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White matter abnormalities associated with disruptive behavior disorder in adolescents with and without attention-deficit/hyperactivity disorder

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ABSTRACT

Disruptive behavior disorders (DBD) are among the most commonly diagnosed mental disorders in children and adolescents. Some important characteristics of DBD vary based on the presence or absence of comorbid attention-deficit/hyperactivity disorder (ADHD), which may affect the understanding of and treatment decision-making related to the disorders. Thus, identifying neurobiological characteristics of DBD with comorbid ADHD (DBD + ADHD) can provide a basis to establish a better understanding of the condition. This study aimed to assess abnormal white matter microstructural alterations in DBD + ADHD as compared to DBD alone and healthy controls using diffusion tensor imaging (DTI). Thirty-three DBD (19 with comorbid ADHD) and 46 age-matched healthy adolescents were studied using DTI. Fractional anisotropy (FA), and mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were analyzed using tract-based spatial statistics (TBSS). Significantly lower FA and higher MD, RD and AD in many white matter fibers were found in adolescents with DBD + ADHD compared to controls. Moreover, lower FA and higher RD were also found in the DBD + ADHD versus the DBD alone group. Alterations of white matter integrity found in DBD patients were primarily associated with ADHD, suggesting that ADHD comorbidity in DBD is reflected in greater abnormality of microstructural connections.

1. Introduction

Oppositional-defiant disorder (ODD) and conduct disorder (CD), collectively referred to as disruptive behavior disorders (DBD), involve persistent symptoms of defiant, disobedient, aggressive and hostile behavior, particularly towards authority figures. This consistent behavior pattern results in problems such as arguing, rule-breaking and, in more extreme forms, aggressive criminal acts (American Psychiatric Association, 1994; Kronenberger and Meyer, 2001; Loeber et al., 2009). The DBD diagnoses are among the most common childhood mental disorders, with CD occurring in 1% to 4% of children and adolescents aged 9 to 17 years and ODD occurring in 1% to 6% of the population (Findling, 2008). The difficulty of treating DBD can be compounded by its high comorbidity with attention-deficit/hyperactivity disorder (ADHD) (Loeber et al., 2000; Burke et al., 2002; Ollendick et al., 2008), as well as depression, substance use, and other conditions (Burke et al., 2002). Thus, identifying neurobiological characteristics of DBD with comorbid disorders can help to improve understanding of these conditions and ultimately contribute to the development of more effective treatments.

Depending on the presence or absence of comorbid ADHD, children and adolescents with DBD may differ in behavioral and neuropsychological characteristics, particularly executive functioning (Oosterlaan et al., 2005; Hummer et al., 2011). Children with ADHD demonstrate inattention, disorganization, impulsivity and hyperactivity, which disrupt the child's functional and adaptive behaviors (American Psychiatric Association, 1994; Kronenberger and Meyer, 2001; Barkley, 2005). These symptoms can be particularly detrimental when DBD is diagnosed with comorbid ADHD, as impulsivity and poor self-regulation may amplify the defiant behavior that characterizes DBD. Much of the published evidence supporting neurobiological models of DBD comes from behavioral performance measures rather than direct assessments of brain functioning (Loeber et al., 2000; Burke et al., 2002; Loeber et al., 2009). As a result, studies identifying the neural deficits that are uniquely related to the development of DBD in youth are still needed (Loeber et al., 2009). Furthermore, there have been very few studies of the role of comorbid ADHD in the neurobiology of DBD.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that provides in vivo information about the direction and integrity of neural fiber tracts (Alexander et al., 2007). Because DTI

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is still an emerging technique, only a limited number of DTI studies to date have investigated white matter differences associated with psychiatric disorders of childhood and adolescence. However, there is converging evidence suggesting that white matter abnormalities are associated with ADHD (Ashtari et al., 2005; Casey et al., 2007; Makris et al., 2008; Pavuluri et al., 2009; Silk et al., 2009). These previous DTI studies mainly focused on fractional anisotropy (FA) as a measure of brain tissue integrity, since FA measures the degree to which water molecules diffuse in a given direction, reflecting white matter fiber density (Beaulieu, 2002). Alternatively, overall diffusivity in a tissue can be quantified by mean diffusivity (MD), which is a directionally averaged measure of the apparent diffusion coefficient and may help to better understand white matter structure (Alexander et al., 2007). Some studies also investigated eigenvalues of the diffusion tensor or their related quantities of radial diffusivity (RD) and axial diffusivity (AD) (Schmithorst and Yuan, 2010). RD and AD can provide more specific information about directional changes in white matter integrity (Alexander et al., 2007). In recent DTI studies, these four DTI parameters, FA, MD, RD and AD, were very useful in characterizing normal regional development in white matter microstructure throughout adolescence (Ashtari et al., 2007; Qiu et al., 2008; Asato et al., 2010; Bava et al., 2010; Schmithorst and Yuan, 2010).

