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.

Key Words: subthreshold depression, MRI, gray matter, white matter

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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 report[8] restricted to the rostral anterior cingulate cortex (rACC) showed that boys with subthreshold depressive symptoms, but not girls, had

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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 depression[25] among the whole cohort. A score of 6 or more has been considered as corresponding to a diagnosis of depression.[26] This cut-off 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 (χ^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