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Neuroimaging markers of adolescent depression in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study

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Abstract

Background: Adolescents are at increased risk of developing major depressive disorder (MDD) than many other age groups. Although the neural correlates of MDD in adults have been studied prospectively, such adolescent depression studies are mainly cross-sectional. We extracted data regarding the relationship between cortical thickness and later development of adolescent MDD from a national community study that uses an accelerated longitudinal design to examine the psychological, environmental, and neural differences related to drinking and brain development.

Methods: 692 subjects (age 12–21 years; 50% female) without a history of MDD were assessed with structural neuroimaging at baseline. We compared those 101 subjects who transitioned to

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Contributors ADM's roles include conceptualization, formal analysis, funding acquisition, investigation, methodology, visualization, and writing (original draft and editing). TB's roles include data curation, resources, supervision, and writing (review and editing). BJN's roles include data curation, funding acquisition, methodology, resources, supervision, validation, and writing (review and editing). FCB's roles include data curation, funding acquisition, methodology, resources, supervision, and writing (review and editing). SAB's roles include data curation, funding acquisition, methodology, project administration, resources, supervision, and writing (review and editing). SFT's roles include data curation, funding acquisition, methodology, resources, supervision, validation, and writing (review and editing).

Conflict of Interest
The authors declare that they have no competing financial and non-financial interests.

Declaration of interests: none

Ethical approval All study procedures were approved by the respective institutional review board at each research site.

Data statement The datasets analyzed for the current study are not publicly available to protect the privacy of participants.

MDD by 1-year follow-up to those who remained non-depressed over the same time period. FreeSurfer's autosegmentation process estimated vertex-wide cortical thicknesses and its Query, Design, Estimate, Contrast (Qdec) application investigated cortical thickness between those who later developed MDD and those who remained without MDD (Monte Carlo corrected for multiple comparisons, vertex-wise cluster threshold of 1.3, $p < 0.01$).

Results: Those who transitioned in the next year to MDD had, at baseline, thinner cortices in the superior frontal cortex, precentral and postcentral regions, and superior temporal cortex, above and beyond effects attributable to age and sex. No cortical thickness sex differences or sex-by-depression interactions were observed.

Limitations: A larger sample size could improve statistical power and future investigations will be needed to confirm our results.

Conclusions: Thinner cortices over frontal and temporal regions may be linked to enhanced vulnerability for future depression during the adolescent–young adulthood transition.

Keywords

adolescence; depression; neuroimaging; longitudinal; cortical thickness; biomarker

Background

Major depressive episodes are debilitating and can be associated with enhanced morbidity and mortality, with the latter including suicide attempts (Hallfors et al., 2004; Pelkonen and Marttunen, 1999). These depressions are seen in an estimated 12% of adolescents before age 18, many of whom fulfill criteria for major depressive disorder (MDD) (Merikangas et al., 2010). Mid-adolescent depression is twice as common in girls compared to boys (Khesht-Masjedi et al., 2017). Such adolescent depressions are strong predictors of recurrent major depressive episodes in adulthood (Fergusson et al., 2005; Klein et al., 2009).

Depressive episodes have been reported to potentially relate to a range of biological attributes, including dysfunctional cortical-subcortical (e.g., limbic) feedback, resulting in self-referential negative thoughts, insomnia, poor concentration, irritable mood, and suicidal thoughts (Drevets et al., 2008). Cross sectional investigations have reported that hippocampal, caudate, anterior cingulate cortex, and prefrontal cortex volumes are lower in youth with depressive symptoms (Jaworska et al., 2016; Pannekoek et al., 2014; Shad et al., 2012). Ducharme *et al.* in 2014 found a positive association of anxious-depressive symptoms with lower cortical thickness in the medial orbito-frontal, gyrus rectus, and subgenual anterior cingulate areas for ages 12 and above (Ducharme et al., 2014). Whittle *et al.* identified volumetric changes in the hippocampus, amygdala, and putamen associated with depression onset from early to mid-adolescence, moderated by sex, with exaggerated growth of the amygdala in females and attenuated growth in males (Whittle et al., 2014). Schmaal *et al.* found attenuated expansion of cortical surface area in the right orbitofrontal cortex in males, and decreased surface areas in the anterior cingulate and orbitofrontal cortex in females during adolescence in worsening depression compared to those with improving depression (L. Schmaal et al., 2017).

