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Subthreshold Depression and Regional Brain Volumes in Young Community Adolescents

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Objective—Neuroimaging findings have been reported in regions of the brain associated with emotion in both adults and adolescents with depression, but few studies have investigated whether such brain alterations can be detected in adolescents with subthreshold depression, a condition at risk for major depressive disorder. In this study, we searched for differences in brain structure at

age 14 years in adolescents with subthreshold depression and their relation to depression at age 16 years.

Method—High-resolution structural magnetic resonance imaging was used to assess adolescents with self-reported subthreshold depression ($n = 119$) and healthy control adolescents ($n = 461$), all recruited from a community-based sample. Regional gray and white matter volumes were compared across groups using whole-brain voxel-based morphometry. The relationship between subthreshold depression at baseline and depression outcome was explored using causal mediation analyses to search for mediating effects of regional brain volumes.

Results—Adolescents with subthreshold depression had smaller gray matter volume in the ventromedial prefrontal and rostral anterior cingulate cortices and caudates, and smaller white matter volumes in the anterior limb of internal capsules, left forceps minor, and right cingulum. In girls, but not in boys, the relation between subthreshold depression at baseline and high depression score at follow-up was mediated by medial–prefrontal gray matter volume.

Conclusion—Subthreshold depression in early adolescence might be associated with smaller gray and white matter volumes in regions of the frontal–striatal–limbic affective circuit, and the occurrence of depression in girls with subthreshold depression might be influenced by medial–prefrontal gray matter volume. However, these findings should be interpreted with caution because of the limitations of the clinical assessment methods.

Keywords

subthreshold depression; MRI; gray matter; white matter

Subclinical depressive symptoms are frequent in adolescence,¹ a critical period for the onset of depressive disorders.² Adolescents with subclinical, subthreshold depressive symptoms may have clinically relevant depressive symptoms and may experience substantial distress or impairment, without meeting criteria for a diagnosis of major depressive disorder (MDD).³ Despite the different definitions of subthreshold depression used in the literature, based on the number, duration, and impact on functioning of symptoms,³ there is consistent evidence that subthreshold depression strongly predicts MDD in adulthood,^{1,4,5} with an estimated risk of escalation to full-syndrome disorder of 67%.⁵ Furthermore, although depressive symptom rates are similar in prepubescent boys and girls, a strong female preponderance in the prevalence of subthreshold and clinical depression emerges after puberty,^{6,7} suggesting that there might be gender differences in the neural circuitry underlying depression.

Despite the frequency of subthreshold depression in adolescents, with a lifetime prevalence reported as high as 26%,⁴ only 1 neuroimaging report⁸ restricted to the rostral anterior cingulate cortex (rACC) showed that boys with subthreshold depressive symptoms, but not girls, had smaller rACC volume than those with no depressive symptoms. The differences are more widespread in adolescents with MDD, as reduced gray matter volumes have been reported in frontal, limbic, and striatal regions such as the prefrontal cortex (PFC),^{9,10} ACC,¹¹ amygdala,¹² hippocampus,¹³ and caudates.^{9,14} A gender effect was reported in 1 study demonstrating smaller nucleus accumbens in girls with depression only, and increased growth of the amygdala during adolescence associated with depression in girls and decreased growth in boys.¹⁵

A further step requires investigating the morphometry on the whole brain and assessing the clinical outcome of adolescents with subthreshold depression, to shed light on the early brain structure variations involved in such emotional dysregulation and the vulnerability to depressive disorders, including vulnerability related to gender. Therefore, we hypothesized that adolescents with subthreshold depression, especially girls, would exhibit structural variations in these frontal, striatal, and limbic regions implicated in mood disorders, and that the structural variations would indicate vulnerability to depression outcome. We searched for differences in regional volumetry of gray (GM) and white matter (WM) in 14-year-old adolescents with subthreshold depression using T1-weighted magnetic resonance imaging (MRI) and whole-brain voxel-based morphometry (VBM). Based on the previous assumptions, we investigated whether these regional differences would mediate the relation between subthreshold depression at age 14 years and depression at age 16 years.

Method

Participants

The study was approved by the ethics committees of all participating institutions. Written informed assent and consent were obtained, respectively, from all adolescents and their parents after complete description of the study.

Neuroimaging and clinical data were obtained from the Imagen database established across 8 European sites in France, the United Kingdom, Ireland, and Germany, which includes 2,223 adolescents recruited in schools around age 14 years (SD = 0.41 year; age range = 12.9–15.7 years). A detailed description of recruitment and assessment procedures, along with exclusion and inclusion criteria, has been published elsewhere.¹⁶ Notably, bipolar disorder, treatment for schizophrenia, and major neurodevelopmental disorders constituted exclusion criteria.

