Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

Impaired functional but preserved structural connectivity in limbic white matter tracts in youth with conduct disorder or oppositional defiant disorder plus psychopathic traits ☆

Elizabeth Carrie Finger [a,*], Abigail Marsh [b], Karina Simone Blair [c], Catherine Majestic [c], Iordanis Evangelou [d], Karan Gupta [a], Marguerite Reid Schneider [c], Courtney Sims [c], Kayla Pope [c], Katherine Fowler [c], Stephen Sinclair [c], Fernanda Tovar-Moll [e], Daniel Pine [c], Robert James Blair [c]

[a] Department of Clinical Neurological Sciences, Schulich School of Medicine, University of Western Ontario, 339 Windermere Road, London, Ontario, Canada N6A 35A5
[b] D|epartment of Psychology, Georgetown University, Washington, DC, USA
[c] Mood and Anxiety Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA
[d] Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA
[e] Cognitive and Behavioral Neuroscience Unit, LABS-D'Or Hospital Network, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

ABSTRACT

Youths with conduct disorder or oppositional defiant disorder and psychopathic traits (CD/ODD + PT) are at high risk of adult antisocial behavior and psychopathy. Neuroimaging studies demonstrate functional abnormalities in orbitofrontal cortex and the amygdala in both youths and adults with psychopathic traits. Diffusion tensor imaging in psychopathic adults demonstrates disrupted structural connectivity between these regions (uncinate fasciculus). The current study examined whether functional neural abnormalities present in youths with CD/ODD + PT are associated with similar white matter abnormalities. Youths with CD/ODD + PT and comparison participants completed 3.0 T diffusion tensor scans and functional magnetic resonance imaging scans. Diffusion tensor imaging did not reveal disruption in structural connections within the uncinate fasciculus or other white matter tracts in youths with CD/ODD + PT, despite the demonstration of disrupted amygdala–prefrontal functional connectivity in these youths. These results suggest that disrupted amygdala–frontal white matter connectivity as measured by fractional anisotropy is less sensitive than imaging measurements of functional perturbations in youths with psychopathic traits. If white matter tracts are intact in youths with this disorder, childhood may provide a critical window for intervention and treatment, before significant structural brain abnormalities solidify.

1. Introduction

A subset of youths with disruptive behavior disorders including conduct disorder and oppositional defiant disorder also display high callous and unemotional traits. This subset is at highest risk for persistent antisocial behaviors and criminality in adulthood (Frick et al., 2003; Dadds et al., 2005; McMahon et al., 2010; Pardini and Fite, 2010). These youths show deficits in emotion processing, including facial expression recognition (Blair et al., 2001), and forms of decision making and learning that rely on processing of positive or negative feedback (Budhani and Blair, 2005; Finger et al., 2011). This behavioral profile has been attributed in part to dysfunction in the role of the amygdala in emotional learning and the role of orbitofrontal cortex in the representation of emotional outcome information (Blair, 2007). Recent functional magnetic resonance imaging (fMRI) studies in youths with disruptive behavioral disorders plus psychopathic traits have demonstrated functional neural abnormalities in the amygdala and ventromedial prefrontal cortex (Marsh et al., 2008; Jones et al., 2009; Finger et al., 2011). In adults with psychopathy, abnormal structural connectivity was recently found in the uncinate fasciculus, the white matter bundle connecting anterior regions of the temporal lobes with the prefrontal cortex (Craig et al., 2009). As youths with disruptive behavioral disorders of conduct disorder or oppositional defiant disorder plus psychopathic traits are at high risk of adult psychopathy (Burke et al., 2007), we hypothesized that their functional abnormalities in medial and anterior temporal lobe structures and ventromedial/orbitofrontal prefrontal cortex may arise from

abnormal white matter connections between these regions. To test this hypothesis, we examined connections between these structures using functional connectivity analysis and two robust approaches to structural white matter tract analysis: first, region of interest analysis and tractography of the uncinate fasiculus and other limbic white matter tracts and, second, whole brain voxel-wise analysis of white matter tracts using tract-based spatial statistics (Smith et al., 2007). Functional connectivity was indexed during performance of the passive avoidance paradigm (Kosson et al., 2006). This task, following animal work on a comparable paradigm, is considered to involve the integrated functioning of the amygdala and orbital frontal cortex (Schoenbaum and Roesch, 2005).

