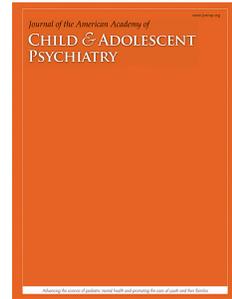


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M. John Broulidakis, MSc, Graeme Fairchild, PhD, Kate Sully, PhD, Thomas Blumensath, PhD, Angela Darekar, PhD, Edmund J.S. Sonuga-Barke, PhD

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Reduced Default Mode Connectivity in Adolescents With Conduct Disorder

RH = Default Mode Network in Conduct Disorder

M. John Broulidakis, MSc; Graeme Fairchild, PhD; Kate Sully, PhD; Thomas Blumensath, PhD; Angela Darekar, PhD; and Edmund J. S. Sonuga-Barke, PhD

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Mr. Broulidakis and Drs. Fairchild, Sully, and Sonuga-Barke are with the Developmental Brain-Behavior Laboratory (DBBL) at the University of Southampton, UK. Dr. Sonuga-Barke is also with Gent University, Belgium. Dr. Blumensath is with the Institute of Sound and Vibration Research (ISVR) at the University of Southampton, UK. Dr. Darekar is with University Hospital Southampton National Health Service Foundation Trust, Southampton, UK.

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Correspondence to Edmund J. S. Sonuga-Barke, PhD, Academic Unit of Psychology, Shackleton Building (B44), Highfield Campus, University of Southampton, Southampton, SO17 1BJ, UK; email: ejb3@soton.ac.uk.

ABSTRACT

Objective: Conduct disorder (CD) is characterized by impulsive, aggressive, and antisocial behaviors that may be related to deficits in empathy and moral reasoning. The brain's default mode network (DMN) has been implicated in self-referential cognitive processes of this kind.

Method: We examined connectivity between key nodes of the DMN in 29 male adolescents with CD and 29 age- and sex-matched typically-developing adolescents. We ensured that group differences in DMN connectivity were not explained by comorbidity with other disorders by systematically controlling for the effects of substance use disorders (SUDs), attention-deficit/hyperactivity disorder (ADHD) symptoms, psychopathic traits, and other common mental health problems.

Results: Only after adjusting for co-occurring ADHD symptoms, the group with CD showed hypo-connectivity between core DMN regions relative to typically-developing controls. ADHD symptoms themselves were associated with DMN hyperconnectivity. There was no effect of psychopathic traits on DMN connectivity in the group with CD, and the key results were unchanged when controlling for SUDs and other common mental health problems.

Conclusion: Future research should directly investigate the possibility that the aberrant DMN connectivity observed in the current study contributes to CD-related deficits in empathy and moral reasoning, and examine self-referential cognitive processes in CD more generally.

Key words: conduct disorder, ADHD, psychopathic traits, default mode network, functional connectivity

INTRODUCTION

Conduct disorder (CD) is defined as a repetitive and persistent pattern of antisocial behavior in which the rights of others or societal norms are violated¹. Symptoms of CD include theft, vandalism, and violence towards other humans and animals. Neuroimaging studies of CD implicate dysfunction in fronto-amygdala and fronto-insula circuits as part of a disrupted ventromedial/orbitofrontal-limbic network²⁻⁴. Several recent studies have also suggested that the brain's default mode network (DMN) could also be implicated⁵⁻⁷. The DMN is comprised of the anterior medial prefrontal cortex (aMPFC), posterior cingulate cortex (PCC), medial temporal lobe, lateral parietal cortex, and temporal-parietal junction⁸⁻¹⁰. The DMN consists of different subsystems^{8,10,11}, namely, the dorsal MPFC (dMPFC) subsystem, the medial temporal lobe (MTL) subsystem, and the aMPFC – PCC core system. These subsystems are thought to play a critical role in self-referential cognitive processing, including the construction of mental representations of the self, as well as one's own and others' possible future actions, thoughts, and feelings^{12,13}. In particular, the dMPFC subsystem is involved in theory of mind and

morality judgments^{13,14}. The MTL subsystem is involved in binding together disparate information to facilitate scene construction⁸ and the aMPFC-PCC core in attaching personal significance to internally focused thoughts⁸ as well as forming the self–other distinctions linked to pro-social behavior¹⁵ and possibly judgments of affective empathy¹⁶. Thus the DMN and its component subsystems represent plausible pathophysiological substrates for deficits in emotion perception¹⁷, empathy,¹⁸ or moral reasoning¹⁹ that have been observed in individuals with CD.