Among the studies that examined MDD, some have highlighted the importance of the frontal and temporal regions in mood disturbances, especially during adolescence. One longitudinal study (n=205) demonstrated that cortical thinning in frontal regions (lateral orbitofrontal and precentral regions) was seen over 5 years on three MRI scans in adolescents who self-reported depressive symptoms during that period compared to those who did not (Bos et al., 2018). Regarding cortical thickening, in typical adolescent brain development, cortical gray matter volume decreases into adulthood (Mills et al., 2014). Cortical thinning also occurs through intracortical myelination during this period (Grydeland et al., 2013). These findings in the context of typical adolescent brain development suggest that adolescent depression is associated with several cortical abnormalities over the lifespan with particular emphasis on the prefrontal and temporal regions.

Promising studies to date have suggested cortical thinning is observed during major depressive episodes or in those with depressive symptoms (Bos et al., 2018). One study with children diagnosed with MDD (N=90) reported global cortical gray matter loss and cortical thinning compared to children without MDD (Luby et al., 2016). It is unclear if the cortical thinning preceded the depression, or developed during the depressive episode.

In a second noteworthy paper, Foland-Ross *et al.* reported that lower cortical thickness of the right medial orbitofrontal, right precentral, left anterior cingulate, and bilateral insular cortex predicted the onset of depression in 18 of 33 adolescent girls with a family history of depression followed for 5 years (Foland-Ross et al., 2015). This study is a single example of a prospective investigation that demonstrated cortical thickness preceded a major depressive episode in adolescents. Several aspects of this study would benefit from further investigation. First, it is not clear whether these results generalize to a larger, nationally-representative sample, or if the findings apply to adolescent males. In addition, the fact that the future depression could have occurred as much as five years later makes it difficult to determine whether the cortical thinning observed 5 year previously contributed significantly to the future depression.

In addition, few studies to date have considered several additional characteristics that could have contributed to both cortical changes and to mood disturbances. Prominent among these is the potential impact of heavy alcohol intake (Hedden et al., 2014; Hingson and White, 2014). This issue might be especially important in adolescents as the late teens to mid-twenties are times when individuals are likely to have their heaviest lifetime drinking. It has been estimated that fourteen percent of 12th graders reported past 2-week consumption of more than 4 or 5 drinks per occasion, a practice referred to as binge drinking (Miech et al., 2020). Thus, it is important to distinguish the effects of binge drinking that may lead to a temporary depressive episode.

Our group is fortunate to have access to data from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study, a national investigation that recruited subjects across ages 12 to 21 to examine the psychological, environmental, and neural changes that occur during adolescent brain development. The NCANDA protocol also records additional characteristics including alcohol consumption. To address the impact of this issue on better understanding depression, we examined the percent of binge drinkers in

our sample. In addition, low socioeconomic status has been associated with a higher prevalence of depression (Freeman et al., 2016). Therefore, we also examined the role of socioeconomic status in our sample.

Studies looking at depressive symptoms during adolescence have been relatively small or more modest in nature (N=205) (Bos et al., 2018), and not representative of national demographics in the United States. They have predominantly focused on markers of existing self-report of depressive symptoms, and it is unclear if some of these morphometric markers existed before the development of depressive symptoms. These studies lay the basis for our neurobiological hypotheses regarding brain imaging differences between a large sample of healthy adolescents with both sexes equally represented who do and do not develop a major depressive episodes using DSM-IV diagnostic criteria in the next year.

We propose two neurobiological hypotheses based on the studies above for investigation in the NCANDA longitudinal sample: First, thinner cortices will precede the development of a major depressive episode during adolescence. Second, the relationship of thinner cortices to a future depressive episode will be observed in both boys and girls. We present findings from the NCANDA longitudinal study that predated and predicted major depressive episodes while controlling for those who have never had a major depressive episode.

Methods

Participants

Using data from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA.org), 1438 individuals were eligible for these analyses among which 831 were selected based on matching national demographic characteristics and being between age 12.0 and 21.9 years at project entry. Since this study examined predictors of new onset of a major depressive episode, participants that met diagnostic criteria for a DSM-IV major depressive episode (Bucholz et al., 1994; Hesselbrock et al., 1999) at baseline (n=139) were excluded from the analysis. The remaining 692 individuals were then divided into two groups that included 101 who developed an episode of major depression in the 12 subsequent months and the 591 who did not.

Measures

Participants were assessed annually with a comprehensive clinical assessment that included the Computerized Semi-Structured Assessment for Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994; Hesselbrock et al., 1999; Schuckit et al., 1995) to provide a diagnostic measure of the presence of a major depressive episode (DSM-IV) and other psychiatric symptoms and disorders. Criteria were identical to DSM-5 for a major depressive episode with the exception of exclusion for bereavement and a mixed episode.