2. Methods

2.1. Participants

Thirty-one children participated in this study, including 15 youths with psychopathic traits (Antisocial Process Screening Device score ≥ 20 and Psychopathy Checklist Youth Version score ≥ 20) and diagnoses of either conduct disorder or oppositional defiant disorder and 16 healthy comparison youths matched for age (mean 14.3 years) and IQ (Table 1) were recruited through newspaper ads, fliers and recruitment tables at community events. Children with conduct disorder or oppositional defiant disorder were also recruited via referrals from area mental health practitioners ($n = 2$). All 31 participants completed the diffusion tensor imaging scans. Twenty-six also completed the fMRI sequencing in the same session (12 of the youths with CD/ODD + PT and 14 healthy comparison youths). The remaining youths did not complete the fMRI scans. Seven of the 15 youths with CD/ODD + PT were on medications related to their behavioral problems (see Supplemental Table). A statement of informed assent and consent was obtained from participating children and parents. This study was approved by the Institutional Review Board of the National Institute of Mental Health.

All children and parents completed the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) assessments with an experienced clinician trained and supervised by expert child psychiatrists, with good inter-rater reliability (kappa > 0.75 for all diagnoses). Parents completed the K-SADS interview and the full Antisocial Process Screening Device. Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, current or lifetime history of psychosis, depression, bipolar disorder, generalized, social or separation anxiety disorder, post-traumatic stress disorder, neurological disorder, history of head trauma, and IQ less than 80.

Children meeting K-SADS criteria for conduct disorder or oppositional defiant disorder who had Antisocial Process Screening Device scores of 20 or greater returned to complete the Youth Personality Inventory and Psychopathy Checklist-Youth Version (PCL-YV) assessments (described below). Children scoring ≥ 20 on the PCL-YV were included in the psychopathic traits group, and those scoring < 20 were excluded from the study. Healthy children did not meet criteria for any K-SADS diagnosis and scored < 20 on the Antisocial Process Screening Device.

2.2. Clinical measures

2.2.1. Antisocial Process Screening Device (Frick et al., 1999)

The Antisocial Process Screening Device (APSD) is a 20-item parent-completed rating of callous-unemotional traits and conduct and impulsivity problems for the detection of antisocial processes in children. A three-factor structure has been derived that comprises the following dimensions: callous/unemotional, narcissism, and impulsivity (Frick et al., 2000). There is no established cutoff score on the APSD for classification of high psychopathic traits (Edens et al., 2001; Frick and Hare, 2001; Murrie and Cornell, 2002).

Following our previous fMRI work with this population (Finger et al., 2008; Marsh et al., 2008), a cutoff score of ≥ 20, one-half the maximum possible of 40 and consistent with the upper tertile of children screened, was chosen for this study.

2.2.2. Psychopathy Checklist: Youth Version (Forth et al., 2003)

The Psychopathy Checklist-Youth Version (PCL-YV) is a 20-item rating scale for assessment of interpersonal, affective and behavioral features related to psychopathic traits in adolescents based on semi-structured interview and collateral information. Items assessed include impression management, grandiosity, stimulation seeking, pathological lying, manipulation, lack of remorse, shallow affect, parasitic orientation, poor anger control, impersonal sexual behavior, early behavior problems, lack of goals, impulsivity, irresponsibility, failure to accept responsibility, unstable interpersonal relationships, serious criminal behavior, violations of conditional release, and criminal versatility. Following our previous fMRI work, a cutoff score of ≥ 20 (one-half the maximum possible) was used to define the high psychopathic traits group, as there are no standard cut point scores for classifying youth on this measure to date (Forth et al., 2004). PCL-YV interviews were conducted by two researchers trained in PCL-YV administration who demonstrated good inter-rater reliability ($R = 0.91$).

2.3. Imaging protocols

Images for diffusion tensor imaging (DTI) analysis were obtained with a 3.0 T GE Signa scanner using an eight-channel receive-only head coil array (MRI Devices, Pewaukee, WI). Diffusion-weighted images were acquired in the axial plan with a single-shot, spin-echo echo-planar sequence in 50 contiguous sections of 2.5-mm thickness, repetition time 13000 ms/echo time 83 ms, matrix 256 × 256, field of view 240 × 240 mm, with an array spatial sensitivity encoding technique acceleration factor of 2. The DTI acquisition consisted of 3 volumes with no diffusion gradients applied ($b = 0$) and 33 volumes with diffusion gradients applied in non-collinear directions, with $b = 1000$ s/mm². Two identical diffusion series were collected. A high resolution anatomical scan (three-dimensional fast spoiled gradient echo sequence; repetition time = 6 ms, echo time = 2.5 ms; field of view = 24 cm; flip angle = 12°; 124 axial slices; thickness = 1.0 mm; 224 × 224 matrix) in register with the diffusion-weighted dataset was obtained covering the whole brain.

