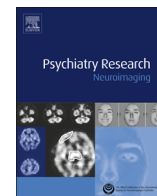




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The relationship of brain structure to age and executive functioning in adolescent disruptive behavior disorder

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ABSTRACT

Characterizing brain maturation in adolescents with disruptive behavior disorders (DBDs) may provide insight into the progression of their behavioral deficits. Therefore, this study examined how age and executive functioning were related to structural neural characteristics in DBD. Thirty-three individuals (aged 13–17) with a DBD, along with a matched control sample, completed neuropsychological testing and underwent magnetic resonance imaging (MRI) to measure gray matter volume and microstructural white matter properties. Voxel-based morphometry quantified gray matter volume, and diffusion tensor imaging measured fractional anisotropy (FA) in white matter tracts. In the anterior cingulate, gray matter volume decreased with age in healthy controls but showed no such change in the DBD sample. In the corpus callosum and superior longitudinal fasciculus (SLF), FA increased with age in the control sample significantly more than in the DBD sample. Executive functioning, particularly working memory, was associated with SLF FA bilaterally. However, the relationship of SLF FA to working memory performance was weaker in the DBD sample. These data suggest that youth with DBD have altered brain development compared with typically developing youth. The abnormal maturation of the anterior cingulate and frontoparietal tracts during adolescence may contribute to the persistence of behavioral deficits in teens with a DBD.

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1. Introduction

Oppositional defiant disorder (ODD) and conduct disorder (CD), collectively known as disruptive behavior disorders (DBDs), are marked by consistent, pervasive behavior that violates societal norms. These disorders become particularly debilitating during adolescence, when increases in risk-taking, reward-seeking, and impulsive behaviors are often in conflict with the maturation of independence skills and higher order cognition (Ernst et al., 2006). These behavioral trends occur simultaneously with a host of neural changes, including the modification of brain regions and circuitry involved in managing such thoughts and behaviors (Sisk and Zehr, 2005).

Alterations to neural development during adolescence likely influence the presence and degree of DBD psychopathology. Therefore, investigating brain development during this time in youth with DBD can provide insight into the etiology and progression of ODD and CD. In addition, given that impulsivity and impaired behavioral control are

key characteristics of DBD, it is important to understand how executive functioning is related to brain structure in these individuals.

Limited research has examined specifically how DBD is related to brain morphometry. Early-onset of conduct disorder has been associated with reduced temporal lobe and prefrontal gray matter volume as well as reduced cortical thickness (Kruesi et al., 2004; Fahim et al., 2011). Sterzer et al. (2007) reported that adolescents with CD had reduced gray matter volume in bilateral insula and left amygdala compared with healthy controls, although these volumes were also negatively correlated with attentional problems. A separate study indicated an overall reduction in bilateral temporal lobe and left orbitofrontal gray matter volume in boys with CD (Huebner et al., 2008). Furthermore, CD symptoms were correlated with volume in temporal (including amygdala) and prefrontal regions, while attention deficit/hyperactivity disorder (ADHD) symptoms correlated, albeit to a lesser degree, with posterior temporal/parietal cortex, fusiform gyrus and prefrontal cortex volume. More recent research has identified lower cortical thickness in adolescents with conduct disorder in a range of temporal and parietal regions (Hyatt et al., 2012; Wallace et al., 2014) as well as reduced amygdala and striatum volumes (Wallace et al., 2014), though relationships to age are unclear. Far more research on brain morphometry has focused on ADHD, finding

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volume reductions in prefrontal cortex, anterior cingulate, corpus callosum, striatal and cerebellar regions (Seidman et al., 2005; Krain and Castellanos, 2006). However, distinguishing how DBD is related to neurodevelopment distinct from ADHD remains understudied.

In addition to volumetric measures, diffusion tensor imaging (DTI) tracks axonal development on a microstructural level. In particular, fractional anisotropy (FA), which reflects fiber organization and coherence (Beaulieu, 2002), typically increases in white matter tracts throughout child and adolescent development (Eluvathingal et al., 2007; Asato et al., 2010). DTI investigations have found higher FA in the uncinate fasciculus of adolescents with CD, relative to FA in healthy teens (Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014). This tract connects orbitofrontal to limbic regions, potentially indicating a higher impact of emotion-sensitive brain regions on decision-making processes. Recently, higher FA in the corpus callosum has also been detected in adolescent males with CD (Zhang et al., 2014).

Problematic behaviors demonstrated by adolescents with DBD may be related to executive function impairments, particularly impulsivity and poor control of inappropriate actions. However, these impairments appear to be driven largely by commonly comorbid ADHD (Oosterlaan et al., 2005; Hummer et al., 2011). Delayed cortical development in ADHD therefore may underlie purported developmental alterations in DBD. ADHD is associated with developmental delays in white matter fiber tracts (Konrad and Eickhoff, 2010), such as the superior longitudinal fasciculus (SLF). The SLF, which connects prefrontal and parietal regions, matures extensively during adolescence (Asato et al., 2010), and its microstructural properties have been consistently associated with neuropsychological performance (Mabbott et al., 2006; Vestergaard et al., 2011). Recent evidence from our laboratory suggests that adolescents with DBD and comorbid ADHD have lower FA in an extensive set of white matter tracts (including the SLF) than both healthy adolescents and youth with DBD and no comorbid disorders (Wang et al., 2012). By examining the relationship between neurobiological characteristics and performance on tests of executive function, we aim to understand the neural substrates driving maladaptive adolescent behavior in youth with DBD.

