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

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Abstract

Youths with conduct disorder or oppositional defiant disorder and psychopathic traits (CD/ODD+PT) are at high risk of adult anti-social behaviour 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 MRI 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.

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Keywords

Psychopathic traits; conduct disorder; oppositional defiant disorder; diffusion tensor imaging; functional connectivity

1. Introduction

A subset of youths with disruptive behaviour disorders including conduct disorder and oppositional defiant disorder also display high callous and unemotional traits. This subset is at highest risk for persistent antisocial behaviours 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., 2010). 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 MRI studies in youths with disruptive behavioural 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., 2010). 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 behavioural 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 fasciculus 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: 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 functional MRI 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 functional MRI scans. Seven of the 15 youths with CD/ODD+PT were on medications related to their behavioural problems (see Supplemental Table). A statement of informed assent and consent was obtained from participating children and parents. This study was approved by the NIMH IRB.

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, PTSD, neurologic 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, 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)—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 characterized comprised of 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), we chose 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)—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 for defining 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 DTI analysis were obtained with a 3.0 Tesla GE Signa scanner using an 8-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, TR 13000ms/TE 83 ms, matrix 256 x 256, FOV 240 x 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 $b = 1000 \text{ s/mm}^2$. 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=24cm; flip angle=12°; 124 axial slices; thickness=1.0 mm; 224x224 matrix) in register with the diffusion weighted dataset was obtained covering the whole brain.

During the same session in the same 3T scanner, participants completed 4 runs of a functional MRI instrumental learning task (Finger et al., 2010) during which a total of 189 functional images per run were taken with a gradient echo planar imaging (EPI) sequence (repetition time=2300ms, echo time=23 ms, 64x64 matrix, flip angle 90°, FOV 24cm). Whole brain coverage was obtained with 34 axial slices (thickness 3.3mm).

2.4 Image Analysis

2.4.1 Preprocessing and generation of FA 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 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 degrees. A fractional anisotropy threshold of 0.1 was selected to permit tracking of regions from cortical and subcortical 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 grey matter regions of interest based on frontal Brodmann areas have identified low 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, anterior and posterior cingulate cortex were selected as regions of interest to identify the uncinate fasciculus, cingulum bundle, and more specific tracts from the amygdala to regions of prefrontal cortex and superior temporal gyrus (Supplemental Figure). Cortical and subcortical regions of interest 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 normalization of individual tensor data, the Wake Forest PickAtlas standard T1 anatomical image and anatomical regions of interest were separately registered to each individual subject's high resolution anatomical image using the Landmarker Program in DTI Studio (www.mristudio.org). Regions of interest pairs were then combined using a "cut" function to identify fiber tracts connecting the two regions. The "not" function in DTI studio was used to exclude contralateral or extra axial fiber tracts (in regions of imperfect skull stripping or medial regions of interest). Fractional anisotropy values for the individual tracts of interest were calculated within DTI Studio.

2.4.3 Tract-based spatial statistics analysis—Voxelwise statistical analysis of the fractional anisotropy data generated above was carried out using the TBSS (Smith et al., 2006) part of the software package in FSL (Smith et al., 2004). All subjects' fractional anisotropy data were aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a, b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean fractional anisotropy image was created and thinned to create a mean fractional anisotropy skeleton which represents the centres of all tracts common to the group. Each subject's aligned fractional anisotropy data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics, using GLM analysis with age and IQ included as covariates, using threshold free cluster enhancement and correcting for multiple comparisons ($p < 0.05$).

2.4.4 Functional Connectivity Analysis—Normalization of brain volumes from age 7–8 years onward does not introduce major age related distortions in localization or time course of the BOLD signal in event related fMRI (Burgund et al., 2002, Kang et al., 2003), so participants' anatomical scans were individually registered to the Talaraich and Tournoux Atlas (Talairach and Tournoux, 1988). At the individual level, functional images from the first 5 trials of each run collected before equilibrium magnetization was reached were discarded. Functional images from the 4 time series were motion corrected and spatially smoothed with a 6 mm full-width half-maximum Gaussian filter. The time series were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression coefficients represented a percent signal change from the mean. A functional connectivity analysis was then performed using prior protocols (Marsh et al., 2008) with a seed in left amygdala that was identified as a peak voxel in this structure showing differential BOLD signal activation as a main effect of diagnosis in youths with CD/ODD+PT relative to healthy comparison youths. A voxel-wise correlation analysis was conducted between each individual voxel's time series (after removing baseline, linear, and quadratic trends) and that of the identified seed. These coefficients were normalized using a Fisher transformation, and compared across groups using *t*-tests. The threshold was set at $p < 0.005$.