During the same session in the same 3 T scanner, participants completed four runs of an fMRI instrumental learning task (Finger et al., 2011) during which a total of 189 functional images per run were taken with a gradient echo planar imaging (EPI) sequence (repetition time = 2300 ms, echo time = 23 ms, 64 × 64 matrix, flip angle 90°, field of view 24 cm). Whole brain coverage was obtained with 34 axial slices (thickness 3.3 mm).

2.4. Image analysis

2.4.1. Preprocessing and generation of fractional anisotropy maps

Diffusion tensor data generation and fiber tracking were conducted in DTI Studio www.mristudio.org (Jiang et al., 2006). To minimize misregistration due to subject motion within and across the diffusion-weighted imaging (DWI) series, an affine transformation was performed in the Automated Image Registration (AIR) (Woods et al., 1998) procedure aligning each image to the first DWI image acquired. The high resolution anatomical image was then co-registered to the combined registered DWI dataset, and subsequently skull stripped using MRICro (Rorden and Brett, 2000). Diffusion-weighted images corrupted by artifact were excluded by manual review of DWI mean and standard deviation maps (by K.G., who was blinded to diagnosis) and with the automatic outlier rejection function in DTI studio. Tensor data were then generated in DTI Studio from the mean DWI dataset with noise threshold of 50. The resultant fractional anisotropy maps and eigen vectors were used in the region of interest and voxel-wise analysis below.

2.4.2. Regions of interest analysis

Fractional anisotropy maps and eigenvectors were used to calculate fiber tracts using a threshold of fractional anisotropy > 0.1 and tract turning angle < 45°. A fractional anisotropy threshold of 0.1 was selected to permit tracking of regions from cortical and subcortical regions of interest (ROIs) based on our hypothesis that abnormalities in white matter tracts in this population would most likely arise from abnormalities in gray matter structures. The cortically centered ROIs were dilated to include the region of white matter immediately adjacent to these structures. Prior studies employing gray matter ROIs based on frontal Brodmann areas have identified low fractional anisotropy (FA) values in this range as optimal for identifying fibers penetrating cortical regions (Thottakara et al., 2006; Rane et al., 2010). The FA threshold of 0.1 was thus selected to maximize identification and inclusion of the white matter fibers arising from these cortically centered ROIs and maximize the sensitivity to detect potential group differences in FA values in these regions. Standardized anatomically based ROIs were generated using the Wake Forest PickAtlas toolbox (Lancaster et al., 2000; Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003) in SPM (Wellcome Trust Centre for Neuroimaging, University College, London). Regions encompassing the amygdala, orbitofrontal cortex, Brodmann areas 10 and 11, superior temporal gyrus, temporal pole, and anterior and posterior cingulate cortex were selected as ROIs to identify the uncinate fasiculus, cingulum bundle, and more specific tracts from the amygdala to regions of prefrontal cortex and superior temporal gyrus (Supplemental Figure). Cortical and subcortical ROIs were dilated by a factor of 3 (by 3 voxels in each direction) to capture white matter adjacent to the structures. To avoid distortion generated by

Table 1
Participant characteristics.

	Psychopathic traits + CD/ODD ($n = 15$)	Comparison youths ($n = 16$)
Age (S.D.)	14.8 (1.8)	13.8 (1.7)
IQ (S.D.)	101 (10)	107 (14)
Male sex, no. [%]	11 [73]	10 [63]
DSM-IV diagnoses (current), no. [%]		
Conduct disorder	10 [67%]	0 [0]
Oppositional defiant disorder	5 [33%]	0 [0]
Attention deficit hyperactivity disorder	10 [67%]	0 [0]
Pediatric Psychopathy Rating Scale score (S.D.)		
Antisocial Process Screening Device	29.4 (4.2)	6.1 (4.0)