The Customary Drinking and Drug Use Record (Brown et al., 1998) was used to assess the use of alcohol, tobacco, cannabis, illicit drugs, and the misuse of prescription medications. A small number of nondrinkers identified as using other drugs (1.4%; n=10) such as synthetic cannabis, amphetamines, ecstasy, and opiates.

A modified version of the MacArthur Sociodemographic Questionnaire (Giatti et al., 2012) was used to assess socioeconomic status; socioeconomic status reflected parental family income except if the youth was living independently, in which case it reflected the youth's own socioeconomic status. Twenty percent of parents endorsed education below a college degree, twenty-seven percent with at least one parent completing college, and fifty-three percent with at least one parent with education beyond a college degree. Annual family income ranged from below $12,000 to greater than $200,000. Eleven percent of the sample did not know or declined to provide income data (Brown et al., 2015).

Reliability across sites and training for assessments was ensured through the development of training manuals, training developed by senior-level staff members (Ph.D./M.D.), mock sessions guided by senior members through feedback, and annual visits to check for interviewer drift and confirmation of training of new staff members (Brown et al., 2015).

Neuroimaging

A whole brain MRI was completed at baseline and at annual follow-up with each study participant. T1-weighted, 3D images were collected in the sagittal plane on systems from 2 manufacturers: 3T General Electric (GE) Discovery MR750 at 3 sites (University of California San Diego, SRI International, and Duke University) and 3T Siemens TIM TRIO scanners at 2 sites (University of Pittsburgh and Oregon Health & Sciences University). The GE sites used an Array Spatial Sensitivity Encoding Technique (ASSET) for parallel and accelerated imaging with an 8-channel head coil and acquired an Inversion Recovery-Spoiled Gradient Recalled (IR-SPGR) echo sequence (TR = 5.904 ms, TI = 400 ms, TE = 1.932 ms, flip angle = 11°, NEX = 1, matrix = 256 × 256, FOV = 24 cm, slice dimensions = 1.2 × 0.9375 × 0.9375 mm, 146 slices). The Siemens sites used a 12-channel head coil and parallel imaging and temporal acceleration with iPAT and acquired an MPRAGE sequence (TR = 1900 ms, TI = 900 ms, TE = 2.92 ms, flip angle = 9°, NEX = 1, matrix = 256 × 256, FOV = 24 cm, slice dimensions = 1.2 × 0.9375 × 0.9375 mm, 160 slices) (Pfefferbaum et al., 2016). The neuroimaging protocol was accomplished in <1 hour. The effect of scanner type (GE or Siemens) was examined alongside depressed status as noted under the, "Statistical analyses," section.

Cortical thickness estimates and cortical surface reconstruction were obtained using FreeSurfer (version 5.1, surfer.nmr.mgh.harvard.edu) (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000). The cross-sectioning process, cortical thickness calculation, and parcellation procedure has previously been described in detail (Jacobus et al., 2015); FreeSurfer processing was completed at SRI International for all sites. Structural scores were computed using FreeSurfer's cross-sectional approach to the skull-stripped MRI of each time point; this refined brain masks by removing voxels having low T2-weighted intensities near the brain surface. Using the refined brain masks, the longitudinal FreeSurfer protocol applied to the aligned baseline and follow-up T1-weighted magnetic resonance images produced bilateral surface area, volume, and thickness measures. The Desikan-Killiany atlas (Fischl, 2012) was used for generating parcellation units. This choice of atlas made the most sense since participants were adolescent through young adulthood, and even at age 12, the head size is close to peak. Use of the Desikan-Killiany atlas for adolescence is

standard practice (Hong et al., 2013; Hoogman et al., 2019; Whitaker et al., 2016). Inter-scanner and intra-scanner reliability were not needed to be measured using phantoms; correcting for global scaling factor by affinely registering the detected sphere centers of the phantom to their ideal location did not significantly alter findings. Harmonizing scores across scanners and visits was achieved by rigidly registering each scan to the SRI24 atlas. Quality checking (QC) of FreeSurfer outputs was completed visually and based on the QC scores of FreeSurfer using the QAtools_v1.2 (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools). Outliers were examined using these QC scores; no failures in processing were identified.