3. Results

3.1 Participants

One way ANOVAs revealed no significant group differences in age ($p > 0.13$) nor in estimated IQ ($p > 0.18$) (see Table 1). As diffusion coefficients and fractional anisotropy values vary across development (Morriss et al., 1999, Mukherjee et al., 2001) and are correlated with IQ (Schmithorst et al., 2002, 2005), age and IQ were included as covariates in both the region of interest and TBSS analysis below. Note, results were not significantly different if IQ and age were not included as covariates.

3.2 ROI Analysis

ANCOVAs were conducted on FA values for each ROI pair with diagnosis as the between subjects factor and IQ and age as covariates. This analysis demonstrated no significant differences in FA values between CD/ODD+PT and comparison youths for the fiber tracts of interest (see Table 2).

3.3 TBSS Analysis

Results of the voxel-wise TBSS analysis demonstrated no significant differences in fractional anisotropy between CD/ODD+PT and healthy comparison youths in any white matter regions at $p < 0.05$ corrected (see Figure 1).

3.4 Functional Connectivity

Analysis of this subset of children who completed both the fMRI study and the DTI study demonstrated abnormal functional connectivity between the rostral anterior cingulate cortex and the amygdala: ($F(1, 23) = 8.36$; $p < 0.01$), mean left amygdala-rostral anterior cingulate cortex connectivity in CD/ODD+PT = -0.11 , mean comparison youths 0.24), as well as in the superior temporal gyrus, insula, and caudate (see Figure 1 and Table 3). Note that relative to comparison youths, reduced BOLD activation was previously observed and reported in youths with CD/ODD+PT in the right amygdala and orbitofrontal cortex (right Brodmann areas 10 and 11) during the instrumental learning task (Finger et al., 2010). However, in contrast with earlier work (Marsh et al., 2008), level of amygdala-cortical connectivity did not predict symptom severity of the youths with CD/ODD+PT as measured by either the PCL-YV or ASPD.

4. Discussion

Youths with CD/ODD+PT demonstrated reduced functional connectivity between the amygdala and regions of prefrontal and superior temporal cortex. In contrast, no significant differences in fractional anisotropy values for any of the ROI pairs were detectable (amygdala-orbitofrontal cortex, amygdala-Brodmann areas 10/11, amygdala-anterior cingulate cortex temporal pole-orbitofrontal cortex, temporal pole- Brodmann areas 10/11, amygdala-superior temporal gyrus, anterior cingulate cortex-posterior cingulate cortex). In addition, results of the voxel-wise TBSS analysis demonstrated no detectable significant differences in fractional anisotropy between CD/ODD+PT and comparison youths any white matter regions. The current findings are important because they indicate that functional measures are more sensitive than diffusion tensor analysis of abnormalities in these youths. Furthermore, if fractional anisotropy measurements are sensitive markers of white matter integrity, abnormalities in fractional anisotropy detected in other studies in the uncinate fasciculus (Craig et al., 2009) may arise later in development (late adolescence or early adulthood) as the frontal lobes and white matter tracts continue to mature, possibly arising from persistent abnormal functional connectivity between the structures.

