Biological Psychiatry

Archival Report

Structural Brain Abnormalities of Attention-Deficit/Hyperactivity Disorder With Oppositional Defiant Disorder

Siri D.S. Noordermeer, Marjolein Luman, Corina U. Greven, Kim Veroude, Stephen V. Faraone, Catharina A. Hartman, Pieter J. Hoekstra, Barbara Franke, Jan K. Buitelaar, Dirk J. Heslenfeld, and Jaap Oosterlaan

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is associated with structural abnormalities in total gray matter, basal ganglia, and cerebellum. Findings of structural abnormalities in frontal and temporal lobes, amygdala, and insula are less consistent. Remarkably, the impact of comorbid oppositional defiant disorder (ODD) (comorbidity rates up to 60%) on these neuroanatomical differences is scarcely studied, while ODD (in combination with conduct disorder) has been associated with structural abnormalities of the frontal lobe, amygdala, and insula. The aim of this study was to investigate the effect of comorbid ODD on cerebral volume and cortical thickness in ADHD.

METHODS: Three groups, 16 ± 3.5 years of age (mean ± SD; range 7–29 years), were studied on volumetric and cortical thickness characteristics using structural magnetic resonance imaging (surface-based morphometry): ADHD+ODD (n = 67), ADHD-only (n = 243), and control subjects (n = 233). Analyses included the moderators age, gender, IQ, and scan site.

RESULTS: ADHD+ODD and ADHD-only showed volumetric reductions in total gray matter and (mainly) frontal brain areas. Stepwise volumetric reductions (ADHD+ODD < ADHD-only < control subjects) were found for mainly frontal regions, and ADHD+ODD was uniquely associated with reductions in several structures (e.g., the precuneus). In general, findings remained significant after accounting for ADHD symptom severity. There were no group differences in cortical thickness. Exploratory voxelwise analyses showed no group differences.

CONCLUSIONS: ADHD+ODD and ADHD-only were associated with volumetric reductions in brain areas crucial for attention, (working) memory, and decision-making. Volumetric reductions of frontal lobes were largest in the ADHD+ODD group, possibly underlying observed larger impairments in neurocognitive functions. Previously reported striatal abnormalities in ADHD may be caused by comorbid conduct disorder rather than ODD.

Keywords: ADHD, Comorbidity, Cortical thickness, ODD, SBM, Structural MRI

http://dx.doi.org/10.1016/j.biopsych.2017.07.008

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders and is defined by developmentally inappropriate levels of inattention, and/or hyperactivity/impulsivity (1). Neuroanatomical findings most consistently reported for ADHD are reduced total gray matter volume and reduced volume of the basal ganglia and the cerebellum. For the latter, cortical thickness abnormalities are also associated with ADHD. In addition, volumetric reductions and reduced cortical thickness of the frontal and temporal lobes have been reported, although less consistently [for reviews, see (2,3)]. Finally, some studies reported volumetric abnormalities in the amygdala and insula to be related to ADHD, but the findings are inconsistent, especially for the amygdala (4–9).

A potential explanation for the inconsistent neuroanatomical findings may be the presence of comorbid disorders in the studied ADHD samples, such as oppositional defiant disorder (ODD). ODD is present in up to 60% of clinically referred children with ADHD (10–12) and is defined by a persistent pattern of irritable and angry mood, vindictiveness, and developmentally inappropriate, negativistic, defiant, and disobedient behavior toward authority figures (1). Compared with individuals with only ADHD or ODD, individuals with ADHD+ODD show an earlier age of onset for both ADHD and ODD symptoms, exhibit more physical aggression and delinquency, show more functional impairments, such as poorer working memory, inhibition, temporal processing, and emotion recognition, and have a considerably worse prognosis (11,13,14).

Surprisingly, most studies on neuroanatomical correlates of ADHD did not investigate or report on the presence of comorbidities, such as ODD, resulting in relatively few studies investigating ADHD-only samples. The few studies in ADHD-only samples were less likely to find volumetric abnormalities in the frontal cortex than studies that included comorbid individuals [for an overview, see (15)]. They also showed that

SEE COMMENTARY ON PAGE e67

accounting for the presence of comorbid ODD significantly influenced findings, with either larger abnormalities in individuals with ADHD+ODD (16) or more abnormalities associated with ADHD after controlling for comorbid ODD (17). In addition, studies assessing ADHD-only groups showed no volumetric abnormalities in the amygdala (4,6,7), and abnormalities in the insula were accounted for by comorbid ODD (8). For cortical thickness, an influential study showed a delay in cortical development for individuals with ADHD, but of that sample 35% of the individuals had a comorbid diagnosis of ODD (3,18). Thus, previous findings may not purely reflect neuroanatomical characteristics of ADHD but may be confounded by comorbid ODD.