Statistical Analyses

The link between cortical thickness at baseline and subsequent major depressive episode at follow-up year 1 was investigated using FreeSurfer's Qdec (Monte Carlo corrected for multiple comparisons, vertex-wise cluster threshold of 1.3, $p < 0.01$) (Hagler et al., 2006). The vertex-wide cluster threshold of 1.3, $p < 0.01$ is widely used in the Qdec literature to minimize false positive findings (Clausen et al., 2020; Worker et al., 2014). Qdec facilitates whole brain analysis using a linear model approach to determine whether differences exist between clusters of vertex-wise cortical thicknesses and the presence of a variable of interest (e.g., major depressive episode diagnosis).

Clusters of regions of cortex at baseline related to the predictor were mapped onto a naming scheme defined based on the Desikan-Killiany atlas (Fischl, 2012). We used a Qdec analysis approach to investigate baseline cortical thickness and: 1) the relationship between major depressive episode at follow-up year 1; 2) sex effects, and 3) scanner type while controlling for age and sex. NCANDA data used were NCANDA_RELEASE_4Y_REDCAP_MEASUREMENTS_V01, 6-JUN-2019 and NCANDA_RELEASE_4Y_STRUCTURAL_MEASUREMENTS_V01, 18-Oct-2019. Differences in participant characteristics at baseline were distinguished using independent t-tests or chi-squared analyses depending on whether the characteristic was continuous or categorical, respectively.

Results

Participant Characteristics

Table 1 presents the total of 692 adolescents with no history of major depressive episodes at baseline, divided into the 101 who went on to develop depression and 591 who did not. At baseline, these groups differed significantly on only 2 characteristics, those who developed a depressive episode were about 1 year older and were more likely to be female. As a result of these differences, the effects of age and sex were controlled for in the analyses. The effect of sex was also analyzed separately. There were no significant differences across the groups for socioeconomic status, ethnicity, or history of binge drinking. At 1 year follow up, the age difference between the groups was no longer significant due to variability around the specific number of months that lapsed between baseline and follow up interviews.

Vertex-wise Analysis of Cortical Thickness

Cortical thickness and depression.—The analyses next turned to the relationship of the future development of a MDD episode and baseline cortical thickness in regions highlighted in the literature, the right medial orbitofrontal, right paracentral, left anterior cingulate and bilateral insular cortex. The evaluations used the Desikan-Killiany atlas that divides the brain into 34 cortical regions to identify 7 clusters in the left and right hemisphere that distinguished between those adolescents who developed depression (N=101; see Figure 1) and those who did not. Details regarding p-values, anatomical locations, coordinates, peak z-value, and cluster size are listed in Table 2. Differences were noted at baseline (i.e., prior to emergence of depressive symptoms) in cortical thickness across the left (L) and right (R) precentral regions, L superior temporal cortex, L inferior parietal cortex, R banks of superior temporal sulcus, L superior frontal cortex, and L postcentral region, above and beyond effects attributable to age and sex.

For all regions, subjects who later developed a major depressive episode demonstrated thinner cortices than those who did not. Average cortical thickness, accounting for future depressed status, between scanner types differed only in the left lateral occipital region ($p=0.04$; negative correlation) and right superior parietal region ($p=0.02$; negative correlation) while controlling for multiple comparisons; no depressed status by scanner type interaction was found in the mean cortical thickness while controlling for multiple comparisons (Table 2).

Cortical thickness and sex.—Given the sex differences in the rates of adolescent MDD and in cortical thickness, data were analyzed separately for males and females. As shown in Table 2, cortical thickness did not differ between males and females, and no sex-depression interaction was observed.

Discussion

We examined neuroanatomical features differentiating youth who subsequently did or did not develop depression in the next year in a large community sample of subjects from the NCANDA study. Results from a Qdec analysis demonstrated that those who would transition into depression had thinner cortices in regions spanning the superior frontal cortex, precentral and postcentral regions, and superior temporal cortex, than those who would remain non-depressed. The role of sex in adolescent depression was also explored, and no sex-depression interaction was observed. Scanner differences (GE, Siemens) did not impact identified significant regions of interest.