There are potential limitations to the present study that should be considered. First, it is possible that the absence of structural connectivity differences could be due to the sample size. However, we consider this to be unlikely as the prior study of adults with psychopathy found a significant effect with a smaller sample size of just 9 adult psychopaths and 9 comparison youths (Craig et al., 2009). Moreover, in the current study, there was clear evidence of reduced functional connectivity in the youth with high psychopathic traits even in the absence of reduced structural connectivity. Second, the lack of significant group differences in the present study could also reflect limited sensitivity of the diffusion tensor imaging techniques or analysis methods employed. We attempted to address this possibility by including two validated methods of analysis- tractography in DTI studio using standardized regions of interest based on the structures most commonly implicated in psychopathy, and whole brain white matter fractional anisotropy analysis using TBSS. However, as both methods assess fractional anisotropy, it is possible that this marker and the DTI methods are simply less sensitive to measuring group differences than the functional imaging techniques. The discrepancy between our results and the prior study demonstrating differences in the uncinate fasciculus in adults with psychopathic traits may also reflect the use manual tracings of ROIs based on white matter regions (Craig et al., 2009), rather than standardized gray matter centered ROIs used here. Third, the purpose of this study was to examine structural and functional connectivity in youth with disruptive behavior disorders and psychopathic traits. It was not however designed to determine whether all youth with disruptive behavioral disorders show deficits or only those with high psychopathic traits; i.e., we did not include a group of youth with disruptive behavior disorders and low

psychopathic traits. It is notable that only approximately 40% of youth with disruptive behavior disorders also show elevated psychopathic traits (Kolko and Pardini, 2010). Data indicate differences in the heritability of antisocial behavior (Viding et al., 2005) as well as differences in functional impairment (Frick et al., 2003, Frick et al., 2005) in youth with elevated aggression and high as opposed to low psychopathic traits (though fMRI studies have only sometimes reported correlations between level of psychopathic traits (Marsh et al., 2008) and other times not (Passamonti et al.). As such, we would not necessarily predict, and definitely would not claim, that impairment in functional connectivity but intact structural connectivity would be found in youth with disruptive behavior disorders without psychopathic traits. Finally, a significant proportion of youths in the CD/ODD+PT group were taking medications at the time of the study. As the number of unmedicated youths with high psychopathic traits precludes a separate analysis, potential effects of the medications on the imaging results, in particular the functional connectivity data, cannot be completely assessed. Of note, in our prior work in a sample with fewer medicated youths, we did find functional abnormalities that were replicated in both the medicated and unmedicated high psychopathic traits youth groups (Finger et al., 2008).

As expected, in the present study there was a high comorbidity between CD/ODD+PT and ADHD. We did not include a separate ADHD comparison group in the current study because our previous studies did not demonstrate functional pathology in the amygdala or orbitofrontal cortex in the youths with ADHD only, though abnormalities were seen in the youths with comorbid CD/ODD+PT and ADHD (Marsh et al., 2008). Additionally, dysfunction in orbitofrontal cortex reward signaling has been found in youths with conduct disorder who do not present with ADHD but not in youths with ADHD (Rubia et al., 2009). Thus, we suggest the present abnormalities in functional connectivity are not due to ADHD but to neural pathophysiology related to CD/ODD+PT.

It is important to note that the claim that functional measures of connectivity *are more sensitive than* diffusion tensor analysis of structural connectivity in youth with CD/ODD+PT may rest on our choice of paradigm to assess functional connectivity. We selected the passive avoidance learning task as this form of instrumental learning is impaired in youths and adults high in psychopathic traits (Lykken, 1957, Newman and Kosson, 1986). Critically, animal work on a comparable paradigm has been shown to involve the integrated functioning of the amygdala and orbital frontal cortex (Schoenbaum and Roesch, 2005). Moreover, fMRI work with healthy adults has shown the involvement of these structures in its performance (Kosson et al., 2006, Finger et al., 2011). As such we “maximized” the possibility for obtaining group differences in functional connectivity. It is possible, though we anticipate otherwise, that group differences in amygdala-orbital frontal cortex functional connectivity may be less prominent, for example, if assessed during rest.

