Biological Psychiatry

Archival Report

Inattention and Reaction Time Variability Are Linked to Ventromedial Prefrontal Volume in Adolescents

Matthew D. Albaugh, Catherine Orr, Bader Chaarani, Robert R. Althoff, Nicholas Allgaier, Nicholas D'Alberto, Kelsey Hudson, Scott Mackey, Philip A. Spechler, Tobias Banaschewski, Rüdiger Brühl, Arun L.W. Bokde, Uli Bromberg, Christian Büchel, Anna Cattrell, Patricia J. Conrod, Sylvane Desrivières, Herta Flor, Vincent Frouin, Jürgen Gallinat, Robert Goodman, Penny Gowland, Yvonne Grimmer, Andreas Heinz, Viola Kappel, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Frauke Nees, Dimitri Papadopoulos Orfanos, Jani Penttilä, Luise Poustka, Tomáš Paus, Michael N. Smolka, Maren Struve, Henrik Walter, Robert Whelan, Gunter Schumann, Hugh Garavan, and Alexandra S. Potter

ABSTRACT

BACKGROUND: Neuroimaging studies of attention-deficit/hyperactivity disorder (ADHD) have most commonly reported volumetric abnormalities in the basal ganglia, cerebellum, and prefrontal cortices. Few studies have examined the relationship between ADHD symptomatology and brain structure in population-based samples. We investigated the relationship between dimensional measures of ADHD symptomatology, brain structure, and reaction time variability—an index of lapses in attention. We also tested for associations between brain structural correlates of ADHD symptomatology and maps of dopaminergic gene expression.

METHODS: Psychopathology and imaging data were available for 1538 youths. Parent ratings of ADHD symptoms were obtained using the Development and Well-Being Assessment and the Strengths and Difficulties Questionnaire (SDQ). Self-reports of ADHD symptoms were assessed using the youth version of the SDQ. Reaction time variability was available in a subset of participants. For each measure, whole-brain voxelwise regressions with gray matter volume were calculated.

RESULTS: Parent ratings of ADHD symptoms (Development and Well-Being Assessment and SDQ), adolescent self-reports of ADHD symptoms on the SDQ, and reaction time variability were each negatively associated with gray matter volume in an overlapping region of the ventromedial prefrontal cortex. Maps of *DRD1* and *DRD2* gene expression were associated with brain structural correlates of ADHD symptomatology.

CONCLUSIONS: This is the first study to reveal relationships between ventromedial prefrontal cortex structure and multi-informant measures of ADHD symptoms in a large population-based sample of adolescents. Our results indicate that ventromedial prefrontal cortex structure is a biomarker for ADHD symptomatology. These findings extend previous research implicating the default mode network and dopaminergic dysfunction in ADHD.

Keywords: Attention-deficit/hyperactivity disorder, Inattention, Multi-informant, Neuroimaging, Reaction time variability, Ventromedial prefrontal cortex

http://dx.doi.org/10.1016/j.biopsych.2017.01.003

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent neuropsychiatric disorders in youths, with approximately 3% to 7% of school-aged children meeting diagnostic criteria (1). Longitudinal studies indicate that functionally impairing symptoms continue into adolescence and adulthood in approximately 60% to 80% of cases diagnosed during childhood (2,3). Extant morphometry studies on ADHD have implicated a number of anatomically related brain areas; however, findings have been inconsistent, with no common structural abnormality emerging across studies. In adults and youths, structural abnormalities have been reported in the basal ganglia (4–10), prefrontal cortex (PFC) (10–12), cerebellum (5,10,13,14), and anterior cingulate cortex (15) and less frequently reported in the hippocampus, amygdala, and thalamus (16,17). Several factors, however, may obscure underlying brain-behavior relationships in the study of ADHD symptomatology, including the use of categorical diagnoses, the lack of multi-informant behavioral ratings, and small sample sizes. To aptly characterize the neuroanatomical substrates of ADHD symptomatology, it is critical to demonstrate convergence across dimensional,

 ISSN: 0006-3223

multi-informant behavioral data using large population-based samples. If possible, findings should also demonstrate convergence with other established features of ADHD symptomatology across different domains, including measures of cognition as well as neurochemistry.