Using independent components analysis (ICA), Dalwani et al.⁶ found that, relative to typically-developing controls, male adolescents with CD showed reduced connectivity between the superior, medial, and middle frontal gyrus, lingual gyrus, retrosplenial cortex, and lateral temporal cortex, reflecting generalized DMN dysregulation in CD. However, all of the participants with CD also had substance use disorders (SUDs), which have been previously shown to be associated with DMN abnormalities²⁰⁻²². Furthermore, the study did not include a dedicated rest period, instead using a task with alternating periods of rest and stimulus processing. This is problematic because DMN connectivity is affected by such variations in task characteristics²³ and instructions²⁴. Another recent small-scale study²⁵ reported DMN hypo-connectivity in male adolescents with CD who were free of comorbid SUDs, also using ICA methods but, in this case, more standard procedures for collecting resting-state functional magnetic resonance imaging (fMRI) data.

In the current study, we extend this analysis of DMN dysregulation in CD in a number of ways. First, we adopted a more theoretically-driven seed-based approach, better suited to investigating which DMN subsystems are impaired by restricting the analysis just to those regions shown to be involved in mental construction, socio- and non–social-cognitive conceptualization and self-referential thinking¹¹. This takes advantage of the functionally dissociable nature of DMN subsystems and has the potential to provide a more straightforward interpretation in terms of underlying cognitive impairments. Indeed, such an approach has already been used to identify DMN subsystem-specific abnormalities in schizophrenia and major depression²⁶⁻²⁸.

Second, we systematically examined the impact of clinical heterogeneity and comorbidity on the relationship between CD and DMN connectivity. In particular, we examined the impact of SUD comorbidity on DMN connectivity in CD, given that all of the participants with CD in the study by Dalwani et al. had comorbid SUDs, whereas none of the participants in the study by Zhou et al. reported SUD comorbidity. Epidemiological studies have shown a high degree of overlap between CD and SUDs^{29,30}, so this is an important clinical issue, and we felt it was important to replicate these findings suggesting that CD is associated with DMN abnormalities, irrespective of SUD comorbidity. We also sought to examine whether DMN abnormalities were

related to psychopathic traits in our CD sample. Psychopathy is a personality disorder characterized by a callous lack of empathy and impulsive antisocial behavior. Although the term psychopathy is not applied to adolescents, high levels of psychopathic traits are nevertheless associated with an increased risk of violent offending in participants with CD,^{31,32} and CD with elevated psychopathic traits has been suggested to represent a more pervasive subtype of CD³³. A number of studies have reported reduced connectivity between brain regions overlapping with core DMN midline regions in psychopathic adults^{34,35}. Interestingly, even within the construct of psychopathy, there are possibly differential effects of the affective/interpersonal and antisocial factors of psychopathy, with the affective/interpersonal factor associated with decreased medial-lateral DMN connectivity and the antisocial factor associated with increased connectivity between prefrontal and parietal DMN components³⁶. However, to date, no study has directly investigated the effects of psychopathic traits on DMN connectivity in participants with CD. Adolescence is a developmental period in which there are widespread changes in structural connectivity³⁷ that may have a bearing on the developmental course of antisocial behavior and psychopathy. This makes it pertinent to examine whether altered DMN connectivity in those with psychopathy is observed at an earlier stage in development. We also examined the association between DMN dysregulation and attention-deficit/hyperactivity disorder (ADHD) symptoms. ADHD is a neurodevelopmental condition characterized by persistent and age-inappropriate levels of inattention, hyperactivity, and impulsivity¹. This condition frequently co-occurs with CD and is present in between 25-30% of boys with CD³⁸. Even in those who do not meet formal diagnostic criteria for ADHD, there is considerable overlap in symptomatology, and symptom dimensions of impulsivity and hyperactivity have been associated with the development of antisocial behavior in childhood³⁹. Notably, ADHD is associated with abnormal DMN connectivity, hypothesized to reflect a disorganization of the network and an inability to appropriately regulate self-generated thought^{40,41}. Finally, we examined whether there were differences in DMN connectivity according to the age-of-onset of CD—i.e., whether DMN connectivity was altered in both childhood-onset and adolescence-onset subtypes of CD, or just the former subtype. Like psychopathy, the age of onset of CD is thought to differentiate between subtypes of CD that differ in terms of etiology and adult outcomes^{1,42}. Childhood-onset CD, which emerges before age 10, has been linked to distinct cognitive⁴³ and neurophysiological⁴⁴ profiles compared to adolescence-onset CD, possibly reflecting the fact that these subtypes have different etiologies⁴⁵, although see⁴⁶ for a review challenging this idea.