The present findings indicate that white matter tract integrity may be preserved in youths with CD/ODD+PT even while current and prior work demonstrates dysfunctional amygdala and orbitofrontal cortex responsiveness (Marsh et al., 2008, Jones et al., 2009, Finger et al., 2010) and decreased amygdala-orbitofrontal cortex and amygdala-rostral anterior cingulate cortex *functional* connectivity (Marsh et al., 2008). Given the recent finding of reduced fractional anisotropy in the uncinate fasciculus in adults with psychopathic traits (Craig et al., 2009), several possible suggestions can be made. First, white matter abnormalities may arise later in development as prefrontal white matter tracts are refined (i.e. late adolescence or early adulthood). Indeed, increased gray matter volumes have been recently reported in youths with psychopathic traits (De Brito et al., 2009) in contrast to the volume reductions consistently found in adults. From this perspective, observed perturbations in functional connectivity could stimulate structural remodeling, only detectable with DTI later in development. Second, white matter abnormalities may arise secondary to later-occurring

complications of psychopathy, particularly substance abuse. Importantly, if indeed white matter abnormalities are not present in these youths, both hypotheses suggest that childhood may provide a critical window for intervention, before significant structural brain abnormalities solidify.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear optimisation. FMRIB technical report TR07JA1. 2007a. www.fmrib.ox.ac.uk/analysis/techrep
- Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear registration, aka Spatial normalisation. FMRIB technical report TR07JA2. 2007b. www.fmrib.ox.ac.uk/analysis/techrep
- Blair RJ, Colledge E, Murray L, Mitchell DG. A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *J Abnorm Child Psychol.* 2001; 29 (6):491–498. [PubMed: 11761283]
- Blair RJR. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends Cogn Sci.* 2007; 11 (9):387–392. [PubMed: 17707682]
- Budhani S, Blair RJ. Response reversal and children with psychopathic tendencies: success is a function of salience of contingency change. *J Child Psychol Psychiatry.* 2005; 46 (9):972–981. [PubMed: 16109000]
- Burgund ED, Kang HC, Kelly JE, Buckner RL, Snyder AZ, Petersen SE, Schlaggar BL. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *Neuroimage.* 2002; 17 (1):184–200. [PubMed: 12482076]
- Burke JD, Loeber R, Lahey BB. Adolescent conduct disorder and interpersonal callousness as predictors of psychopathy in young adults. *J Clin Child Adolesc Psychol.* 2007; 36 (3):334–346. [PubMed: 17658978]
- Craig MC, Catani M, Deeley Q, Latham R, Daly E, Kanaan R, Picchioni M, McGuire PK, Fahy T, Murphy DG. Altered connections on the road to psychopathy. *Mol Psychiatry.* 2009; 14(10):946–953. 907. [PubMed: 19506560]
- Dadds MR, Fraser J, Frost A, Hawes DJ. Disentangling the underlying dimensions of psychopathy and conduct problems in childhood: a community study. *J Consult Clin Psychol.* 2005; 73 (3):400–410. [PubMed: 15982138]
- De Brito SA, Mechelli A, Wilke M, Laurens KR, Jones AP, Barker GJ, Hodgins S, Viding E. Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain.* 2009; 132 (Pt 4):843–852. [PubMed: 19293245]
- Edens JF, Skeem JL, Cruise KR, Cauffman E. Assessment of “juvenile psychopathy” and its association with violence: a critical review. *Behav Sci Law.* 2001; 19 (1):53–80. [PubMed: 11241681]
- Finger EC, Marsh AA, Blair KS, Reid ME, Sims C, Ng P, Pine DS, Blair RJ. Disrupted reinforcement signaling in the orbitofrontal cortex and caudate in youths with conduct disorder or oppositional defiant disorder and a high level of psychopathic traits. *Am J Psychiatry.* 2011; 168 (2):152–162. [PubMed: 21078707]
- Finger EC, Marsh AA, Blair KS, Reid ME, Sims C, Ng P, Pine DS, Blair RJR. Disrupted Reinforcement Signaling in Orbital Frontal Cortex and Caudate in Youths with Conduct Disorder/ Oppositional Defiant Disorder and High Psychopathic Traits. *American Journal of Psychiatry.* 2010 In Press.