In the present study, we extend this previous work by examining how both gray and white matter characteristics are associated with age in youth with DBD during mid-adolescence. To this end, voxel-based morphometry (VBM) and DTI techniques were used to quantify neural structural properties. In addition, we examined how neuropsychological measures of executive function were related to both gray matter volume and white matter maturity in youth with DBD. The relationships of neural characteristics with biological age and executive function characteristics were then compared with findings in a matched sample of healthy control adolescents. We hypothesized that abnormal development of prefrontal cortical regions would be present in DBD. In addition, we expected SLF maturity to be related to executive functioning in youth with and without DBD.

2. Methods

2.1. Subjects

Adolescents (age range 13–17; Table 1) were recruited using informational flyers and contacts with clinics, schools, and other community organizations to participate in a larger study of aggressive behavior, disruptive behavior disorder, and media exposure. Thirty-three participants were diagnosed with DBD (ODD: $n=11$; CD: $n=22$), 19 of whom were also diagnosed with ADHD, all based on the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS), Behavioral Disorders Module. Participants were also required to have at least one recurrent CD symptom of aggressive behavior toward people or animals within the past 6 months, to obtain a DBD sample with a history of aggression. The K-SADS interview was performed by trained research personnel under the supervision of a licensed clinical psychologist. Seven participants were taking stimulant medication and were instructed to withhold this medication for at least 24 h before both study visits (under direction of the study psychiatrist). Two of these participants were also taking antidepressants, which were not withheld.

An age- and sex-matched sample of 33 healthy controls (HC) with no psychiatric disorder, based on the K-SADS and the Adolescent Symptom Inventory-4 (ASI-4) (Gadow and Sprafkin, 1998) parent-report behavior checklist, was also examined. Adolescents in the HC group had no contact with a mental health professional for treatment of a behavioral or emotional problem within the past 3 years. These samples partially overlap with that of previous work from our laboratory (Wang et al., 2012), yet this report focuses on neuropsychological relationships with brain structure, instead of the presence or absence of ADHD.

2.2. Procedure

The study was approved by the local Institutional Review Board, and written informed consent was obtained from subjects and their caregivers before study procedures. During the first study visit, subjects completed diagnostic interviews (K-SADS), questionnaires, and neurocognitive tests. Intelligence was tested using the Matrices (nonverbal) subtest of the Kaufman Brief Intelligence Test (K-BIT-2) (Kaufman and Kaufman, 2004). In addition, neuropsychological tests were administered to quantify executive function, as described below. For all tests, raw scores, rather than age-normalized T -scores, were used, in order to establish measures of neurocognitive function that increase with typical brain development.

2.2.1. Stroop Color-Word test (SCWT)

The color-word portion of the Stroop test (Golden, 1978) is a measure of inhibition and interference control in which participants identify the ink color of words that spell out a different color (e.g., "RED" in blue ink). Participants received a score on the Stroop color-word test based on how many color words they named in 45 s.

2.2.2. Counting interference test (CIT)

A numerical analog to the SCWT is the number-count section of the CIT (Hummer et al., 2011), which requires individuals to report the number of numerals for each item in a list (e.g., 2, 33, 111). This test likewise measures inhibitory processes and is scored based on the number of responses in a 45-s time period.

2.2.3. Digit span

The Children's Memory Scale (CMS) (Cohen, 1997) numbers subtest is a digit span test in which the experimenter reads a series of numbers aloud. The participant must then repeat back these numbers in either forward or backward order, in successive versions of the test. Digit span tests are measures of verbal short-term and working memory capabilities.

Table 1
Demographics and neurocognitive performance.

	Control ($n=33$)	DBD ($n=33$)	DBD-ADHD ($n=14$)	DBD+ADHD ($n=19$)
Age	15.4 (1.2)	15.3 (1.4)	15.3 (1.3)	15.4 (1.5)
Sex (M:F)	24:9	24:9	8:6	16:3
Race (Cau:Afr:Bi:Other)	24:6:0:1	19:8:5:1	6:5:3:0	13:3:2:1
K-BIT-2 matrices standard score	106.9 (10.9)	102.7 (13.4)	102.5 (11.2)	102.8 (15.1)
Interference factor score	0.26 (0.81)	-0.35 (1.08)	-0.05 (0.84)	-0.57 (1.20)
Working memory factor score	-0.12 (1.20)	0.05 (0.75)	0.42 (0.57)	-0.23 (0.76)

Note: Mean (standard deviation) of age and test scores of each group are reported. Data from disruptive behavior disorder (DBD) subsamples with (DBD+ADHD) and without (DBD-ADHD) a diagnosis of attention deficit/hyperactivity disorder (ADHD) also listed. Race abbreviations: Cau, Caucasian (including Hispanic); Afr, African-American; Bi, Biracial (Caucasian/African-American).

* $p < 0.01$, significant group effect on interference factor score when DBD+ADHD and DBD-ADHD subsamples are treated as separate groups.

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