In summary, we examined DMN connectivity in adolescents with CD using a more hypothesis-driven approach than has been used previously to investigate distinct subsystems of the DMN. To this end, we

employed a seed-based approach, measuring connectivity between a priori regions of interest (ROIs) in limited components of the extended DMN that are potentially involved in deficits in empathy and moral decision-making observed in young people with CD¹¹. We predicted that adolescents with CD would display a generalized reduction in DMN connectivity that would be especially pronounced in the subgroup with elevated psychopathic traits. We also predicted that these effects would not be accounted for by other comorbid conditions and would therefore persist when controlling for the effects of SUDs, ADHD, and other common mental disorders.

METHOD

Participants

Seventy male adolescents aged between 13-18 years were recruited from schools, colleges, pupil referral units, and Youth Offending Teams in the Hampshire area of the UK. Of this total sample, 6 were excluded due to gross neurological abnormalities (gray- or white-matter abnormalities and cysts), 3 for excessive head movement, and 3 due to major depressive disorder (MDD) and/or general anxiety disorder (GAD) comorbidity. This meant that data from 58 participants (29 CD and 29 controls) were available for analysis. Sixteen participants had childhood-onset CD (i.e., at least one CD symptom prior to age 10) and 13 had adolescence-onset CD (i.e., symptoms only after age 10¹). Seven participants with CD had comorbid ADHD but were otherwise free of all other common co-occurring disorders (with the exception of oppositional defiant disorder [ODD]). Healthy control participants screened negative for current psychiatric disorders using the same diagnostic instrument (see below).

Diagnostic Assessment

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL⁴⁷) was used to assess CD, and other common mental disorders (e.g., MDD, GAD, ODD, ADHD, obsessive-compulsive disorder [OCD], and posttraumatic stress disorder [PTSD]). The K-SADS-PL is a semi-structured interview based on *DSM-IV* criteria⁴⁸. If a symptom is endorsed at threshold by either the child or the parent, it is considered present⁴⁷. Participants were given a research diagnosis of CD if they (or their parents) endorsed at least three CD symptoms in the last 12 months. Control participants were screened using the same instrument and were free of all assessed disorders, as well as past diagnoses of CD or ODD. All participants also completed the self-report Youth Psychopathic traits Inventory (YPI⁴⁹) to assess psychopathic traits. The YPI measures psychopathy as a multi-component construct encompassing a grandiose and manipulative interpersonal style (factor 1), a callous and unemotional affective style (factor 2), and

impulsive and irresponsible behavior (factor 3). Substance use was assessed using the problem severity scale of the Personal Experience Screening Questionnaire (PESQ)⁵⁰. In line with recommended scoring guidelines, participants aged below 16 years with scores >30 or those aged 16 and above with scores >35 were assessed as being at high risk for substance use disorders. Sixteen of the 58 participants (12 from the CD group, 4 from the control group) were excluded from the supplementary analyses testing for group differences in the subsample without substance use disorder. Handedness was measured using the Edinburgh Handedness Inventory⁵¹.

Procedure

Initial assessment and screening took place on a day prior to the MRI scan. During this time informed consent was obtained from the participant or the primary caregiver if the participant was <16 years of age. Additional exclusion criteria were: 1) a clinical diagnosis of a neurodevelopmental (e.g., Down's Syndrome) or pervasive developmental disorder (i.e., autism spectrum disorder); 2) an estimated IQ <75, as assessed using the two-subtest version of the Wechsler Abbreviated Intelligence Scale⁵²; and 3) standard MRI exclusion criteria (cardiac pacemaker, metal in body, claustrophobia, etc.). Eligible participants were invited to take part in an MRI scan lasting 35-40 minutes on a separate day.

Image Acquisition.

fMRI data were acquired on a 1.5-Tesla Siemens Avanto (Siemens AG, Erlangen, Germany) MRI scanner at Southampton General Hospital in the UK. A 12-channel head coil was used to detect and receive the magnetic resonance signal. T1-weighted (MP-RAGE) three-dimensional datasets (voxel size=1.2x1.2x1.2 mm, repetition time = 2400ms, flip angle = 8°, 160 slices) were acquired, with an acquisition time of 7 min 41 sec. These were obtained for the purposes of registration and to create white matter (WM) and cerebrospinal fluid (CSF) masks used to generate confound regressors. Resting state fMRI data were acquired using a T2*-weighted gradient echo planar imaging (EPI) sequence (repetition time = 3600ms, 35 slices, voxel size= 3.26 x 3.26 x 3.26 mm, in an interleaved acquisition, flip angle = 90°, 123 volumes). The resting state scan lasted 6 min 10 sec. During the scan, participants were asked to relax and fixate on a red crosshair presented against a white background (i.e., eyes-open acquisition). Participants underwent the structural scan prior to the resting state scans.

