Thinner Medial Temporal Cortex in Adolescents With Attention-Deficit/Hyperactivity Disorder and the Effects of Stimulants

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Objective: Attention-deficit/hyperactivity disorder (ADHD) has been associated with widespread changes in cortical thickness (CT). Findings have been inconsistent, however, possibly due to age differences between samples. Cortical changes have also been suggested to be reduced or to disappear with stimulant treatment. We investigated differences in CT between adolescents/young adults with and without ADHD in the largest ADHD sample to date, the NeuroIMAGE sample. Second, we investigated how such differences were related to age and stimulant treatment.

Method: Participants (participants with ADHD = 306; healthy controls = 184, 61% male, 8–28 years of age, mean age = 17 years) underwent structural magnetic resonance imaging. Participants and pharmacies provided detailed information regarding lifetime stimulant treatment, including cumulative intake and age of treatment initiation and cessation. Vertexwise statistics were performed in Freesurfer, modeling the main effect of diagnosis on CT and its interaction with age. Effects of stimulant treatment parameters on CT were modeled within the sample with ADHD.

Results: After correction for multiple comparisons, participants with ADHD showed decreased medial temporal CT in both left ($p_{CLUSTER} = .008$) and right ($p_{CLUSTER} = .038$) hemispheres. These differences were present across different ages and were associated with symptoms of hyperactivity and prosocial behavior. There were no age-by-diagnosis interaction effects. None of the treatment parameters predicted CT within ADHD.

Conclusion: Individuals with ADHD showed thinner bilateral medial temporal cortex throughout adolescence and young adulthood compared to healthy controls. We found no association between CT and stimulant treatment. The cross-sectional design of the current study warrants cautious interpretation of the findings.

Key Words: ADHD, stimulant treatment, cortical thickness, long-term effects, MRI

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Magnetic resonance imaging (MRI) has revealed structural and functional brain changes associated with attention-deficit/hyperactivity disorder (ADHD).[1-3] Surface-based reconstruction of the cortical sheet allows quantification of different features of cortical structure, including volume, thickness, surface area, and curvature. Such features may represent distinct developmental processes having separate developmental trajectories.[4] Changes in different features may be associated with distinct forms of psychopathology.[5] Volumetric studies have consistently reported global cortical volume reduction in individuals with ADHD.[2,6] Widespread reductions of cortical thickness (CT) have also been implicated in ADHD. Children and adults with ADHD have shown decreased CT in the frontal cortex,[7-12] inferior and superior parietal cortex,[10-12] temporal pole, and medial temporal cortex.[11,13] However, patterns of ADHD-related cortical changes differ widely across studies. There have been multiple reports of increased rather than decreased CT in individuals with ADHD,[14,15] and other studies have found no association between CT and clinical features of ADHD.[8,12]

Discrepant patterns of CT changes in ADHD between studies may result from age differences in groups under study. ADHD often persists into adulthood,[16] typically showing reduced hyperactivity but persistent inattention throughout adolescence. In typical development, CT increases during childhood to reach its peak in early adolescence, after which it decreases again. The "maturational delay" hypothesis of ADHD proposes that CT changes observed in children with ADHD reflect the ADHD group lagging behind the typically developing group and reaching peak CT at a later age.[17] As they grow older, adolescents with ADHD are proposed to "catch up" with their unaffected peers, resulting in fewer or no cortical changes along with a decline in clinical symptoms at later age (remission). The hypothesis is supported by an impressive longitudinal sample of children and adolescents, with an average age of 12 years.[17] A substantial proportion of children with ADHD, however, continue to have symptoms in late adolescence

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and adulthood.[18] Differences in CT in adults with ADHD have also been reported,[14,15] suggesting that individuals with persistent ADHD do not show cortical normalization during late adolescence. Unfortunately, the majority of studies focused on either children or adults, and the development of CT in (late) adolescent ADHD has not extensively been documented. One cross-sectional study found both increases and decreases in CT in older adolescents/young adults with ADHD.[14] Zooming in on the late adolescent phase could aid in further elaboration of cortical development in ADHD.