Participants were also followed up 2 years later except for neuroimaging assessment.

Baseline Assessment—Adolescent psychiatric symptoms were assessed with the Development and Well-Being Assessment (DAWBA; www.dawba.com), a self-administered diagnostic questionnaire consisting of both open and closed questions.¹⁷ The DAWBA generates the probabilities of having *DSM-IV* diagnoses that are subsequently validated by experienced clinicians. It is designed to maintain consistency across multiple cultural and language groups, as diagnoses are made by clinical raters who share a common training and who participate in regular cross-language training and consensus meetings. All of the raters were able to read at least 2 of the relevant languages.

Psytools software (Delosis Ltd, London, UK) was used to conduct the following assessments via its Internet-based platform. The assessment battery was self-administered both in participants' homes and at the neuroimaging facilities. Substance use was reported using the Alcohol Use Disorders Identification Test (AUDIT)¹⁸ and the European School Survey Project on Alcohol and Drugs (www.espad.org). The Substance Use Risk Profile Scale (SURPS), which assesses personality risk for pathology along 4 dimensions (Sensation-Seeking, Impulsivity, Anxiety-Sensitivity, Hopelessness), was also used.¹⁹ Hopelessness and

Anxiety-Sensitivity dimensions have been reported to be risk factors for depressive and anxiety disorders, respectively.²⁰ Other assessments included the Neo Five-Factor Inventory (Neo-FFI),²¹ the Strengths and Difficulties Questionnaire (SDQ),²² handedness, pubertal status using the Pubertal Development Scale (PDS) questionnaire,²³ parental history of depression, using a modified version of the Family Interview for Genetics Studies, the Genetic Screening and Family History of Psychiatric Disorders Interview (GEN),¹⁶ and life events using the Life-Events Questionnaire (LEQ).²⁴

The participant selection is described in Figure S1 (available online). Participants with any validated diagnosis (e.g., MDD, bipolar disorder, attention-deficit/hyperactivity disorder), any history of lifetime drug taking, or any symptoms of alcohol abuse or dependence (AUDIT score >4) were excluded from this study, as those disorders have neural correlates that would have biased our neuroimaging investigation.

The group with subthreshold depression included 119 adolescents. Adolescents were included in the group with subthreshold depression if they self-reported having experienced, in the last 4 weeks, at least 3 depressive symptoms including at least 1 core symptom (abnormally depressed, irritable mood, or loss of interest) and 2 or more other *DSM-IV* depressive symptoms, without fulfilling criteria for MDD in terms of duration, symptom number, or significant impact on functioning, as assessed using the DAWBA.

The control group matched for gender with the group with subthreshold depression included 461 adolescents with fewer than 3 symptoms of depression and a probability of having an MDD diagnosis of less than 0.1% according to the DAWBA. Most participants in the database actually had fewer than 3 symptoms, with an 85.1% prevalence (see Figure S2, available online).

No participant or parent reported being prescribed antidepressants, mood stabilizers, anxiolytics, antipsychotics, or hypnotics.

Follow-Up Assessment—Participants were reassessed using Web-based self-reports 2 years after completion of the baseline study. The assessment was similar to baseline assessment with the addition of the Adolescent Depression Rating Scale (ADRS), a validated 10-item self-rated scale that was introduced to specifically assess adolescent depression²⁵ among the whole cohort. A score of 6 or more has been considered as corresponding to a diagnosis of depression.²⁶ This cutoff provides maximum sensitivity and specificity in screening for MDD according to the *DSM-IV*, with clinically relevant intensity.²⁵

Subthreshold depression at follow-up was defined using the same criteria as for baseline.

Follow-up of the initial control group and the group with subthreshold depression (Figure S1, available online) retrieved 63.9% (n = 76) and 59.7% (n = 275) of the participants, respectively ($\chi^2[1, N = 580] = 0.54, p = 0.46$).

