HEALTHY CONTROLS > DEPRESSED ADOLESCENTS

Healthy controls > depressed patients (FWE corrected)					
Brain region	k	T	Z	x,y,z	Brain subregion
Frontal cortex	751	7.86	6.31	48 38 – 14	Inferior frontal gyrus
		7.54	6.13	34 24 6	Inferior frontal gyrus (BA 45)
		6.69	5.63	– 50 36 – 12	Inferior frontal gyrus
	291	7.52	6.12	– 36 56 – 8	Middle frontal gyrus
		6.10	5.25	– 42 48 – 12	Middle frontal gyrus
		406	6.10	5.25	– 24 44 – 14
	6.00	5.18	– 24 32 – 18	Middle frontal gyrus	
		6.07	5.23	10 68 2	Superior frontal gyrus (BA 10)
		155	5.13	4.57	18 62 – 14
	118	6.48	5.49	24 32 – 18	Middle frontal gyrus
		6.26	5.36	26 46 – 14	Middle frontal gyrus
	Striatum	400	9.64	7.21	12 8 14
8.65			6.73	14 20 2	Caudate head
8.51			6.66	16 – 4 22	Caudate body
339			9.39	7.10	– 12 8 14
Limbic areas	155	6.11	5.26	34 18 – 38	Superior temporal gyrus (BA 38)
		5.88	5.10	42 20 – 30	Superior temporal gyrus (BA 38)
		5.75	5.01	46 4 – 40	Middle temporal gyrus (BA 21)
		6.02	5.20	50 – 22 – 8	Middle temporal gyrus
Thalamus	339	7.73	6.24	– 10 – 30 2	Thalamus (pulvinar)
		7.72	6.23	10 – 28 6	Thalamus
Cerebellum	278	6.39	5.44	14 – 80 – 48	Cerebellum posterior lobe
		406	6.17	5.29	– 44 – 48 – 48
	6.02	5.19	– 14 – 76 – 50	Cerebellum	
		5.93	5.14	– 14 – 88 – 34	Cerebellum uvula

FWE = Family-Wise Error.

Bold face type are peak voxels.

commonly co-occur in depressed adolescents and exclusion of participants with these co-morbid conditions would not have yielded a representative sample (Calles 2007).

Based on converging evidence from cognitive (Merriam et al. 1999), structural neuroimaging (Botteron et al. 2002; Bremner 2002; Steele et al. 2007; Drevets et al. 2008), functional neuroimaging (Drevets et al. 2008; Grimm et al. 2008), and postmortem (Rajkowska et al. 2007) studies, changes in PFC have been observed frequently in association with major depression. This is especially true for the DLPFC and OFC subregions of the PFC, which play a pivotal role in self-monitoring and decision making and provide executive control on other PFC regions, such as the medial PFC, as well as monitoring of the limbic system (MacDonald et al. 2000; Ridderinkhof et al. 2004). It is, however, important to mention that not all structural imaging studies have reported PFC changes in adolescent depression. For example, an earlier ROI-based study failed to observe a significant difference in OFC volume between depressed adolescents and controls (Chen et al. 2008). These conflicting results might be due to methodological differences between the VBM and ROI-based approaches.

Limbic regions have been frequently implicated in the pathophysiology of depression. Although neuroimaging studies have demonstrated functional and morphological changes in limbic structures (Drevets et al. 1997; Drevets 2001; Bremner 2002), and particularly the hippocampus (Bremner et al. 2000; Mervaala et al. 2000; Steffens et al. 2000; Sheline et al. 2002; Vythilingam et al. 2002; Hastings et al. 2004), in depressed adults (Ongür et al. 1998; Rajkowska et al. 1999; Cotter et al. 2001), it is not known whether similar findings also exist in the depressed adolescents. The current study is the first to report a reduction in gray matter volume in the

superior temporal gyrus (STG; BA 38) and MTG (BA 21) in depressed adolescents. The STG is a complex brain region involved in the processing of sensory inputs to visceral emotional responses (Ding et al. 2009), and the MTG has been linked to decision making in the presence of stimulus conflict (Wendelken et al. 2009). Therefore, gray matter deficits in STG and MTG along with those in the DLPFC and OFC (also observed in this study) may provide the neuroanatomical basis for emotional dysregulation and impaired decision making in depressed adolescents, respectively (Cella et al. 2010).