Image Preprocessing.

The FSL version 5 software package (<http://fsl.fmrib.ox.ac.uk>) and the Connectivity Toolbox version 13 (<http://www.nitrc.org/projects/conn>⁵³) were used for image preprocessing. The first three volumes of each functional time-series were discarded to allow for magnetic saturation effects. Participants were excluded if: 1)

relative head displacement was > 3 mm in x, y, or z coordinates and 2) the maximum rotation encompassing yaw, pitch and roll was $> 2^\circ$. Preprocessing steps included: 1) identifying outlier time-points that were included as confound regressors in the first level general linear model (motion scrubbing); 2) a rigid-body correction for head motion; 3) nonlinear registration of functional data to a T1-weighted Montreal Neurological Institute (MNI) template that was resampled to $4 \times 4 \times 4$ mm³; 4) spatial smoothing (a gaussian full width at half-maximum kernel of $6 \times 6 \times 6$ mm³); 5) an anatomical component-based strategy⁵⁴ (aCompCore) that involved regression of subject-specific time-series from 6 components estimated from WM and CSF masks using principle components analysis; 6) band-pass filtering (0.008 – 0.09 Hz), and 7) despiking using a hyperbolic tangent function to reduce the influence of outlier scans.

Regions of Interest (ROIs).

Eleven a priori ROIs were selected from coordinates provided by Andrews-Hanna et al.¹¹ to study connectivity in all three subsystems of the DMN associated with different internally mediated cognitive processes (see Table 1 for details and the relevant coordinates). Andrews-Hanna et al. identified these seeds in a young adult sample. While there is evidence that long-range connectivity within the DMN continues to develop well into adolescence, by adolescence these changes are limited to increases in functional connectivity between nodes, with all major DMN nodes fully formed in childhood^{55,56}. Therefore, we felt justified in using these seeds in an adolescent population. All seeds were 8mm radius spheres created using FSL. Consistent with previous studies^{11,27,28}, only left lateralized and midline regions were investigated in this study to prevent biasing connectivity to mirrored ROIs.

[Insert Table 1 here]

Statistical Analysis

The specific time-series were computed by averaging the temporally-filtered residual time series for each voxel within each seed. For each seed bivariate correlation matrices were calculated yielding group-level β values that were Fisher transformed. Group comparisons used analysis of covariance (ANCOVA) to compare all participants with CD with healthy controls in the first instance; we also compared the adolescence-onset and childhood-onset CD subgroups with healthy controls, and directly compared the adolescence-onset and childhood-onset CD subgroups. The influence of psychopathic traits on DMN connectivity was investigated using a linear regression analysis on the summed total YPI scores and each of the three separate factors of psychopathy (i.e., interpersonal, affective, and behavioral). For all second-level contrasts, age, IQ, and ADHD symptoms were included as covariates of no interest. ADHD is a disruptive behavior disorder that frequently co-

occurs with CD and is independently associated with atypical DMN connectivity⁵⁷. It was also important to control for age and IQ, given that development of the DMN continues well into adolescence⁵⁶ and intelligence has been associated with connectivity strength⁵⁸. Results are reported at a threshold of $p < .05$ (two-tailed), false discovery rate (FDR) correction at the level of the entire analysis (i.e., controlling for each seed and each target seed simultaneously). Given the reduced sample size, comparisons between the childhood-onset and adolescence-onset subtypes of CD and healthy controls were performed at an uncorrected alpha level of $p < .01$ (two-tailed).

Ethics Approval.

This study was reviewed and approved by the University of Southampton Ethics Committee, the University Research Governance Office, the Hampshire County Council Research and Evaluation Unit, Southampton City Council Children's Services Research Governance Committee, and the University Hospital Southampton National Health Service (NHS) Trust's Research and Development Office.

RESULTS

[Insert Table 2 here]

The groups were well matched in age and handedness. The CD group had lower IQ scores, more ADHD symptoms, and higher levels of psychopathic traits than the control group (Table 2).