MRI Data

Magnetic resonance imaging at age 14 years was performed on 3 Tesla scanners (General Electric, Siemens, and Philips) from the 8 European sites. High-resolution anatomical MR images were obtained using a standardized 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence based on the ADNI protocol (<http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition/>). Acquisition parameters were similar across sites (e.g., sagittal slice plane, repetition time = 2,300 milliseconds; echo time = 2.8 milliseconds, flip angle = 8°; 256 × 256 × 170 matrix, 1.1 × 1.1 × 1.1 mm voxel size).¹⁶ Image preprocessing was performed with Statistical Parametric Mapping 8 software (SPM8) using voxel-based morphometry.²⁷ A detailed description of the MRI data acquisition and preprocessing is provided in Supplement 1, available online. Briefly, T1-weighted images were segmented and normalized using customized tissue probability maps. Then, the normalized, segmented, and modulated GM and WM images were smoothed using a 10-mm full-width at half-maximum (FWHM) Gaussian kernel. Global GM, WM, and cerebrospinal fluid (CSF) volumes were computed for each participant. Total intracranial volume (TIV) was defined as the sum of GM, WM, and CSF volumes. Head size was measured by the volume scaling factor (<https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV>), computed as the determinant of the affine transform performed during the spatial normalization.

Statistical Analyses

Voxel-Based Analyses—Whole-brain voxelwise comparisons were carried out within the general linear model (GLM) framework using SPM8. We first incorporated group (subthreshold depression/control) and gender as main factors and group-by-gender interaction in the model to explore a potential gender effect. Head size, type of scanner (to account for variance among manufacturers; Table S1, available online) and age were entered as confounding variables. If the interaction term was not statistically significant, only group as main factor was considered, and gender was added as a confounding factor. At the voxel level, statistical significance was set at $p < .05$ FWE (familywise error) corrected for multiple comparisons. Cluster size was at least 50 voxels. Brain locations were reported as x, y, and z coordinates in Montreal Neurological Institute (MNI) space.

Other Analyses—Group comparisons for socio-demographic and clinical data and global brain volumes were performed within the framework of the GLM using R software (<http://cran.r-project.org>). As in voxel-based analyses, group-by-gender interactions were tested before considering group as main factor and gender as confounding factor. Age, TIV, and type of scanner were entered as confounding variables to compare global GM, WM, and CSF volumes.

Causal mediation analyses were conducted to determine whether the GM and WM clusters previously identified in SPM between-group analyses could mediate the relation between subthreshold depression at age 14 years and depression at age 16 years. The analyses were performed with a validated algorithm using a set of GLM to derive the mediation and direct effects from the total effect.²⁸ Cut-off ADRS score = 6 at age 16 years was entered as a dependent factor, and group (subthreshold depression/control) as an independent factor

within a logistic regression model. For each SPM cluster, raw volume was extracted from the smoothed, normalized, and modulated images and entered as a mediator variable. To explore a potential gender effect on the mediation model, we added interaction terms for gender in the models to perform a so-called moderated mediation analysis. Type of scanner, TIV, and age were entered as confounding variables. This mediation model was performed using 5000 Monte Carlo draws for nonparametric bootstrap. In causal mediation analysis, a significant mediating effect is defined as a 95% confidence interval that does not include 0. All statistics were corrected for multiple comparisons.

Results

Participant Characteristics

As expected at baseline, adolescents with subthreshold depression had significantly higher scores on the SURPS dimensions of Hopelessness, Anxiety-Sensitivity, and Impulsivity, and on the NEO-FFI dimension of Neuroticism, along with lower scores on Extraversion, Agreeableness, and Conscientiousness (Table 1). They also had higher impact scores on the SDQ and lower LEQ total score, corresponding to a higher level of negative life events. No difference was found between groups regarding age, pubertal status, handedness, or parental history of depression, but adolescents with subthreshold depression were more likely to have at least 1 nonwhite parent. No gender-by-group interaction was found for any clinical characteristics.

At follow-up, adolescents with subthreshold depression similarly differed from controls except for ethnicity (Table 1). In addition, they reported significantly more self-harm since baseline and were more likely to have subthreshold depression and clinical scores indicating ongoing depression (ADRS $\geq 6/10$).

Because of the longitudinal design of the IMAGEN study, very few follow-up DAWBA diagnoses were validated at the time of analysis. Therefore, it was not possible to retrieve the final diagnoses for all participants. To assess their clinical depression outcome, we used the ADRS cut-off score as a proxy for depression, and considered adolescents having an ADRS score $\geq 6/10$ as adolescents with “depression.”

There was a significant gender-by-group interaction effect regarding depression outcome ($F = 8.17$; $p = .005$). Although there was no difference between boys and girls with subthreshold depression ($p = .14$; odds ratio[OR] = 2.42, 95% CI = 0.74–8.00), control girls were more likely to have an ADRS score $\geq 6/10$ than control boys ($p = .02$; OR = 5.30, 95% CI = 1.23–125.27).