An alternative explanation for the inconsistent neuroanatomical findings for ADHD could be the age of included participants. According to the maturational delay hypothesis (18), individuals with ADHD show a maturational lag in brain development compared with typically developing control (TDC) subjects. According to this theory, the maturational lag is most prominent in prefrontal regions and has been reported to correspond with a 3-year delay, with TDC subjects attaining their peak cortical thickness at 7.5 years of age and individuals with ADHD at 10.5 years of age (18). In addition, it has been reported that structural abnormalities in the basal ganglia normalize with age (2,19). However, in contrast with the maturational delay hypothesis, structural abnormalities in the anterior cingulate cortex seem to persist into adulthood (2,20). Hence, studying the impact of comorbid ODD and age is pivotal to understanding the heterogeneity in findings.

So far, no studies on neuroanatomical correlates exclusively focused on individuals with ODD-only or on ADHD+ODD. Rather, studies included mixed samples of children with ADHD with and without comorbid ODD, or included children with both (comorbid) ODD and conduct disorder (CD) (a related disorder for which ODD is often a precursor) (21). The studies that focused on volumetric characteristics of individuals with ODD/CD with and without comorbid ADHD consistently reported reduced volumes of the amygdala, insula, and frontal lobe [for a review, see (21)]. Furthermore, it has been reported that CD is associated with volumetric abnormalities in frontal areas, while this association seemed relatively weak for ADHD-only (15). In terms of cortical thickness, one study investigated an ODD/CD sample and reported a decreased overall mean cortical thickness and thinning of the cingulate, prefrontal, and insular cortices (22).

To summarize, while neuroanatomical abnormalities in ADHD-only appear to be most strongly related to the frontal regions, ADHD+ODD appears associated with abnormalities in the frontal regions, amygdala, and insula. The overlap in affected brain areas may explain inconsistencies in reported abnormalities for frontal areas in ADHD, because these may be driven (partly) by the presence of comorbid ODD or by a combined effect of both disorders. So far, the literature does not answer the question on whether previously reported abnormalities in ADHD reflect neuroanatomical characteristics of ADHD or rather of comorbid ODD. Therefore, a comparison between individuals with ADHD+ODD and individuals with ADHD-only would be highly informative in terms of specificity of findings for ADHD. This may also clarify whether previously reported structural abnormalities in the amygdala and insula were driven by comorbid ODD.

The current study aimed to disentangle brain abnormalities associated with ADHD versus ADHD+ODD by comparing these diagnostic groups to TDC subjects across a broad age range from childhood to late adolescence. We studied the impact of age in order to test whether individuals with ADHD showed a maturational delay in neuroanatomical development. To meet these aims, neuroanatomical volumes and cortical thickness were compared between a large sample of individuals with ADHD without ODD (ADHD-only), individuals with ADHD and ODD (ADHD+ODD), and TDC subjects. We hypothesized that 1) abnormalities in the basal ganglia and cerebellum would be strongly associated with ADHD and therefore present in both diagnostic groups and that 2) abnormalities in the amygdala and the insula would be driven by ODD rather than by ADHD and hence would be predominantly present in the ADHD+ODD group rather than the ADHD-only group. Furthermore, we speculated that 3) abnormalities in the frontal lobes would be more pronounced in the ADHD+ODD group than in the ADHD-only group but would be present in both, given that previous studies have implicated the frontal lobe in both ADHD and ODD.

METHODS AND MATERIALS

Participants

Participants were selected from the NeuroIMAGE cohort [for a full description, see the Supplement and (23)]. Inclusion criteria for the current study were as follows: European Caucasian descent, IQ $\geq$ 80 (as estimated with the vocabulary and block design subtests of an age-appropriate Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale), and no diagnosis of autism/Asperger's/anxiety disorder/depression/epilepsy/general learning difficulties/brain disorders/known genetic disorders (e.g., fragile X syndrome or Down syndrome). Control subjects were not allowed to have a previous or current diagnosis of ADHD, ODD, or any other psychiatric disorder. A total of 1069 participants contributed data to NeuroIMAGE: 751 participants from ADHD families (participants in the ADHD-only or ADHD+ODD group and their biological siblings) and 318 participants from control families [participants in the TDC group and their biological siblings (23)]. For the current study, only individuals with a current ADHD diagnosis, with comorbid ODD (n = 67) and without comorbid ODD (n = 243), and TDC subjects (n = 233) were included. Not all participants in the NeuroIMAGE study underwent a magnetic resonance imaging (MRI) scanning session because of contraindications for MRI.

Diagnostic Assessment

A full description of the diagnostic assessment has been provided in previous work [Supplement and (24)]. In short, participants were diagnosed with ADHD or ODD according to DSM-IV criteria. Individuals in the ADHD+ODD group qualified for a diagnosis of both ADHD and ODD, while individuals in the ADHD-only group only qualified for a diagnosis of ADHD. A diagnostic algorithm was applied to create a combined symptom count from the questionnaires and interview.