Over the last few decades, empirically based assessment of psychopathology has revealed aspects of dimensionality with regard to many psychiatric conditions, including ADHD (18). Such findings have been difficult to reconcile with the categorical taxonomy espoused by DSM. Although numerous studies have tested for brain differences between ADHD patients and typically developing control subjects, few studies have investigated brain correlates of attention problems in the general population. Following from a dimensional conceptualization of psychopathology, it is reasonable to postulate that both clinical and normative levels of a given psychiatric syndrome will be underpinned by overlapping neural substrates. Mous *et al.* (19) recently reported that cortical thickness in bilateral postcentral gyri was negatively associated with parent-reported attention problems in a population-based sample of 444 6- to 8-year-old children. Ducharme *et al.* (20) found that subclinical attention problems in typically developing youths 6 to 18 years old were associated with a decreased rate of cerebral cortical thinning within prefrontal and parietal cortical regions—brain areas that have been implicated in the pathophysiology of clinically significant attention problems (i.e., ADHD) (21,22). Similarly, Shaw *et al.* (23) reported an association between subclinical symptoms of hyperactivity and impulsivity in typically developing youths and delayed cortical thickness maturation. Such evidence supports the use of dimensional measures of psychopathology, as emphasized by the National Institute of Mental Health Research Domain Criteria program (24). Taken together, there is compelling evidence that subclinical variation in ADHD symptoms is tied to brain structure and development and that these associations may be obfuscated by a strict categorical DSM approach.

In the assessment of developmental psychopathology, informants represent an important source of variance (18). The current DSM taxonomy does not offer clear, standardized methods for synthesizing reports from multiple informants. Martel *et al.* (25) recently reported that information from multiple informants increases the validity of assessing ADHD and that averaging ratings is the optimal method for integrating multi-informant data. Dimensional ratings from multiple informants also allow for more sophisticated methods of integrating data, such as latent variable approaches. Unfortunately, few neuroimaging studies have used dimensional assessments of ADHD symptoms from multiple informants.

In addition to using quantitative, multi-informant behavioral ratings, we aimed to demonstrate convergence across different domains with measures previously associated with ADHD symptomatology. Reaction time variability refers to the degree of intraindividual variation in responding to a target stimulus, and increased reaction time variability on attention tasks has been commonly reported in youths with ADHD (26,27). Lesion studies indicate that frontal lobe damage is accompanied by increased reaction time variability (28). There is also evidence that individual differences in reaction time variability predict inhibitory success (29). Furthermore, subjects with increased reaction time variability exhibit greater activation within inhibitory regions of the brain during tasks of response inhibition (29). Thus, reaction time variability may serve as an objective neurocognitive marker for ADHD symptomatology. However, it remains unclear the extent to which such cognitive measures are related to parent and self-report ratings of ADHD symptoms as well as brain structure in the general population.

Finally, patterns of gene expression may provide additional support in identifying potential brain-based markers for ADHD symptomatology. The brain's dopaminergic system has been strongly implicated in a wide variety of cognitive functions, including attention, and repeatedly linked to the pathophysiology of ADHD symptomatology. Indeed, some medications that have proven efficacious in the treatment of ADHD work by blocking dopamine reuptake and/or stimulating dopamine release, increasing extracellular dopamine levels. It is reasonable to postulate that regions of the brain that are volumetrically related to ADHD symptomatology will be tied to the expression of genes encoding for dopaminergic receptors.

In this article, we investigate the relationship between dimensional measures of ADHD symptomatology and brain structure in a large population-based sample of adolescents, using multi-informant behavioral ratings. In a subset of participants, we also investigate relationships between reaction time variability, measures of ADHD symptomatology, and brain structure. Finally, using publicly available gene expression data collected as part of the Allen Human Brain Atlas (30), we test the extent to which the relationship between brain structure and ADHD symptomatology is correlated with patterns of dopaminergic gene expression. To our knowledge, this study represents the first voxel-based morphometry (VBM) of ADHD symptomatology using a population-based sample of youths.

METHODS AND MATERIALS

Sample

Neuroimaging and behavioral data were obtained from the IMAGEN study conducted across eight European sites in France, the United Kingdom, and Germany, which includes 2223 adolescents recruited from schools at 14 years of age (SD 0.41 year; age range, 12.9–15.7 years). A detailed description of recruitment and assessment procedures has been published elsewhere (31). The present study included 1538 participants with multi-informant psychopathology data, quality-controlled neuroimaging data, and complete demographic data (Table 1). Behavioral data for the stop signal task (SST) were available in only a subset of participants (n = 767).

Psychopathology Assessment

The Development and Well-Being Assessment (DAWBA) (32) is a computer-based package of questionnaires, interviews, and rating techniques used to assess adolescent psychopathology. In the present study, ADHD symptom counts were derived from the parent version of the DAWBA—youths did not complete the DAWBA ADHD module. In addition to total symptom count, the parent version of the DAWBA yielded separate symptom counts for both hyperactivity/impulsivity and inattention.