There was also a significant gender-by-group interaction effect regarding pubertal status at age 16 ($F = 5.30$; $p = .02$). In both groups, girls had higher PDS scores than boys, but this difference was more pronounced in controls ($\beta = 0.46$; $p < .001$ in controls; $\beta = 0.28$; $p < .001$ in adolescents with subthreshold depression).

Lost-to-follow-up participants did not differ from those followed up in any characteristic, but they were more likely to be boys (93 boys/136 girls versus 106 boys/245 girls, respectively, $\chi^2[1, N = 580] = 6.21; p = .01$).

Global Brain Tissue

Volumes At baseline, WM volume was significantly smaller, and CSF volume significantly higher, in adolescents with subthreshold depression than in controls (Table 1). In addition, there was a trend toward smaller GM volume in adolescents with subthreshold depression. No between-group difference was found in the TIV measure. No gender-by-group interaction was found regarding global brain tissue volumes.

Voxel-Based Morphometry

Compared with controls, adolescents with subthreshold depression had significantly smaller GM volume in the medial PFC (mPFC), in a cluster encompassing the left ventromedial prefrontal (vmPFC) and the right rACC cortices, and in the caudate head bilaterally (Figure 1, Table 2). Similarly, adolescents with subthreshold depression had significantly smaller WM volumes in the anterior limb of the internal capsule (ALIC) bilaterally, left forceps minor, and right cingulum (Figure 1, Table 2).

No region with larger GM or WM volume was found in adolescents with subthreshold depression.

No gender-by-group interaction was found in any of the whole-brain analyses.

Causal Mediation Analyses

Moderated causal mediation analyses showed that smaller mPFC volume accounted for 32.42% ($p = .02$) of the total effect in girls (Figure 2; Table S2, available online) but did not mediate the association in boys ($p > .99$). No mediation effect was found with caudates or WM cluster volumes.

Discussion

For the first time, to our knowledge, GM and WM volume differences were identified using a whole-brain voxel-based approach in 14-year-old adolescents with subthreshold depression. Smaller GM volumes were detected in the mPFC, including the left vmPFC and right rACC, and in the caudate heads, whereas smaller WM volumes were found in nearby regions, including left forceps minor, right cingulum, and bilateral ALIC. Higher scores on several emotional and personality dimensions both at baseline and at follow-up indicated persistent risk for psychopathology in this group. At follow-up, adolescents with subthreshold depression were more likely to have above-the-cut-off depression scores, indicating ongoing depression. Causal mediation analysis showed that mPFC GM volume at age 14 years explained a significant fraction of the relation between subthreshold depression at age 14 years and depression at age 16 years in girls but not in boys.

The present findings confirm and extend the only previous report in adolescents with subthreshold depressive symptoms showing smaller GM volume in rACC,⁸ and highlight a

cluster of regions central to the recent models of affective processes.²⁹ The mPFC, spanning from the ACC toward the frontal pole, is conceived as an integrative center for affective appraisal. It is unique among cortical regions, as it projects directly to nuclei involved in affect and peripheral regulation, and is essential to integrating functions leading to affective meaning through its subcortical connections.³⁰ Here, the adolescents with subthreshold depression had a smaller volume of perigenual mPFC, a subdivision associated with impaired positive valence.³¹ Thinner cortical thickness of the vmPFC has been associated with a decreased capacity to appropriately assign affective meaning to sensory and internal cues, which may bias towards negative information, particularly in early adolescence.³² The Hopelessness and Neuroticism dimensions were consistently higher in our group with subthreshold depression. The vmPFC, together with the caudates, is part of the brain reward network that mediates behaviors usually driven by positive valence, such as pleasure and motivation.³³ The rACC, conceived as a “transition zone” with connectivity to both regions, would play a role in translating between affective meaning and action.³⁰

Besides GM variations, we found that adolescents with subthreshold depression had smaller WM volumes in nearby tracts that mature through adolescence.^{34,35} The forceps minor, a bundle constituted by thinner axons in the genu of the corpus callosum, connects the medial surfaces of the frontal lobes, and the cingulum bundle originates in the cingulate cortex and projects rostrally to the ACC and the PFC.³⁶ The ALIC spans between the PFC and the striatum.