Thus far, there are only a very limited number of DTI research studies in DBD samples. Our previously conducted DTI study had assessed structural abnormalities in subjects with DBD compared to healthy controls (Li et al., 2005), where we found significant differences in regions including the anterior region of the corona radiata and bilateral superior longitudinal fasciculus, potentially indicating deficits in connection between frontal and subcortical or parietal regions in DBD. However, it failed to investigate the potential confound of comorbid ADHD among youth with DBD, a limitation that this current study aims to address. The present study is further delineated from prior research by using an automated, unbiased whole-brain analysis method of tract-based spatial statistics (TBSS) (Smith et al., 2006). We examined the microstructural properties of white matter in adolescents with diagnoses of DBD and comorbid ADHD (DBD + ADHD), DBD alone (DBD − ADHD), and controls with no psychiatric diagnosis. To the best of our knowledge, our study is the first to assess DTI characteristics in adolescents with DBD with and without ADHD. As a result, this study offers the potential to contribute important novel information about DBD diagnoses and comorbidities.

2. Methods

2.1. Participants

The study was approved by the local Institutional Review Board, and written informed consent was obtained from subjects and their caregivers prior to any study procedures. Adolescents (13–17 years) with and without DBD diagnoses were recruited via informational flyers posted in community settings. Diagnoses of ODD, CD, and/or ADHD were made based on results of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS) (Kaufman et al., 1996). The semistructured Diagnostic Interview (Behavior Disorders Module) was performed. Thirty-three subjects with a DBD diagnosis (ODD: $n=11$; CD: $n=22$) met criteria for the present study. These criteria included diagnosis of ODD or CD based on the K-SADS, completion of a valid MRI DTI scan, and presence of at least one recurrent Conduct Disorder symptom of aggressive behavior toward people or animals within the past 6 months (as determined with the K-SADS interview). The presence of an aggressive symptom was required to differentiate between subjects with significant aggressive/antisocial DBD behaviors as compared to more minor, avoidant, rule-breaking behaviors. In additional, 46 age matched healthy controls were recruited using the same method (average age; control: 15.4 ± 1.2 years; DBD: 15.3 ± 1.5 years).

Participants in the DBD alone group (DBD − ADHD; $n=14$) were required to have three or fewer inattentive ADHD symptoms and to have three or fewer hyperactive-impulsive ADHD symptoms, based on the K-SADS semistructured diagnostic interview. Participants in the DBD with comorbid ADHD group (DBD + ADHD; $n=19$) met criteria for ADHD (any subtype), based on the K-SADS interview. Participants with no psychiatric disorders (healthy controls [HC]; $n=46$) had no DSM-IV diagnosis, based on results of the K-SADS interview and the Adolescent Symptom Inventory-4 (ASI-4) (Gadow and Sprafkin, 1998) parent-report behavior checklist, and had three or fewer inattentive ADHD symptoms and three or fewer hyperactive-impulsive ADHD symptoms on the K-SADS. Adolescents in the HC group also had no contact with a mental health professional for treatment of a behavioral or emotional problem within the past 3 years. Participants with a current diagnosis of major depressive disorder or substance abuse/dependence were excluded from the study, as were those with a current or past diagnosis of bipolar disorder or schizophrenia. No subject (of both control and DBD groups) had a history of brain injury.

Seven participants with DBD were taking psychotropic medication (three mixed-salts amphetamines (Adderall); one bupropion; one methylphenidate and atomoxetine; one bupropion and methylphenidate; and one methylphendiate, aripiprazole, oxcarbazepine and citalopram) for their disorder. In order to limit potential effects on DTI measurements, those subjects were requested to withhold their stimulant medications for at least 24 hours (> 3 half-lives) prior to the start of the study session during which MRI was conducted. All medication instructions were performed under the direction of the study psychiatrist (D.W.D.).