We found thinner superior frontal, precentral and postcentral, and superior temporal cortices in healthy 12 to 21 year-olds who developed an episode of MDD in the subsequent year, in a relatively large, diverse sample. These results complement the findings of a smaller longitudinal study in children, which found increased global cortical gray matter loss and thinning over the preschool to school age developmental period in children who developed MDD compared to children without MDD (Luby et al., 2016). Our findings in the frontal cortex support the results of another longitudinal study that observed that thinner cortices in frontal cortex predict depressive symptoms in adolescents (Bos et al., 2018). However,

unlike the results of the large cross-sectional Enhancing Neuro Imaging Genetics through Meta-Analyses (ENIGMA) study that reported differences in cortical surface area but not cortical thickness in adolescents with MDD (L Schmaal et al., 2017), our study found thinner cortices in brain regions important for the cognitive control, emotional regulation, and default mode networks prior to MDD episode onset. In accord with this finding, a resting state fMRI study showed that hypoconnectivity between subgenual anterior cingulate cortex and inferior parietal lobule and between left and right dorsolateral prefrontal cortices predicted MDD onset in adolescence (Hirshfeld-Becker et al., 2019).

Longitudinal data in adolescent populations can inform the field about neuro-mechanisms. Faster maturation leading to cortical thinning in these specific regions suggests that these differences may influence risk for MDD in the developing, adolescent brain. Cortical thinning may increase vulnerability towards the future development of adolescent depression and has been found to be such a marker in familial depression (Hao et al., 2017). Our novel findings suggest that cortical thickness in regions of the brain involved in cognitive control, emotional regulation, and default mode networks show differences before an adolescent becomes symptomatic with an episode of MDD. Longitudinal MRI studies can pave the way towards neurobiological risk identification and possible primary prevention of youth MDD.

Girls are twice as likely as boys to develop depression, and there are known sex differences in the expression of depressive symptoms (Cyranowski et al., 2000). Thus, we were surprised that no differences in cortical thickness were found between males and females in our sex-balanced, well-powered sample. Other studies have tried to examine this question previously, but lacked sufficient sex composition to make a comparison of cortical thickness between the sexes (Ramezani et al., 2014). The lack of differences in cortical thickness may suggest that other neurobiological features could mediate sex differences in depression risk in adolescents.

Limitations

While the present findings suggest differences found between adolescent depression and cortical thickness, these findings are not without limitations. First, while the NCANDA study has major strengths of being a large, nationally-representative, and sex-balanced sample for imaging data (n=692, with 101 depressed subjects at Follow up Year 1), the sample size was not sufficiently large to split in half for validation to compute measures such as a Cohen's *d* or *t*-test. Future longitudinal designs with larger sample sizes such as ABCD (Hagler et al., 2019) will more definitively address the relationship of adolescent depression and cortical thickness. Second, the present study was strengthened by focusing on predicting a diagnosis of a MDD episode, based on DSM-IV criteria in contrast to other studies that used self-report; similar analysis to that above using SSAGA's continuous measures of the number of DSM-IV depressive symptoms to examine sub-syndromal depression did not reveal significant clusters in the NCANDA dataset. Future studies in ABCD or other longitudinal studies may clarify whether these cortical thickness measures also predict the development of sub-syndromal depression (Das et al., 2013; Vulser et al., 2015), or predict the progression of depression over time in a larger sample. Third, NCANDA's focus on adolescent alcohol use distinguished itself from other studies that have

a limited examination of the important role of binge drinking in the development of major depressive episodes. While having the major strength of assessing for binge drinking, family history of depression was not able to be considered due to NCANDA's focus on adolescent alcohol use rather than depression. Longitudinal studies such as ABCD (Hagler et al., 2019) may more definitively be able to examine whether those who develop depression were at familial risk for depression. Fourth, the use of the Qdec software facilitated a helpful depiction of structural differences between those adolescents who went on to develop depression and those who did not. However, any differences in color (i.e., heatmap granularity) in Figure 2 are artifacts created by the Qdec software and do not indicate meaningful information. Fifth, the vertex-wide cluster threshold of 1.3, $p < 0.01$ applied in this study is widely used in the Qdec literature (Clausen et al., 2020; Worker et al., 2014). However, a more stringent threshold could further minimize false positive rates based on established rates (Greve and Fischl, 2018).

Conclusions

We found reduced thickness of specific cortical regions among adolescents who transitioned into depression one year later, compared to those who did not develop depression, in a large, diverse longitudinal sample. Reduced cortical thickness, therefore, could be a predictor of increased vulnerability towards the future development of adolescent depression and used as a diagnostic marker for providing earlier interventions for at-risk individuals. Future larger studies such as ABCD will be able to build on the early findings identified here.