Thus, our findings point to both GM and WM variations in regions involved in emotion appraisal and reward systems. The GM regions detected here in adolescents with subthreshold depression have been implicated in the pathophysiology of depression in adults and adolescents,^{9–11,14,29} and altered WM microstructure within tracts connecting these regions has been reported in adolescents with MDD.³⁷ In addition, functional impairments within the reward system have been hypothesized to contribute to the onset of depressive disorders in adolescence.³⁸ Adolescence is critical for the maturation of these regions, with subcortical structures such as the caudates maturing before cortical prefrontal regions.³⁹ The resulting enhanced bottom–up emotional processing in subcortical regions relative to less effective top–down modulation of affective information in prefrontal regions has been hypothesized to account for greater emotional reactivity and sensitivity during adolescence, which might underlie vulnerability to affective disorder onset.⁴⁰ Peak cortical thickness is attained in the mPFC between ages 10 and 13 years, followed by cortical thinning through adolescence,⁴¹ whereas the caudate volume decreases when the pubertal stage reaches a Tanner score of 2 to 3, corresponding to age 10 to 12 years.⁴² In this study, both adolescent groups had similar mean PDS score. Thus, our findings would suggest an accelerated GM thinning at both the cortical (mPFC) and subcortical (caudates) levels in the adolescents with subthreshold depression, which might account for emotional dysregulation and lead to enhanced vulnerability to affective disorder onset.⁴⁰

Furthermore, consistent with the literature, we observed that control girls at age 14 years were at higher risk for depression at age 16 years than control boys.⁷ Conversely, there was no difference between boys and girls with subthreshold depression regarding depression outcome, in agreement with previous studies.^{4,5} However, our results further suggest that

smaller GM volumes in the mPFC region mediated a substantial part of the relation between subthreshold depression at age 14 years and high depression scores (indicating pathology) at age 16 years in girls only. Thus, the risk of developing depression might be enhanced in girls who have a reduced mPFC volume. This gender difference might be related to the observed gender-by-group interaction effect of pubertal status at age 16 years. However, including PDS score at age 16 years as a confounding covariate in the mediation analyses did not change the result (29.65%; $p = .02$ in girls and $p > .99$ in boys). Thus, a distinct developmental pattern in that core emotion regulation region may play an important role in the transition to full-depression disorder during female adolescence.

Thus, overall, our findings suggest that the development of a depressive syndrome in adolescence, particularly in girls, is influenced by early pre-existing mPFC volume changes that may be associated with other structural changes in the striatum.

Of note, the psychometric characteristics of the present group with subthreshold depression were comparable to those reported in the literature on this condition.⁷ Along with a number of depression symptoms, the adolescents with subthreshold depression had marked indices of negative or unstable emotional valence denoted by high Neuroticism, Hopelessness, Anxiety-Sensitivity, and Impulsivity scores. These characteristics were constant over time with the follow-up 2 years later, denoting the consistency and stability of the definition criteria used in this study. In particular, the follow-up findings confirm that adolescents with subthreshold depression are more likely to convert to depression later on⁵ and have an increased risk of self-harm.⁷

These findings should be seen in the light of several limitations. First, due to inclusion/exclusion criteria and cultural differences, the proportions of control adolescents and those with subthreshold depression differed between sites (see Table S3, available online). For instance, fewer adolescents were eligible as controls in London. However, including site instead of scanner as confounding covariate in the analyses did not change the results, either at voxel level or at the cluster level. In addition, even though we controlled for scanner type in the analyses, the among-scanner variability in our measurements (see Table S1, available online) may have underpowered the detection of the effects of interest and needs to be considered as a limitation of our study.

Second, the symptom rating was self-administered, and it cannot be ruled out that some participants might have misunderstood some questions, which could have biased the diagnostic ratings. Moreover, the closed questions in the DAWBA provide information only about the past 4 weeks rather than lifetime depression. Thus, although the DAWBA interview includes open comments from the participant, which allows trained clinicians to check for consistency between ratings and comments and to check for any report of affective episode history, it cannot be ruled out that some adolescents might have experienced a past major depressive episode. If this were the case, the findings would point to early alterations associated with a depressive disorder, and not to vulnerability features in at-risk adolescents.

Third, the use of the DAWBA at age 14 years to assess general adolescent psychiatric symptoms allowed us to select adolescents with subthreshold depression and to exclude

those with validated psychiatric diagnoses. At follow-up, the validation of diagnoses was not yet effective, and the ADRS score was used as a proxy for depression. Thus, using different methods of assessing depressive symptoms at baseline and follow-up might have biased the causal mediation analysis. However, the ADRS cut-off score has been shown to discriminate between adolescents defined as having or not having depression according to the *DSM-IV*. Thus, it is likely that the adolescents with a high ADRS score would have been given the diagnosis had the rating been available. Another limitation is that the ADRS was available only at age 16 years, and it was not possible to assess changes from baseline to follow-up regarding depression scores.