A substantial proportion of individuals with ADHD are prescribed stimulants. MRI studies investigating the effect of methylphenidate treatment on brain volume and function in children with ADHD have suggested at least partially normalizing effects.[1,2,19,20] Very few have studied the effect of stimulants on CT. In a longitudinal study, Shaw *et al.*[21] showed normalized developmental trajectories of CT in stimulant-treated but not in nontreated children with ADHD. Treatment effects were local rather than global, affecting CT in the left dorsolateral prefrontal cortex, and right motor and posterior parietal cortex. By contrast, other studies have reported greater CT abnormalities in previously medicated patients[12] or have observed no differences between stimulant-naive and stimulant-treated patients.[10]

The investigation of long-term treatment effects in pediatric groups is complex. Long-term effects (spanning multiple years) may be assessed only in observational studies in which individuals with ADHD have not been randomized over stimulant and nonstimulant treatment. This creates the possibility of confound by indication, that is, non–stimulant-treated cases may be less severe or may differ from stimulant-treated cases in other ways. An advantage of observational studies, however, is that study samples are typically representative of the study population. To investigate stimulant treatment effects on brain structure, "treated" and "untreated" individuals with ADHD are typically compared. However, this distinction is rather crude and neglects between-subject variation in treatment history. Whereas some classify past users as "treated,"[21] others may classify them as "untreated"[22] or may exclude such participants.[23] Investigating treatment heterogeneity in more detail may reveal mechanisms by which stimulant treatment may affect brain structure.

In the current study, we compared CT in a large sample of adolescents/young adults with ADHD (n = 306) to that of a healthy control sample (n = 184). In addition, the linear and nonlinear effects of age on changes in CT associated with ADHD (if any) were investigated. Finally, we tested the effect of multiple well-defined stimulant treatment parameters. The current study adds to the previous volumetric findings of our group with ADHD being associated with global rather than local volume reductions.[6] Other neuroimaging studies based on the same sample have investigated volumetric features,[24-26] structural connectivity,[27-29] or functional MRI.[30-33] To the best of our knowledge, CT has not previously been studied in an ADHD sample of this size.

METHOD

Participants

Participants were selected from the Dutch follow-up phase of the International Multicenter ADHD Genetics (IMAGE) study.[34-36] ADHD diagnosis, ADHD severity, and presence of comorbid disorders were established using an algorithm based on both the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS[37]) and Conners' ADHD questionnaires for parents,[38] teachers,[39] and adult participants.[40] (See von Rhein *et al.*[41] and Supplement 1 (available online) for more details and relevant publications regarding the sample and diagnostic algorithm.) IQ was estimated from the subtests "vocabulary" and "block design" of the Wechsler Intelligence Scale for Children–Version III[42] (participants ≤16 years of age) or the Wechsler Adult Intelligence Scale–Version III[43] (participants >16 years of age). The subtest "digit span" was administered as an indication of working memory capacity. In addition, the Strengths and Difficulties Questionnaire for Children (CSDQ) was administered.[44] Socioeconomic status (SES) was calculated as the average (of both parents) number of years of education. Participants withheld use of psychoactive drugs for 48 hours before their visit. Informed consent was signed by all participants and parents (only parents signed informed consent for participants <12 years of age). Testing took place at the University Medical Center of either Amsterdam or Nijmegen. The study was approved by the local ethical committee. The final sample consisted of 306 participants with ADHD and 184 healthy control participants between the ages of 8.3 and 27.8 years old (mean = 17.05, SD = 3.33).

Assessment of Medication History

Lifetime medication transcripts from pharmacies were available for 74% and covered the lifespan for 25% of participants with ADHD. In addition, a questionnaire was administered to all participants and parents, which assessed lifetime history of psychoactive medication. When pharmacy transcripts did not fully cover the self-reported treatment period, medication parameters of the missing period(s) were calculated from the questionnaire data and were added to the measures derived from the pharmacy. Retrospective assessment of ADHD medication has shown good to excellent concordance between parent- and physician-report, even after multiple years.[45] The following indices of stimulant treatment (methylphenidate immediate/extended release and dexamphetamine preparations) were calculated: history of treatment (stimulant-exposed vs. stimulant-naive); start age; stop age; median age of exposure (age in years at the median of all exposed days); treatment duration corrected for age (treatment duration divided by [age minus the minimum start-age within the sample, i.e., age 2.3]); mean daily dose (average dose in milligrams for all exposed days; dexamphetamine dose was multiplied by 2); cumulative intake corrected for age (corrected treatment duration multiplied by mean daily dose); and time since last treatment (age minus stop age). For stimulant-naive patients, mean daily dose, treatment duration, and cumulative intake were 0; start age was imputed as the participant's age at scan (mimicking late initiation), and stop age was imputed as age 2.3 (mimicking early cessation).

MRI Acquisition and Analysis

MRI data was acquired at 1.5 Tesla on a Siemens Sonata scanner at the University Medical Center in Amsterdam, and on a Siemens Avanto scanner in Nijmegen, with an identical 8-channel phased array coil and identical acquisition parameters. There were no major hardware upgrades on either of the scanners during the study. Comparability of MRI data from the 2 sites has extensively been