- Finger EC, Marsh AA, Mitchell DG, Reid ME, Sims C, Budhani S, Kosson DS, Chen G, Towbin KE, Leibenluft E, Pine DS, Blair JR. Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Arch Gen Psychiatry*. 2008; 65 (5):586–594. [PubMed: 18458210]
- Forth, A.; Kosson, DS.; Hare, RD. Hare Psychopathy Checklist-Youth Version. Toronto: Multi-Health Systems Inc; 2004.
- Forth, AE.; Kosson, DS.; Hare, RD. The Hare Psychopathy Checklist: Youth Version. Toronto: Multi-Health Systems; 2003.
- Frick PJ, Bodin SD, Barry CT. Psychopathic traits and conduct problems in community and clinic-referred samples of children: further development of the psychopathy screening device. *Psychol Assess*. 2000; 12 (4):382–393. [PubMed: 11147105]
- Frick PJ, Cornell AH, Barry CT, Bodin SD, Dane HE. Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and self-report of delinquency. *J Abnorm Child Psychol*. 2003; 31 (4):457–470. [PubMed: 12831233]
- Frick, PJ.; Hare, RD. Antisocial Process Screening Device. Toronto: Multi-Health Systems Inc; 2001.
- Frick PJ, Lilienfeld SO, Ellis M, Loney B, Silverthorn P. The association between anxiety and psychopathy dimensions in children. *J Abnorm Child Psychol*. 1999; 27 (5):383–392. [PubMed: 10582839]
- Frick PJ, Stickle TR, Dandreaux DM, Farrell JM, Kimonis ER. Callous-unemotional traits in predicting the severity and stability of conduct problems and delinquency. *J Abnorm Child Psychol*. 2005; 33 (4):471–487. [PubMed: 16118993]
- Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed*. 2006; 81 (2):106–116. [PubMed: 16413083]
- Jones AP, Laurens KR, Herba CM, Barker GJ, Viding E. Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *Am J Psychiatry*. 2009; 166 (1):95–102. [PubMed: 18923070]
- Kang HC, Burgund ED, Lugar HM, Petersen SE, Schlaggar BL. Comparison of functional activation foci in children and adults using a common stereotactic space. *Neuroimage*. 2003; 19 (1):16–28. [PubMed: 12781724]
- Kolko DJ, Pardini DA. ODD dimensions, ADHD, and callous-unemotional traits as predictors of treatment response in children with disruptive behavior disorders. *J Abnorm Psychol*. 2010; 119 (4):713–725. [PubMed: 21090875]
- Kosson DS, Budhani S, Nakic M, Chen G, Saad ZS, Vythilingam M, Pine DS, Blair RJ. The role of the amygdala and rostral anterior cingulate in encoding expected outcomes during learning. *Neuroimage*. 2006; 29 (4):1161–1172. [PubMed: 16387514]
- Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp*. 2000; 10 (3):120–131. [PubMed: 10912591]
- Lykken DT. A study of anxiety in the sociopathic personality. *Journal of abnormal and social psychology*. 1957; 55:6–10.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003; 19 (3):1233–1239. [PubMed: 12880848]
- Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, Towbin KE, Leibenluft E, Pine DS, Blair RJ. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry*. 2008; 165 (6):712–720. [PubMed: 18281412]
- McMahon RJ, Witkiewitz K, Kotler JS. Predictive validity of callous-unemotional traits measured in early adolescence with respect to multiple antisocial outcomes. *J Abnorm Psychol*. 2010
- Morriss MC, Zimmerman RA, Bilaniuk LT, Hunter JV, Haselgrove JC. Changes in brain water diffusion during childhood. *Neuroradiology*. 1999; 41 (12):929–934. [PubMed: 10639670]