Fourth, the high rate of loss to follow-up could have biased the assessment of depression outcomes. However, this rate did not differ between the control group and the group with subthreshold depression.

Fifth, previous studies of adolescents at familial risk for depression^{43,44} have reported smaller hippocampal volumes. In contrast, the present adolescents, controls, and those with subthreshold depression had no difference in family history of depression and no between-group difference in hippocampal volumes. This result is in line with other neuroimaging studies in adolescents with MDD that did not report smaller hippocampal volumes either^{9,12}; rather, hippocampal volume reductions in adolescents have been attributed to illness duration.⁴⁵ Similarly, although studies of pediatric depression have reported reduced amygdala volumes¹² or a decreased volume related to comorbid anxiety disorders,¹³ we did not observe smaller amygdala volumes in adolescents with subthreshold depression. Thus, these negative findings are consistent with studies relating amygdala–hippocampal volume alterations to disease progression, comorbidities, or family load.^{13,43–45} Finally, the study was not designed to include scanning of the participants at age 16 years, and thus it was not possible to assess the neuroimaging longitudinal correlates of the progressing clinical changes.

Overall, smaller gray and white matter volumes, located in core regions of emotion regulation, were detected in 14-year-old community adolescents with subthreshold depression. Medial–prefrontal volume differences might denote high risk of depression in juveniles, notably in girls. &

Supplementary Material

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Clinical Guidance

- In 14-year-old adolescents with self-reported subthreshold depression with no other comorbidity, we observed smaller gray and white matter volumes in frontal–striatal–limbic regions compared to those in control participants. These regions are involved in affective regulation and have consistently been reported as altered in MDD.
- Consistent with the literature, we observed that subthreshold depression is a condition at risk for later MDD, notably in girls. Furthermore, in girls with subthreshold depression, transition to MDD at age 16 years might be influenced by smaller mediallyprefrontal gray matter volume at age 14 years. A distinct developmental pattern in that core emotion regulation region may play a role in the transition to full-depression disorder during female adolescence.
- As adolescents with subthreshold depression are at risk for developing depression, all the more since they have significant changes in emotion regulation brain networks, we suggest that more attention should be paid to subthreshold depression in adolescence, and that intervention strategies should be developed.

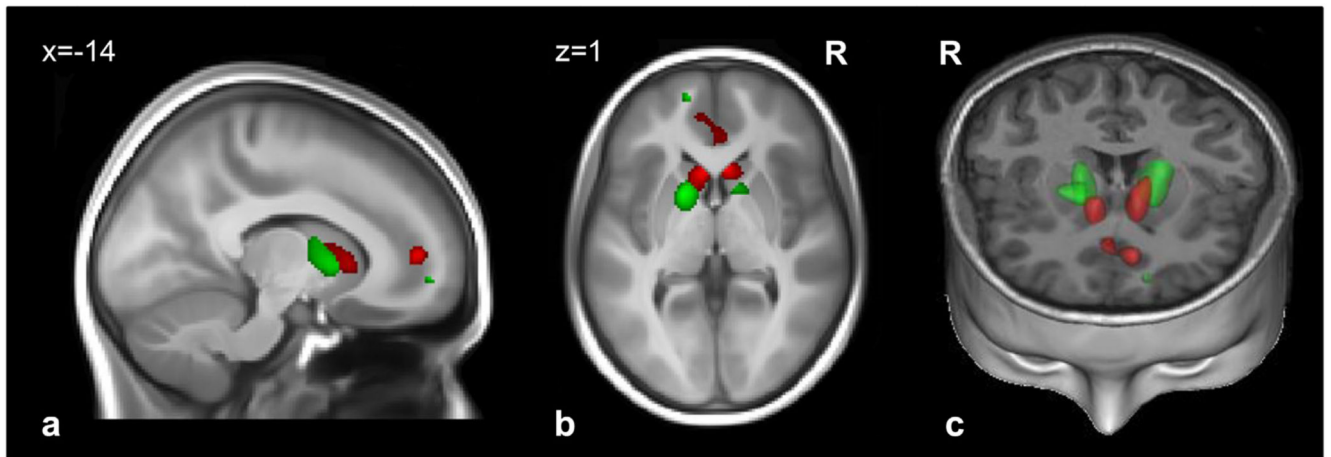


Figure 1.

