



DTI-measured white matter abnormalities in adolescents with Conduct Disorder



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ABSTRACT

Emerging research suggests that antisocial behavior in youth is linked to abnormal brain white matter microstructure, but the extent of such anatomical connectivity abnormalities remain largely untested because previous Conduct Disorder (CD) studies typically have selectively focused on specific frontotemporal tracts. This study aimed to replicate and extend previous frontotemporal diffusion tensor imaging (DTI) findings to determine whether noncomorbid CD adolescents have white matter microstructural abnormalities in major white matter tracts across the whole brain. Seventeen CD-diagnosed adolescents recruited from the community were compared to a group of 24 non-CD youth which did not differ in average age (12–18) or gender proportion. Tract-based spatial statistics (TBSS) fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) measurements were compared between groups using FSL nonparametric two-sample *t* test, clusterwise whole-brain corrected, $p < .05$. CD FA and AD deficits were widespread, but unrelated to gender, verbal ability, or CD age of onset. CD adolescents had significantly lower FA and AD values in frontal lobe and temporal lobe regions, including frontal lobe anterior/superior corona radiata, and inferior longitudinal and fronto-occipital fasciculi passing through the temporal lobe. The magnitude of several CD FA deficits was associated with number of CD symptoms. Because AD, but not RD, differed between study groups, abnormalities of axonal microstructure in CD rather than myelination are suggested. This study provides evidence that adolescent antisocial disorder is linked to abnormal white matter microstructure in more than just the uncinate fasciculus as identified in previous DTI studies, or frontotemporal brain structures as suggested by functional neuroimaging studies. Instead, neurobiological risk specific to antisociality in adolescence is linked to microstructural abnormality in numerous long-range white matter connections among many diverse different brain regions.

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1. Introduction

Conduct Disorder (CD) is defined by the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) as characterized by a pattern of antisocial behavior before age 18, including aggression, damage of property, deceitfulness or theft, and rules violations. Because early life onset of antisocial behavior increases the risk for persistent disorder, other mental health problems, and delinquency (Moffitt et al., 2008; Moffitt and Caspi, 2001), researchers have sought to identify neural correlates of

antisocial behavior that might clarify etiological mechanisms, or represent risk for antisociality. Studies of brain structure in antisocial adults consistently have found gray matter volume deficits in orbitofrontal and dorsolateral prefrontal cortex (Yang and Raine, 2009) and in medial and lateral temporal lobe regions (Weber et al., 2008). Studies of antisocial youth typically have confirmed adult findings with evidence for orbitofrontal, anterior cingulate, insular cortex, and bilateral temporal lobe (amygdala, hippocampus, and lateral surface) volume reductions (Passamonti et al., 2012; Vloet et al., 2008) (see (De Brito et al., 2009) for a contrary report). Review of functional neuroimaging CD literature has noted that many of these regions have abnormal activation in antisocial samples (Rubia, 2011), particularly medial temporal lobe (e.g., amygdala) and prefrontal regions (e.g., anterior cingulate (Passamonti et al., 2012; Weber et al., 2008; Yang and Raine,

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2009) and orbitofrontal cortex (Finger et al., 2008; Rubia et al., 2009b)).

This evidence supports theories that frontotemporal brain abnormalities are associated with antisocial behavior disorders (Vloet et al., 2008), driven in large part because frontotemporal regions have been linked to cognitive and emotional functions impaired in antisocial behavior (Blair and Mitchell, 2009). In accord with these findings, studies using diffusion tensor imaging (DTI) methods to measure white matter microstructure (Basser and Pierpaoli, 1996) in antisocial adults scoring high on the Psychopathy Checklist-Revised (Hare, 2003) had reduced fractional anisotropy (FA) values measuring preferential diffusivity along white matter structures in the uncinate fasciculus – a tract that connects limbic system brain regions in the temporal lobe to orbitofrontal cortex (Craig et al., 2009; Sundram et al., 2012). Attempts to replicate this in youth diagnosed with Conduct Disorder using tractography methods either have found no uncinate abnormalities (Finger et al., 2012) or increased FA (Passamonti et al., 2012; Sarkar et al., 2013), interpreted as abnormal maturation of neural pathways involved in emotion or emotional control. Recent studies of antisocial adults have found numerous other DTI-measured white matter deficits (Sundram et al., 2012). However, little is known about whether other white matter tracts are abnormal in antisocial youth. One whole brain DTI study of CD/Oppositional Defiant Disorder (ODD)-diagnosed youth high on callous/unemotional traits found no abnormalities when testing other major tracts in the brain (Finger et al., 2012), while another found only external capsule FA differed from controls after correcting for multiple comparisons (Passamonti et al., 2012).