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Abbreviations:

Qdec	Query design estimate contrast
MDD	Major depressive disorder
ENIGMA	Enhancing Neuro Imaging Genetics through Meta-Analyses
NCANDA	National Consortium on Alcohol and Neurodevelopment in Adolescence
SES	Socioeconomic status
SSAGA	Semi-Structured Assessment for Genetics of Alcoholism
DSM	Diagnostic and Statistical Manual of Mental Disorders

GE	General Electric
ASSET	Array Spatial Sensitivity Encoding Technique
IR-SPGR	Inversion Recovery-Spoiled Gradient Recalled

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Highlights

- A large, national, sex-balanced, adolescent longitudinal study was used.
- No cortical thickness sex differences were seen.
- Thinner frontal & temporal cortices reflected vulnerability for future depression.

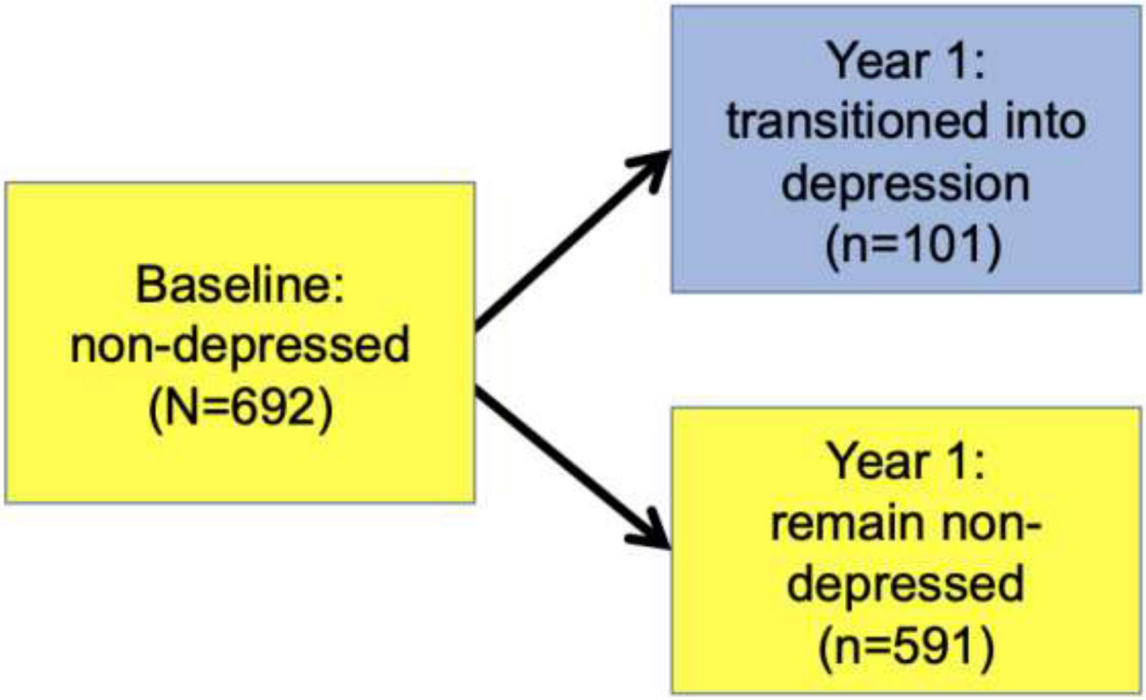
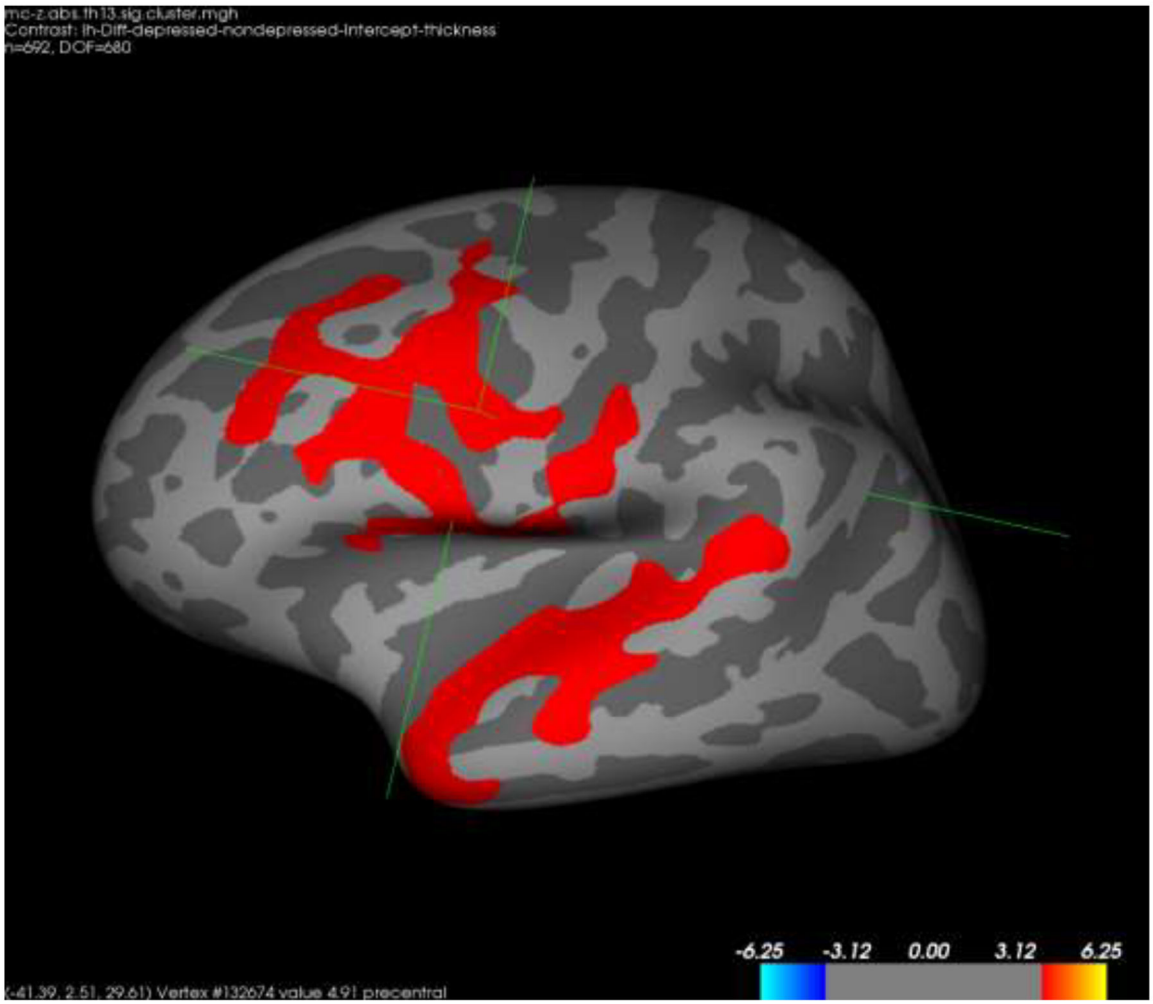