- Mukherjee P, Miller JH, Shimony JS, Conturo TE, Lee BC, Almli CR, McKinstry RC. Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. *Radiology*. 2001; 221 (2):349–358. [PubMed: 11687675]
- Murrie DC, Cornell DG. Psychopathy screening of incarcerated juveniles: a comparison of measures. *Psychol Assess*. 2002; 14 (4):390–396. [PubMed: 12501564]
- Newman JP, Kosson DS. Passive avoidance learning in psychopathic and nonpsychopathic offenders. *J Abnorm Psychol*. 1986; 95 (3):252–256. [PubMed: 3745647]
- Pardini DA, Fite PJ. Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial maladjustment in boys: advancing an evidence base for DSM-V. *J Am Acad Child Adolesc Psychiatry*. 2010; 49 (11):1134–1144. [PubMed: 20970701]
- Passamonti L, Fairchild G, Goodyer IM, Hurford G, Hagan CC, Rowe JB, Calder AJ. Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry*. 2010; 67 (7):729–738. [PubMed: 20603454]
- Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol*. 2000; 12 (4):191–200. [PubMed: 11568431]
- Rubia K, Smith AB, Halari R, Matsukura F, Mohammad M, Taylor E, Brammer MJ. Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. *American Journal of Psychiatry*. 2009; 166:83–94. [PubMed: 18829871]
- Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ. Non-rigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging*. 1999; 18 (8):712–721. [PubMed: 10534053]
- Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology*. 2002; 222 (1):212–218. [PubMed: 11756728]
- Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. *Hum Brain Mapp*. 2005; 26 (2):139–147. [PubMed: 15858815]
- Schoenbaum G, Roesch M. Orbitofrontal cortex, associative learning, and expectancies. *Neuron*. 2005; 47 (5):633–636. [PubMed: 16129393]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006; 31 (4):1487–1505. [PubMed: 16624579]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23(Suppl 1):S208–219. [PubMed: 15501092]
- Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, Robson MD, Jones DK, Klein JC, Bartsch AJ, Behrens TE. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nat Protoc*. 2007; 2 (3):499–503. [PubMed: 17406613]
- Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15 (1):273–289. [PubMed: 11771995]
- Viding E, Blair RJ, Moffitt TE, Plomin R. Evidence for substantial genetic risk for psychopathy in 7-year-olds. *J Child Psychol Psychiatry*. 2005; 46 (6):592–597. [PubMed: 15877765]
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC. Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr*. 1998; 22 (1):153–165. [PubMed: 9448780]

Figure 1.

Functional Connectivity Analysis demonstrating reduced functional connectivity between the amygdala and rACC and in CD/ODD+PT youths (effects significant at $p < 0.005$, picture shown at $p < 0.01$ to demonstrate full extent of activation).

Table 1

Participant Characteristics.

<u>Measure</u>		
	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)

Table 2

Adjusted mean FA values (s.e.) for white matter tracts of interest defined by ROIs from Wake Forest Picture Atlas. No significant group differences were found.

ROI		Comparison youths	Psychopathic Traits
Amygdala to BA 10+11	(L)	0.38 (0.01)	0.41 (0.01)
	(R)	0.41 (0.02)	0.43 (0.02)
Amygdala to OFC	(L)	0.36 (0.02)	0.32 (0.02)
	(R)	0.41 (0.02)	0.37 (0.01)
Amygdala to anterior cingulate cortex	(R)	0.37 (0.02)	0.38 (0.02)
	(L)	0.36 (0.04)	0.36 (0.04)
Amygdala to STG	(L)	0.38 (0.02)	0.34 (0.02)
	(R)	0.37 (0.01)	0.35 (0.01)
Temporal pole to BA 10+11	(L)	0.37 (0.01)	0.40 (0.01)
	(R)	0.43 (0.02)	0.40 (0.02)
Temporal pole to OFC	(L)	0.34 (0.02)	0.36 (0.01)
	(R)	0.35 (0.02)	0.34 (0.02)
Anterior to posterior Cingulate cortex	(L)	0.49 (0.03)	0.50 (0.02)
	(R)	0.49 (0.02)	0.45 (0.02)
Thalamus to BA 4	(L)	0.51 (0.01)	0.48 (0.01)
	(R)	0.52 (0.01)	0.51 (0.01)

Regions Demonstrating Reduced Functional Connectivity with the Amygdala Seed in the Youths with Psychopathic Traits

Table 3

Region	L/R	BA	x	y	z	volume
Rostral anterior cingulate cortex	L	32	-1	44	13	240
Middle frontal gyrus	R	6	9	-22	51	288
Insula	R	22	45	-13	-3	384
	R	13	45	-18	12	367
Posterior cingulate gyrus	R	31	43	-48	39	2000
Superior temporal gyrus/insula	R	13	43	-45	15	2648
Cuneus	L	18	-3	-78	13	736
Middle occipital gyrus	R	19	37	-76	5	480
Caudate tail	R		21	-33	18	336

MINI coordinates of peak activation. Regions and BA areas according to Talairach Daemon Atlas. All regions thresholded at $p < 0.005$.