In addition to the limbic system, several studies in depressed adults revealed gray matter deficits in the striatum, especially in the caudate nucleus (Krishnan et al. 1992; Krishnan et al. 1993; Parashos et al. 1998; Kim et al. 2008; Koolschijn et al. 2009; Pizzagalli et al. 2009), although not all studies replicated this finding (Greenwald et al. 1997; Pillay et al. 1998; Lacerda et al. 2003). Reduced gray matter volume in the caudate nucleus also was found in the current study, suggesting that changes in the striatum might occur in the initial presentation of MDD.

Gray matter deficits also were found in the thalamus, cerebellum, and frontopolar cortex in the depressed group. Although reduced thalamic volume was reported in adult women with MDD (Kim et al. 2008), this may be the first report of such deficits during early-onset depression. Interestingly, a postmortem study in depressed adults reported an increase in the number of neurons in the mediodorsal and anteroventral/anteromedial nuclei of the thalamus that connect subcortical limbic system structures (such as the amygdala) with the prefrontal and cingulate cortices (Young et al. 2004). Furthermore, an association between history of antidepressant use and reduction in the volume of various thalamic nuclei in

FIG. 1. Cross hairs showing (A) orbitofrontal, (B) superior temporal gyrus, (C) caudate, and (D) dorsolateral with reduced gray matter volume in the depressed adolescents compared with controls. A color version of this figure is available in the online article at www.liebertpub.com/jcap.

depressed subjects (Young et al. 2008) suggests a potential antidepressant effect on the thalamus. In the current study, most of the depressed participants were never exposed to psychotropic agents and in the small subgroup (18%) that had ever been exposed to antidepressant agents, the duration of exposure was relatively brief (<2 months) and also not in close proximity to the MRI study. Therefore, medication exposure was unlikely to have a significant impact on brain structural changes.

With regards to the cerebellum, earlier studies documented decreased volume in the cerebellar vermis (Shah et al. 1998) and mean cerebellar volume (Escalona et al. 1993) in adults with MDD. A more recent study reported lower gray matter volume in the left cerebellum in patients with first-episode depression (Peng et al. 2011). These findings provide preliminary evidence that structural deficits in the cerebellum may be incorporated in the neuroanatomical model of mood disorders.

Gray matter changes in the frontopolar region (BA 10), as observed in this study, have never been reported in any prior adolescent or adult studies. It has been proposed that this region is involved in the processing of "cognitive branching" (Koechlin and Hyafil 2007). Cognitive branching is a process through which memory of a previously ongoing task is maintained for subsequent retrieval and completion. Thus, gray matter deficits in this brain

region in depressed adolescents may reflect a compromised ability for multitasking and scheduling operations.

Consistent with findings of the current study, an earlier VBM study failed to detect white matter deficits in depressed adults (Kim et al. 2008). Additionally, structural deficits in prefrontal regions, such as the subgenual anterior cingulate cortex (sgACC), frequently linked to depression in adults (Drevets et al. 1997; Hirayasu et al. 1999; Botteron et al. 2002; Hastings et al. 2004; Coryell et al. 2005; Drevets et al. 2008) and adolescents (Botteron et al. 2002), were not observed in this study. Since most of these studies were conducted in adults, the lack of gray matter deficits in the sgACC in depressed adolescents may be an age effect. It is also possible that this study may not have captured relatively small gray matter deficits, such as the sgACC, because the VBM analysis was thresholded at a large voxel size (i.e., >100 voxels). Also, this study failed to find gray matter deficits in the hippocampus, a brain region that implicated in adults (Campbell et al. 2004; Videbech and Ravnkilde 2004; Caetano et al. 2007) and adolescents with major depression (MacMaster and Kusumaker 2004; Rao et al. 2010). The reduced hippocampal volume associated with depression appears to be influenced by the number and duration of depressive episodes, suggesting greater variability in studies recruiting first-episode cases (Videbech and Ravnkilde 2004). On the other hand, hippocampal changes also

maybe detected prior to the onset of illness in at-risk individuals (MacQueen and Frodl 2011; Rao et al. 2010).

Conclusion

Although several neuroimaging studies have revealed gray matter deficits in depressed adults, to our knowledge, this is the first report of gray matter changes in the frontolimbic areas and caudate in adolescent depression. These findings support the notion that structural deficits may be present at the onset of depressive illness. However, longitudinal studies in larger samples are required to confirm these results, controlling for the confounding effects of age, gender, SES, antidepressant pharmacotherapy, and duration of illness.

Clinical Significance

This, to our knowledge, is the first study to report gray matter deficits in frontolimbic and striatal cortex in depressed adolescents using voxel-based morphometry. These findings suggest that structural deficits may be present at the onset of depressive illness and may provide neuroanatomical markers for early depression.

Disclosures

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