Trajectories of Cerebral Cortical Development in Childhood and Adolescence and Adult Attention-Deficit/Hyperactivity Disorder

Philip Shaw, Meaghan Malek, Bethany Watson, Deanna Greenstein, Pietro de Rossi, and Wendy Sharp

Background: Childhood attention-deficit/hyperactivity disorder (ADHD) persists into adulthood in around half of those affected, constituting a major public health challenge. No known demographic, clinical, or neuropsychological factors robustly explain the clinical course, directing our focus to the brain. Herein, we link the trajectories of cerebral cortical development during childhood and adolescence with the severity of adult ADHD.

Methods: Using a longitudinal study design, 92 participants with ADHD had childhood (mean 10.7 years, SD 3.3) and adult clinical assessments (mean 23.8 years, SD 4.3) with repeated neuroanatomic magnetic resonance imaging. Contrast was made against 184 matched typically developing volunteers.

Results: Attention-deficit/hyperactivity disorder persisted in 37 (40%) subjects and adult symptom severity was linked to cortical trajectories. Specifically, as the number of adult symptoms increased, particularly inattentive symptoms, so did the rate of cortical thinning in the medial and dorsolateral prefrontal cortex. For each increase of one symptom of adult ADHD, the rate of cortical thinning increased by .0018 mm (SE = .0004, $t = 4.2$, $p < .0001$), representing a 5.6% change over the mean rate of thinning for the entire group. These differing trajectories resulted in a convergence toward typical dimensions among those who remitted and a fixed, nonprogressive deficit in persistent ADHD. Notably, cortical thickening or minimal thinning (greater than −.007 mm/year) was found exclusively among individuals who remitted.

Conclusions: Adult ADHD status is linked with the developmental trajectories of cortical components of networks supporting attention, cognitive control, and the default mode network. This informs our understanding of the developmental pathways to adult ADHD.

Key Words: Attention, cerebral cortex, cognition, development, neuroimaging, recovery

Many children with attention-deficit/hyperactivity disorder (ADHD) do not simply grow out of their ADHD; around half of affected children will continue to meet full criteria for ADHD as adults (1,2). Deficits in attention are more persistent than hyperactivity and impulsivity (3,4) and are strongly linked with academic underachievement, underemployment, and problems with interpersonal relationships (5,6). The public health impact of ADHD that persists into adulthood is substantial, given that ~2.5% of adults have the disorder (7,8). The costs arising from direct health care and loss of productivity lie between $3,000 to $11,000 each year for every affected individual, an estimate that does not include less quantifiable factors such as the adverse effects on quality of life, self-esteem, and impact on family members (9,10).

From the Section on Neurobehavioral Clinical Research (PS, MM, BW, DG, PdR), Social and Behavioral Research Branch, National Human Genome Research Institute; and Intramural Program of the National Institute of Mental Health (PS, WS), Bethesda, Maryland; and Neurosciences, Mental Health and Sensory Functions Department (PdR), School of Medicine and Psychology, Sapienza University, Sant'Andrea Hospital, Rome, Italy.

Address correspondence to Philip Shaw, M.D., Ph.D., National Human Genome Research Institute, Social and Behavioral Research Branch, Section on Neurobehavioral Clinical Research, Building 31, B1 B37, Room 3N 202, Bethesda, MD 20892; E-mail: shawp@mail.nih.gov.

Received Nov 27, 2012; revised Apr 10, 2013; accepted Apr 11, 2013.

Understanding the pathophysiological mechanisms underpinning variable clinical outcome of ADHD and other neuropsychiatric disorders is thus a public health priority. It is also a precursor for eventually developing tools to assist in the early identification of those who are likely to show persistence, as opposed to remission, of ADHD symptoms. Epidemiologic, clinical, and neuropsychologic studies have generally not yielded findings that robustly explain clinical outcome: this includes variables such as gender, ethnicity, socioeconomic class, and childhood symptom severity (11–15). Indeed, only the presence of other comorbid childhood diagnoses emerges as a consistent predictor of persistence of ADHD into adulthood, and the link is not strong (2,16). This prompted a search for changes in brain structure that may more directly drive clinical outcome.

We focused on cerebral cortical structure, specifically its thickness, given that studies have found that the cortical mantle is thinner in adults with ADHD in regions important for cognitive control and attention—principally the cingulate cortex and the dorsolateral prefrontal cortex (17–20). A thinner cortex has also been reported in the more posterior cortical regions, particularly midline regions such as the precuneus and cuneus (18). While highly informative, previous imaging studies have been exclusively cross-sectional, which limits the delineation of the neurodevelopmental trajectories that might characterize ADHD, particularly its variable clinical outcome.

We thus examined the association between trajectories of cerebral cortical development during childhood and adolescence and adult ADHD symptoms. Based on our previous preliminary work, we reasoned that clinical improvement would be associated with a convergence toward typical cortical dimensions and persistence with a divergence away from typical dimensions (21,22). To examine this question, we used a unique data set

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.04.007

that combines repeated clinical assessment from childhood into adulthood with neuroanatomic magnetic resonance imaging (MRI) to link the trajectories of cerebral cortical development with adult symptoms of ADHD.