2.2. Procedure

Individuals participated in two separate study visits. During the first visit, subjects completed a psychological evaluation consisting of clinical interviews, questionnaires and neurocognitive tests of executive functioning. Adults identifying themselves as the primary caregiver for the teens completed questionnaires as well. Diagnostic measures completed at the first visit included the K-SADS (Kaufman et al., 1996) and ASI-4 (Gadow and Sprafkin, 1998). IQ was screened using the Matrices (nonverbal) subtest of the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 1990). To assess executive functioning behaviors in everyday life, caregivers filled out the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000). The BRIEF yields a Behavioral Regulation Index (BRI) and a Metacognition Index (MI), reflecting impulse-behavioral and attentional-cognitive (respectively) aspects of executive functioning in daily behavior.

The second visit involved MRI scanning. The MRI measurements were acquired on a 3 T Tim Trio scanner (Siemens, Germany) using an eight-channel phased array head coil. DTI was measured along 60 non-collinear directions. A single-shot spin-echo echo-planar DTI sequence was performed using the following parameters: matrix = 128 × 128; field of view = 256 × 256 mm; echo time/repetition time = 100/10100ms; 60 transversal continuous slices with 2-mm thickness; diffusion-weighted factor $b=1000$ s/mm^2; additional 10 images without use of a diffusion gradient ($b=0$ s/mm^2).

2.3. Data analysis

Head movement during DTI acquisition was measured using the AFNI software (http://afni.nimh.nih.gov/afni/) by registering all DTI images to the first *b0* image using a 12 degree-of-freedom affine correction with mutual information as the cost function (Ling et al., 2012). No significant difference was found between groups in maximal rotation (in degree; HC: 0.44 ± 0.30; DBD − ADHD: 0.43 ± 0.32; DBD + ADHD: 0.54 ± 0.23; $F=0.862$, $p=0.43$) or maximal displacement (in mm; HC: 0.84 ± 0.46; DBD − ADHD: 0.74 ± 0.47; DBD + ADHD: 0.83 ± 0.44; $F=0.282$, $p=0.76$).

The DTI data were further analyzed using the FSL package (FMRIB Center, Oxford, United Kingdom). Preprocessing included correction for motion and eddy current effects in DTI images. FMRIB's Diffusion Toolbox (Behrens et al., 2003) was used to fit the tensor model and to compute the FA, MD, RD and AD maps. Next, voxel-wise TBSS analysis was performed with the following steps (Smith et al., 2006). All individual FA maps were nonlinearly registered to the template and then affine-transformed into standard Montreal Neurological Institute (MNI) space. A mean skeleton map of white matter tracts was generated based on the mean FA image of all subjects. Each subject's aligned FA image was projected onto the FA skeleton, resulting in a skeletonized FA map for each individual. TBSS analyses of MD, RD and AD were conducted in the same manner and aligned to the FA skeleton.

Finally, all skeletonized DTI maps were fed into a voxel-wise group ANCOVA (analysis of covariance) using a General Linear Model approach with age and gender as covariates. Inference on these statistics was carried out using the "randomise" program within FSL, which performs permutation testing that does not rely on a Gaussian distribution (Westfall and Young, 1993; Nichols and Holmes, 2002). We used threshold-free cluster enhancement (TFCE), a new method for finding significant clusters in MRI data without having to define them as binary units (Smith and Nichols, 2009). The statistics were built up over 5000 random permutations with the maximum TFCE recorded at each permutation. The 95th percentile of this distribution was then used as a TFCE threshold and the significance level calculated from this distribution. Thus, significant clusters were fully corrected for familywise error at $p<0.05$ (Westfall and Young, 1993; Smith and Nichols, 2009). With this approach, voxel-wise post-hoc comparisons between groups were assessed. Age and gender were also included as covariates. Anatomical localization of each significant cluster was determined using the pertinent available anatomic templates (ICBM-DTI-81 parcellation map and Johns Hopkins University DTI-based WM atlas) (Mori et al., 2008).

In an additional exploratory analysis, the presence of correlations between BRIEF measures of executive functioning (BRI and MI scores) and mean DTI indices was assessed. Regions of interest (ROIs) were created from clusters showing significant differences of FA in the contrast of DBD + ADHD versus healthy subjects. An individual mean DTI index value of each ROI was extracted per subject, which was implemented using the FSL package. Partial correlation analysis controlling for age and gender was conducted using SPSS 17.0 (SPSS Inc., Chicago, IL).