Despite the unencouraging lack of findings from some previous CD DTI studies, it is important to note that they all examined antisocial samples highly comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD), or that had high rates of ADHD symptoms. As we (Stevens and Haney-Caron, 2012) and others (Rubia et al., 2010, 2009a, 2009b) have previously shown, examination of noncomorbid CD samples can reveal important brain structure and function distinctions between relatively “pure” samples of CD and ADHD, as statistical covariance methods cannot completely control for neurodevelopmental differences arising from distinct etiological contributions to each disorder. The present study used DTI to determine whether CD-diagnosed adolescents had clearer evidence for white matter microstructural abnormalities. Our primary hypothesis was that CD adolescents who were largely free of other psychopathology would indeed show FA deficits in the major tracts connecting frontal and temporal lobe brain regions most often implicated by functional neuroimaging studies to be abnormal in adolescent and adult antisocial samples (e.g., uncinate fasciculus). We also predicted FA abnormalities in tracts that connect frontal lobe with other brain regions (e.g., superior longitudinal fasciculi or fronto-occipital fasciculi) or temporal lobe with other regions (e.g., inferior longitudinal fasciculus). Our second aim was to determine whether or not FA-measured white matter microstructure was abnormal in other major tracts throughout the brain. Such findings would be important, as current neurobiological theories of CD do not emphasize the anatomical connectivity of other brain regions. We therefore hypothesized that CD-diagnosed adolescents would have decreased FA in other major white matter connections among posterior brain regions, subcortical structures, or the cerebellum. Finally, because recent research has suggested that other DTI diffusivity indices might capture neurobiologically-specific aspects of microstructural abnormality, we supplemented the FA analyses with analyses of axial diffusivity (AD) or radial diffusivity (RD) to aid interpretation of any study findings.

2. Methods and materials

2.1. Participants

Participants were recruited as part of a National Institute of Mental Health (NIMH)-funded study of brain structure and function (K23 MH070036). Participants for this CD versus non-CD study were recruited using community advertisements (controls) and letters sent to families of youth on probation in the Connecticut Court Support Services Division following adjudication (CD). Written informed assent and parental permission to participate were obtained jointly from participants and a parent/legal guardian. All consent and study procedures were approved by the Hartford Hospital Institutional Review Board.

Although CD is commonly associated with other psychiatric diagnoses when presenting clinically (Ollendick et al., 2008), numerous studies have reported comorbidity rates of as low as 7–28% for ADHD, depression or anxiety in community-recruited CD youth (Angold et al., 1999). Therefore, our objective was to assess relatively “pure” (i.e., noncomorbid) CD youth so that any abnormal findings could be more confidently ascribed to neurobiological factors contributing to antisociality itself and not another disorder. This approach can be a significant strength when attempting to distinguish complex, multifactorial etiological influences on disorders defined by broad behavioral phenotypes. Psychiatric diagnoses for research purposes were established uniformly using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (Present and Lifetime Version; K-SADS-PL) semi-structured interview, which provides reliable and valid DSM-IV diagnoses based on multiple informants (Kaufman et al., 1997) to discriminate CD from other disruptive disorders (e.g., ADHD or ODD). Interviews of each participant and a parent/guardian were conducted by experienced bachelor's- and master's-level research assistants supervised by a clinical psychologist experienced in supervising K-SADS-PL interviews (MCS). Information from both informants was synthesized, then discussed within weekly research group consensus meetings for final formulation once sufficient information was judged present to have diagnostic confidence. If K-SADS-PL identified other (even marginally subthreshold) diagnoses, these participants did not undergo MRI. $N = 17$ CD adolescents without any significant psychiatric or substance disorder comorbidities provided usable DTI data. As intended, CD participants typically had no other lifetime or current diagnosable psychiatric or substance disorders. For example, nearly all CD participants reported only 0 or 1 ADHD symptoms, the disorder most frequently comorbid with CD (Ollendick et al., 2008) (CD group mean = 1.06 of 18 ADHD symptoms). One exception was a single CD participant who met criteria for cannabis abuse. This participant was retained because studies have not confirmed an effect of even prolonged regular use on brain structure (Quickfall and Crockford, 2006). Indeed, when the primary study analysis was re-run omitting this subject, the results did not change. Seven CD participants would have qualified for ODD diagnosis if not better accounted for by CD, as per DSM-IV guidelines. CD participants were compared to $n = 24$ non-CD control participants without current/lifetime DSM-IV diagnoses or meaningful sub-threshold symptomatology. All participants were 12–18 years old. Final CD and non-CD study dataset sizes differed for several reasons, including study attrition over a multi-day assessment protocol, failure to provide adequate quality MRI data, or time constraints on MR assessment days. All participants were medically healthy as determined from medical questionnaire parent responses. All tested negative for recent marijuana, cocaine, and heroin use on a urine drug screen the day of MRI. All participants received identical clinical and cognitive evaluations.

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