Regions with smaller gray matter volume (red) and white matter volume (green) in 119 adolescents with subthreshold depression versus 461 controls. Note: voxel level was set at $p < .05$ (familywise error-corrected for the whole brain). Results are superimposed on a T1-weighted magnetic resonance imaging scan of an adolescent brain from the Imagen database. (a) Sagittal slice; (b) transversal slice; (c) 3-dimensional representation (coronal and transversal slices). R = right.

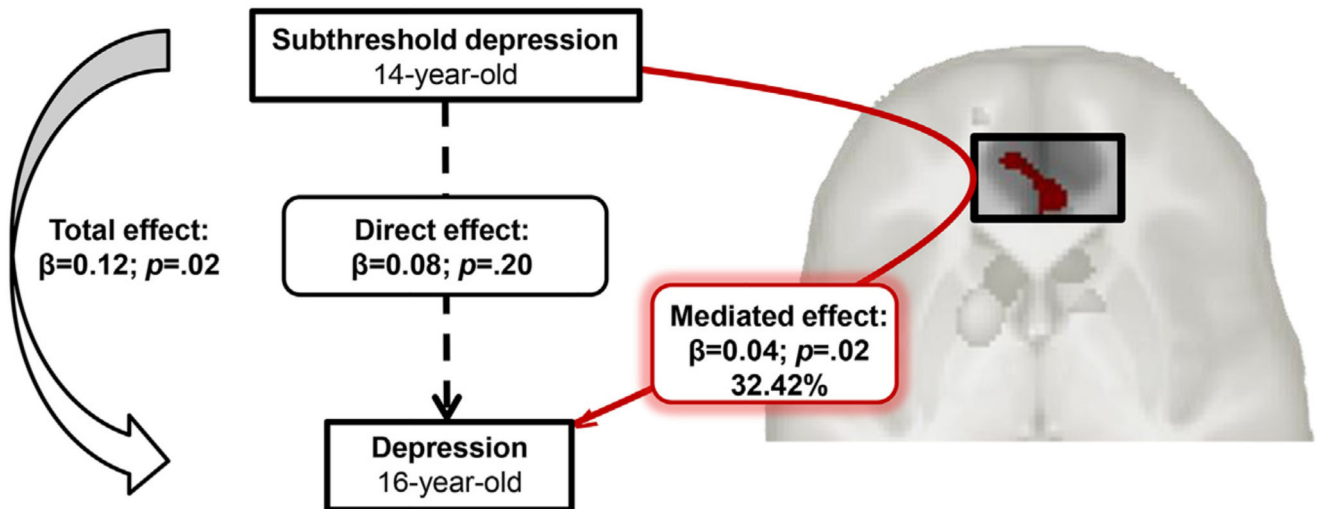


Figure 2. Mediation of the gray matter medial prefrontal cortex on the relationship between subthreshold depression at age 14 years and depression at age 16 years in girls, using causal mediation analysis.

Table 1
Clinical Characteristics in Adolescents With Subthreshold Depression Compared With Controls at Baseline and Follow-Up

Characteristic	Baseline						Follow-Up					
	sDep n = 119		Controls n = 461		Statistic 1, n = 580		sDep n = 76		Controls n = 275		Statistic 1, n = 351	
	n	%	n	%	χ^2	p	n	%	n	%	χ^2	p
Gender (female)	78	65.55	303	65.73	0.00	1	53	69.74	192	69.82	0.00	1
Handedness (right-handed)	99	83.19	406	88.07	1.77	.18	62	81.58	244	88.73	2.12	.15
Parental history of depression	8	6.72	30	6.51	0.00	1	4	5.26	17	6.18	0.00	.98
Nonwhite ethnicity	23	13.33	41	8.89	9.45	.002	6	7.89	21	7.64	0.00	1
Subthreshold depression at age 16	-	-	-	-	-	-	19	25.00	26	9.45	11.52	<.001
Depression (ADRS 6)	-	-	-	-	-	-	18	23.68	12	4.36	26.02	<.001
Self-harm since age 14 y	-	-	-	-	-	-	23	30.26	27	9.82	18.09	<.001
	Mean	SD	Mean	SD	$F_{1,570}$		Mean	SD	Mean	SD	$F_{1,341}$	
Age, y	14.45	0.36	14.40	0.41	2.40	.12	16.49	0.54	16.45	1.14	0.04	.85
	Mean	SD	Mean	SD	$F_{1,569}$		Mean	SD	Mean	SD	$F_{1,340}$	
Pubertal status (PDS score)	3.01	0.51	2.95	0.51	0.93	.34	3.46	0.34	3.44	0.40	0.02	.88
SDQ impact score	1.24	1.83	0.13	0.59	99.18	<.001	1.09	1.73	0.34	0.95	22.37	<.001
	Mean	SD	Mean	SD	U		Mean	SD	Mean	SD	U	
NEO-FFI												
Neuroticism	28.97	7.67	21.03	6.73	12,219	<.001	27.38	7.17	20.96	7.50	9,736	<.001
Extraversion	28.05	6.63	30.92	5.39	34,209	<.001	27.66	6.21	30.37	5.81	22,248	.007
Openness	26.29	6.61	26.41	5.62	28,002	.73	27.88	6.29	27.47	5.87	17,351	.46
Agreeableness	26.66	5.43	30.79	4.94	39,419	<.001	27.51	4.91	31.43	5.25	25,043	<.001
Conscientiousness	26.64	7.26	28.86	6.69	32,500	.002	26.80	7.88	29.72	6.96	21,941	.002
SURPS												
Hopelessness	14.80	3.82	12.45	2.63	17,555	<.001	14.21	4.11	12.52	2.91	13,428	<.001
Anxiety-sensitivity	11.87	2.52	11.08	2.28	22,921	.005	11.57	2.77	10.95	2.38	15,944	.06
Impulsivity	13.08	2.31	11.52	2.01	17,035	<.001	12.03	2.03	10.87	2.04	12,466	<.001
Sensation-seeking	16.09	2.99	15.60	3.06	25,225	.17	13.86	2.63	13.72	2.73	17,836	.80