Figure 1:
Transition from non-depressed status into major depression diagnosis 1 year later, using SSAGA DSM-IV criteria.

(a) Left hemisphere



(b) Right hemisphere

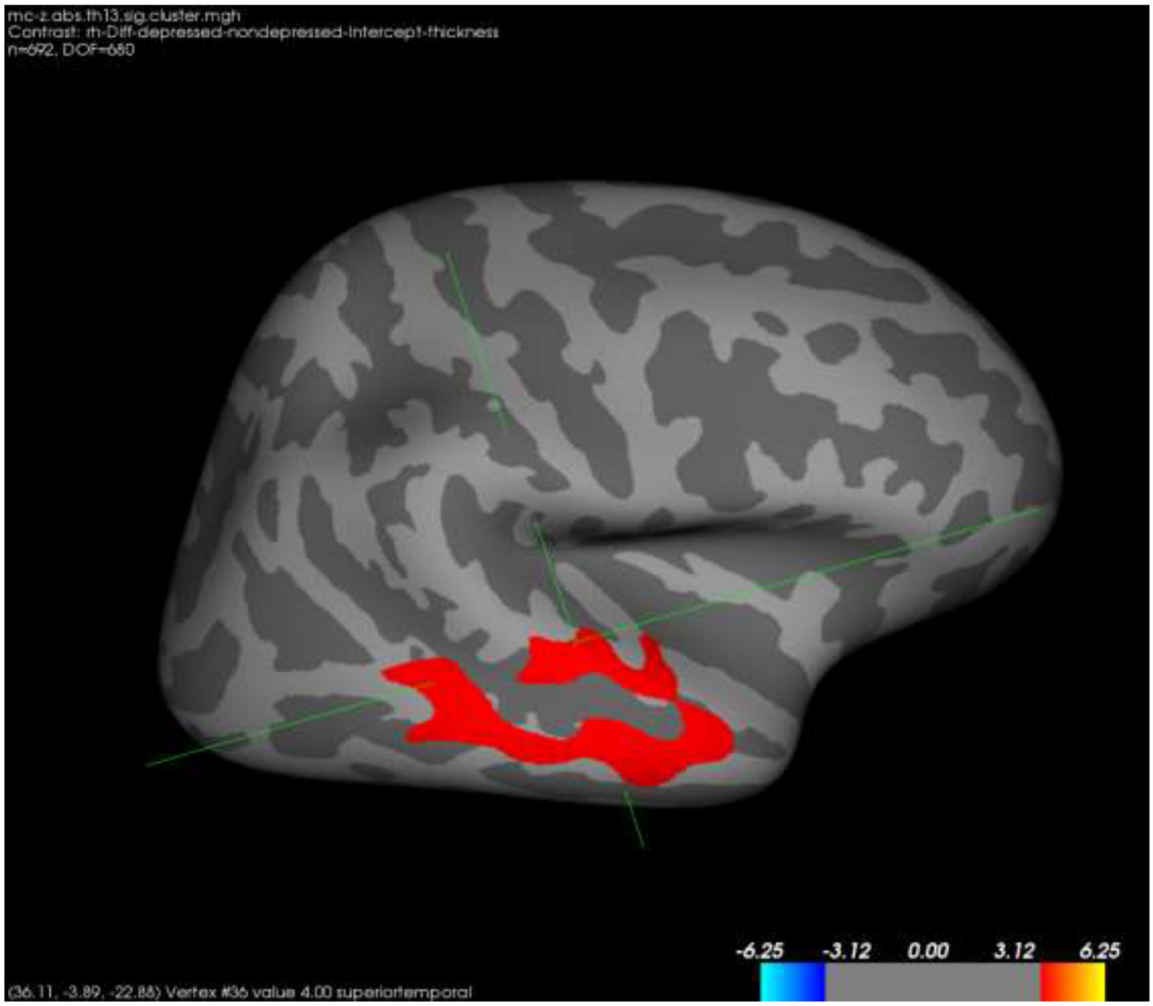


Figure 2: Whole-brain differences based on Table 2 between youth who transitioned into depression (n=101) and those who remained nondepressed (n=591).

Colored areas highlight significantly thinner cortices from Table 2 clusters for those who later transitioned into depression, compared to those who remained non-depressed, based on Monte Carlo simulations corrected for multiple comparisons (vertex-wise cluster threshold of 1.3, $p < 0.01$; color bar legend corresponds to z-value of clusters; z range 3.2 to 4.9). This pictorial depiction highlights thinner cortices identified at baseline in the precentral region, superior temporal cortex, inferior parietal cortex, superior temporal sulcus, superior frontal cortex, and postcentral regions.

Table 1.

Nationally Representative and Sex Balanced Participant Characteristics (N=692)

	Transition into Depression (n=101)		Remain Non-depressed (n=591)		t-test or X^2
BASELINE	M±SD or %	Range	M±SD or %	Range	p-value
Age (years)	16.7±2.5	12–21	15.8±2.5	12–21	0.002[b]
Socioeconomic status[1]	6.9±3.1	0–10	7.4±2.8	0–10	0.28
Sex (% male)	41.2	-	52.1	-	0.001[b]
Ethnicity (% white)	73%	-	71%	-	0.62
Major depressive episode diagnosis lifetime (%)	0%	-	0%	-	-
Lifetime Binge Drinking (%)	12%	-	13%	-	0.76
YEAR 1					
Age (years)	17.1±2.1	13–22	16.6±2.1	13–22	0.10
Major depressive episode diagnosis (%)	0%	-	100%	-	-

[a] $p < 0.05$

[b] $p < 0.01$,

[c] $p < 0.001$

[1] modified version of the MacArthur Sociodemographic Questionnaire used to assess socioeconomic status; higher values indicate higher socioeconomic status

M - mean

S - standard deviation

Table 2:

Regions showing cortical thickness differences at baseline between those who transitioned into depression (n=101) and those who remained non-depressed (n=591), controlling for age and sex

Cluster	Region of peak z-value	Cluster-wise P-value	x, y, z coordinates	Peak z-value	Cluster Size(mm^2)
1	L Precentral region	0.0001	−41,2,26	4.9	4180
2	R Precentral region	0.0479	49,−4,8	4.9	833
3	L superior temporal cortex	0.0001	−53,−25,3	4.6	3146
4	L inferior parietal cortex	0.002	−42,−53,13	4.2	1352
5	R banks of superior temporal sulcus	0.0001	60,−41,−2	3.8	1963
6	R superior frontal cortex	0.0245	23,12,42	3.7	932
7	L Postcentral region	0.0339	−33,−27,59	3.2	885

L - left

R - right