Widespread Cortical Thinning Is a Robust Anatomical Marker for Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: This cross-sectional study sought to confirm the presence and regional profile of previously reported changes in laminar cortical thickness in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) compared with typically developing control subjects. **Method:** High-resolution magnetic resonance images were obtained from 22 (19 male and 3 female subjects; mean age 11.7 years) children and adolescents with ADHD and 22 age- and sex-matched control subjects (mean age 11.7 years). Brain tissue volumes were estimated for each subject. Cortical pattern matching methods were used to sample measures of laminar thickness at high spatial frequency across homologous regions of the cortex. Volume and thickness measures were compared across diagnostic groups with and without controlling for general intelligence. False discovery rate correction confirmed regional results. **Results:** The subjects with ADHD exhibited significant reductions in overall brain volume, gray matter volume, and mean cortical thickness compared with the controls, whereas white matter volumes were significantly increased in ADHD. Highly significant cortical thinning (false discovery rate–corrected $p < .0006$) was observed over large areas of the frontal, temporal, parietal, and occipital association cortices and aspects of motor cortex but not within the primary sensory regions. **Conclusions:** Cortical thickness reductions present a robust neuroanatomical marker for child and adolescent ADHD. Observations of widespread cortical thinning expand on earlier cross-sectional findings and provide further evidence to support that the neurobiological underpinnings of ADHD extend beyond prefrontal and subcortical circuits. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(10):1014–1022.

Key Words: gray matter thickness, cortex, pediatric, structural imaging.

Attention-deficit/hyperactivity disorder (ADHD) represents one of the most common psychiatric disorders of youths, affecting approximately 5% to 12% of children and adolescents, according to recent estimates, and approximately 4% to 5% of adults.[1–3] This high prevalence, coupled with the increased risk for comorbid conditions including disruptive behavior disorders (~50%)[4–6] and substance abuse/dependence (~40%),[7,8] underscores the morbidity of this disorder and the need for a better understanding of the underlying neurobiology.

Symptom clusters of inattention, impulsivity, and/or hyperactivity are diagnostic of ADHD but seem partially distinct, rendering it difficult to link these behavioral characteristics to specific neurobiological factors. Likewise, although previous brain imaging studies support that significant neuroanatomical differences exist between populations with and without ADHD, the extent, timing, and regional specificity of morphometric changes remain less certain. To identify the neuroanatomical correlates of ADHD, the majority of previous structural imaging studies have assessed volumetric changes in cortical and subcortical regions.

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Qualitative and quantitative reviews of the literature support that children and adolescents with ADHD exhibit reductions in cerebral and cerebellar volumes, where volume/area deficits of the cerebellar vermis, the caudate, and the pallidum and mid-sagittal callosal splenium appear among the most reproducible regional findings.[9–12] Consistent with the hypothesis that disturbances in fronto-subcortical and frontal-striatal-cerebellar networks play an important role in the pathophysiology of ADHD, previous investigations have focused on and have reported volumetric reductions of prefrontal brain tissue.[13–15] Although less frequently investigated, studies surveying multiple brain regions have also documented volumetric reductions in parietal,[13,16] temporal,[13] and occipital cortices,[14,17] although negative findings exist.[14]

Recently, more advanced computational image analysis strategies that allow simultaneous assessment of both global and local changes in anatomy have been applied to reveal imaging markers potentially more closely associated with ADHD-related pathophysiological processes than volume changes in arbitrarily defined regions of interest. For example, voxel-based morphometry methods have been applied to reveal hemisphere-specific changes in gray matter density across several brain regions including frontal, parietal, temporal, and cerebellar cortices in children and adolescents with ADHD.[17] A recent meta-analysis of six voxel-based morphometry studies of ADHD, however, could only confirm regional gray matter reduction within the right putamen/globus pallidus region, although no brain region showed significant increases in gray matter density.[18] With the use of a three-dimensional (3D) surface-based approach to align gyral anatomy, brain surface deformations indexing local brain size reductions have been reported across both lateral prefrontal and temporal areas, although increased gray matter density was observed in posterior temporal/inferior parietal cortices bilaterally in the children and adolescents with ADHD compared with the controls.[19] A study using deformation-based morphometry methods further suggests local volume reductions across most lobar regions and the basal ganglia in ADHD, although volume enlargements were observed in the occipital lobe.[20]

Cortical thickness presents a measure of brain structure that may more closely reflect alterations of neural cytoarchitecture associated with neurobehavioral disturbances in ADHD. A few previous studies have assessed cortical thickness changes in children and adolescents with ADHD. Specifically, Shaw et al.[21] used a fully automated measurement approach to show global cortical thinning in a large sample of children with ADHD, where significant regional findings were observed in superior prefrontal and precentral and anterior temporal cortices. Using a combined cross-sectional and longitudinal study design, these authors further demonstrated that cortical thinning remains constant over time in ADHD in all cortical regions with the exception of the right parietal cortex. However, a larger follow-up study also demonstrated that the normal developmental trajectories for obtaining peak cortical thickness are delayed in ADHD across widespread areas of the cortex including the prefrontal regions.[22] Furthermore, observations of reduced cortical thickness in adults with childhood-onset ADHD within the prefrontal, lateral inferior parietal, and cingulate cortices suggest that cortical thickness deficits persist, at least in individuals that remain symptomatic.[23] One independent study of child and adolescent ADHD by Wolosin et al.,[24] however, failed to detect ADHD-associated changes in cortical thickness in any of the 34 gyral regions of interest examined.

To confirm and clarify the existing literature concerning cross-sectional changes of cortical thickness in childhood and adolescent ADHD, we used a sophisticated computational image analysis approach to map highly localized changes of laminar thickness between diagnostic groups. To increase statistical power, the subjects with ADHD were compared with a well-matched sample of typically developing controls. Potentially confounding effects of overall brain size and general intellectual ability were additionally assessed.

METHOD

Subjects

Twenty-two children and adolescents with ADHD (19 male and 3 female subjects) and 22 control subjects matched for sex and age (ADHD: mean age 11.7 years, SD 2.5, range 7.2–16.0 years, controls: mean age 11.7 years, SD 2.5, range 7.7–16.0 years) participated in this study. Parents of all subjects signed consents, and all of the subjects signed assents approved by the University of California–Los Angeles institutional review board. The participants were recruited from local schools, pediatricians and clinics, and from ongoing studies of normal development at the University of California–Los Angeles. Affected subjects met criteria for ADHD both according to a clinical interview with parents and the National Institute of Mental Health Diagnostic Interview Schedule for