Methods and Materials

All participants were part of a longitudinal study into the neurobiology of ADHD at the intramural program of the National Institutes of Health. The principal inclusion criterion for initial study entry was childhood ADHD, diagnosed using DSM-IV criteria and determined using the Parent Diagnostic Interview for Children and Adolescents (23). All participants had a Hyperactivity rating greater than 2 SD above age and sexspecific means in the Conners' Teacher Rating Scales. Exclusion criteria were a full-scale IQ of less than 80, evidence of medical or neurological disorders, or any other Axis I psychiatric disorder requiring treatment with medication at study entry. All participants had at least one MRI of the brain acquired below the age of 17 years. Socioeconomic status was defined using the Hollingshead Four-Factor Index of Socioeconomic Status (24) and intelligence quotient was estimated using an age-appropriate version of the Wechsler intelligence scales.

Inclusion into this follow-up study was based on age: eligible individuals had to have reached the age of 17 years or over at the time of the study. Assessment of adult ADHD (at age17 years or older) was obtained through clinical interviews (either P.S. or W.S.) using the clinician administered ADHD Rating Scale, Version IV, providing examples and prompts appropriate for late adolescent and young adult groups (25). The interviewer rated each of the nine possible DSM-IV-Revised symptoms of inattention and nine symptoms of hyperactivity/impulsivity on a 4-point Likert scale: 0 = none; 1 = mild; 2 = moderate; and 3 = severe. In the primary analysis, we used a rating of severe as the cutoff to define symptom presence. We also repeated analyses using the moderate cutoff for symptoms (and obtained very similar results). Attention-deficit/hyperactivity disorder, combined type, is diagnosed when an individual has both six or more symptoms of inattention and six or more symptoms of hyperactivity/impulsivity. The inattentive or hyperactive/impulsive subtypes are diagnosed when symptoms are confined to these domains. Interrater reliability was high ($\kappa > .92$). Presence of other Axis I psychiatric diagnoses was established through the Structured Clinical Interview for DSM Axis I Disorders. Also obtained was the Conners Adult ADHD Rating Scales long version, which provides self-assessment of severity of ADHD symptoms and has a well-established factor structure, reliability, and validity (26). The proportion of time that subjects were treated with psychostimulants throughout the study was determined from patient records.

Comparison was made against typically developing control subjects, drawn from a study of typical brain development. Two comparison subjects were drawn for each ADHD individual. All comparison subjects remained free of all Axis I DSM-IV mental disorders throughout the duration of the study. The ADHD and typically developing control groups were matched on sex, age of assessments, socioeconomic status, and intelligence.

Two hundred three individuals from the original cohort of children with ADHD were 17 years or older at the time of the follow-up study (2006–2011) and thus eligible for follow-up. At study entry, 191 (94%) of these individuals had combined type ADHD, 8 (4%) had inattentive subtype, and 3 (2%) had predominately hyperactive-impulsive subtype. Of these 203 individuals, reassessment in adulthood was completed in 111 (55%). The reasons for loss to follow-up are given in Figure S1 in Supplement 1. Of these 111 subjects, 19 had MRI data that showed movement or others artifacts. This left 92 individuals with both clinical assessments and neuroimaging acquired in childhood and adulthood. This group of 92 individuals was the basis for the primary longitudinal analyses. At study entry, the mean age of this group was 10.7 years (SD 3.3). Of these 92 individuals, at study entry, 87 had combined type ADHD, 3 had predominately inattentive subtype, and 2 had predominately hyperactive-impulsive subtype. This group of 92 individuals had a higher socioeconomic status than those lost to follow-up and a trend to higher estimated intelligence but did not differ significantly in sex, age of study entry, or baseline clinical symptom severity (Table S1 in Supplement 1). The mean age of final assessment of these 92 individuals was 23.8 years (SD 4.3) and the mean duration of follow-up was 13.1 years (SD 3.6 years). Scans in the different outcome groups were well balanced in terms of the date of acquisition.

The institutional review board of the National Institutes of Health approved the research protocol, and written informed consent and assent to participate in the study were obtained from parents and children, respectively.

Neuroanatomic Methods

T1-weighted images with contiguous 1.5-mm axial slices were obtained using three-dimensional spoiled gradient recalled echo in the steady state on a 1.5-Tesla GE Signa scanner (General Electric Co., Milwaukee, Wisconsin). Imaging parameters were as follows: echo time = 5 msec, repetition time = 24 msec, flip angle = 45°, acquisition matrix = 256 × 192, number of excitations = 1, field of view = 24 cm. The same scanner was utilized throughout the study. Native MRI scans were masked using the Brain Extraction Tool (27), registered into standardized stereotaxic space using a nine-parameter linear transformation (28), corrected for nonuniformity artifacts (29), and segmented (30,31). The constrained Laplacian anatomic segmentation using proximity surface extraction procedure generated surface meshes representing white and gray matter interfaces (32). The root mean square thickness between corresponding nodes on the surface meshes was calculated in native space. A 30-mm surface blurring algorithm, which preserves cortical topologic features, was used to reduce noise in thickness measurements (33). Thickness measurements were aligned using surface registration to maximize thickness value correspondence between participants in terms of gyral patterning (34).

Analyses

In the primary analysis, we determined where the trajectory of cortical development from childhood into adulthood was associated with the number of ADHD symptoms in adulthood. We treated symptom scores as a continuous variable in this analysis. Symptom scores provide more variance as an outcome measure than categories and thus may augment the detection of outcome-related cortical changes. Additionally, there is ongoing discussions on the appropriate number of symptoms required to make a diagnosis of adult ADHD in the forthcoming revision of the DSM (35). We thus regressed cortical thickness against symptom score, age, and the interaction between symptom score and age using mixed-model regression. This approach was taken, as our data contained different numbers of observations in