Characteristic	Baseline						Follow-Up											
	sDep n = 119			Controls n = 461			Statistic 1, n = 580			sDep n = 76			Controls n = 275			Statistic 1, n = 351		
	n	%	SD	n	%	SD	Mean	SD	χ^2	p	n	%	n	%	χ^2	p		
LEQ total score	-2.09	4.68		-0.54	4.30				32.504	.002***	-1.80	4.93	-0.27	4.46	19,630	.13		
Brain tissue								F_{1,574}										
Gray matter (cm ³)	743.62	55.81		749.21	61.49				3.41	.065	-	-	-	-	-	-		
White matter (cm ³)	467.42	38.60		474.44	41.21				11.51	<.001***	-	-	-	-	-	-		
Cerebrospinal fluid (cm ³)	367.95	36.57		364.24	40.10				13.00	<.001***	-	-	-	-	-	-		
Total intracranial volume (cm ³)	1,5791	11		1,588	126				0.21	.64	-	-	-	-	-	-		

Note: *ADRS* = Adolescent Depression Rating Scale; *F* = analysis of variance *F* value; *LEQ* = Life-Events Questionnaire; *NEO-FFI* = NEO Five-Factor Inventory; *PDS* = Pubertal Development Scale; *sDep* = adolescents with subthreshold-depression; *SDQ* = Strengths and Difficulties Questionnaire; *SURPS* = Substance Use Risk Profile Scale; *U* = Mann-Whitney-Wilcoxon *U* value.

* *p* 0.05;

** *p* 0.01;

*** *p* .001.

Table 2
Regions of Smaller Gray and White Matter Volume in 119 Adolescents With
Subthreshold Depression Compared With 461 Controls

Brain Region	Cluster Level			Voxel Level				
	BA	k	P	MNI Coordinates (mm)			p^a	t
				x	y	z		
Gray matter								
Left caudate head	–	400	.001**	–6	18	3	.001**	5.37
Right caudate head	–	234	.004**	6	20	3	.001**	5.35
Left ventromedial PFC	10	369	.002**	–12	50	6	.001**	5.24
Right anterior cingulate	24/32			3	36	0	.018*	4.63
White matter								
Left forceps minor	–	69	.019*	–14	57	–2	.001**	5.09
Left ALIC	–	1288	<.001***	–16	6	3	.001**	5.06
Right ALIC	–	462	.002**	12	10	–2	.006**	4.69
Right cingulum	–	191	.008**	12	32	25	.007**	4.68

Note: Empty cell indicates that region is included in the same cluster as the region immediately above. ALIC = anterior limb of internal capsule; BA = Brodmann Area; k = cluster size in number of voxels (voxel size = 3.375 mm³); MNI = Montreal Neurological Institute coordinates; PFC = prefrontal cortex.

^a Statistics at voxel level set to $p < .05$, familywise error corrected for the whole brain, height threshold $t = 4.36$ (gray matter), $t = 4.16$ (white matter); extent threshold $k = 50$ voxels.

* $p < .05$;

** $p < .01$;

*** $p < .001$.