Conduct Disorder and Default Mode Network (DMN) Connectivity

CD was associated with reduced DMN connectivity specifically between the anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex (PCC); $t(53) = 3.69$, $p(\text{corr}) = .03$ (see Figure 1a). Connectivity between other DMN subsystems was unrelated to group status. This reduction in connectivity in the core aMPFC-PCC subsystem remained significant when excluding 16 participants with probable substance use disorders, although at an uncorrected alpha level only ($t[37] = 2.75$, $p[\text{uncorrected}] = .009$; [Figure 1b]). When either the adolescence-onset or childhood-onset CD subgroups were compared with the control group, we continued to find lower aMPFC to PCC connectivity at an uncorrected alpha level (for the adolescence-onset group only: $t[37] = 2.86$, $p[\text{uncorrected}] = .006$; for the childhood-onset group only: $t[43] = 3.39$, $p[\text{uncorrected}] = .0015$). There were no significant differences in connectivity between the childhood-onset and adolescence-onset CD subgroups, even at an uncorrected level. Interestingly, the CD-related effects were not significant if ADHD symptoms were not included as a covariate, suggesting that important changes in DMN connectivity in patients with CD and comorbid ADHD may be obscured by the fact that CD and ADHD symptoms have opposing effects on DMN connectivity.

[Insert Figure 1a/b here]

To investigate this effect further and study the relative contributions of CD and ADHD to DMN connectivity, we tested the relationship between DMN connectivity and ADHD symptoms. Adopting the reverse approach to that described above by controlling for group status (i.e., CD versus control group), we found that ADHD symptoms were positively correlated with DMN connectivity (see Figure 2). Specifically, functional connectivity between the aMPFC and the PCC ($t[53]=3.74$, $p[\text{corr}] = .03$) and the aMPFC and retrosplenial cortex ($t[53]=3.48$, $p[\text{corr}] = .03$) increased as a function of ADHD symptoms. These findings suggest that ADHD is linked to DMN hyperconnectivity, whereas CD is linked to hypoconnectivity in the core DMN subsystem (aMPFC-PCC) only. There were no significant correlations when testing for the effects of the inattentive or hyperactive symptom dimensions of ADHD on DMN connectivity (for all seed-to-seed correlations, all $p[\text{corr}]$ values $>.10$).

[Insert Figure 2 here]

Psychopathy and DMN Connectivity

There were no significant associations between total psychopathy scores and DMN connectivity within the CD group. This was also the case for the three psychopathy subfactors (i.e., interpersonal, affective, and behavioral); for all seed-to-seed correlations, all $p(\text{corr})$ values $>.70$.

Potential Confounding Factors

Excluding participants with probable substance use disorders or comorbid ADHD and left-handers did not substantially affect our findings (see Table S1, available online).

Given that the CD and control groups differed in IQ, we also tested for correlations with IQ across all participants to examine whether IQ influenced functional connectivity. We found no significant correlations between IQ and DMN connectivity (for all seed-to-seed correlations, all $p[\text{corr}]$ values $>.40$).

DISCUSSION

We tested the hypothesis that CD is associated with reduced connectivity in the DMN, a network previously shown to be important for self-referential and other-referential cognitions. This was done using a seed-based approach to examine connectivity between brain regions known to make up the subsystems of the extended DMN. There were a number of findings of note.

First, in support of our hypothesis, we obtained evidence that CD is linked to significantly reduced anterior medial prefrontal cortex to posterior cingulate cortex connectivity, suggesting impairment in the core hub of the DMN. This effect survived statistical correction for multiple comparisons and was present when

controlling for comorbid ADHD symptoms, or, at an uncorrected threshold, when excluding participants with probable substance use disorders or full ADHD diagnoses. Importantly, these effects did not extend to other DMN subsystems and therefore differed from the findings of Dalwani et al.,⁶ who demonstrated a more generalized DMN deficit in adolescents with CD and comorbid substance use disorders. Our results are consistent with the recent findings of Zhou et al., who also identified DMN hypoconnectivity centered in posterior midline components of the DMN²⁵. However, unlike the study by Zhou et al.²⁵, we controlled for group differences in IQ and ADHD symptoms, which have previously been shown to be associated with DMN connectivity^{38,58}. This is important given the degree of clinical overlap between ADHD and CD, as well as the robust association between CD and lower IQ^{59,60}.

Second, we did not find effects of psychopathic traits or age-of-onset of CD, two factors suggested to delineate between meaningful subtypes of CD, on DMN connectivity. This challenges the view that age of onset can be used to differentiate neurophysiologically distinct subgroups⁴² and extends the literature by demonstrating that DMN abnormalities are observed in both childhood-onset and adolescence-onset CD subgroups. We also found no effect of psychopathic traits on DMN connectivity. This finding contradicts earlier evidence from adult prisoners that has demonstrated lower DMN connectivity in individuals with high levels of psychopathic traits relative to typically-developing adults. For example, Pujol et al.³⁴ compared prisoners with high levels of psychopathic traits with healthy controls, and Motzkin et al.³⁵ compared prisoners with high versus low levels of psychopathy. Both studies found connectivity between anterior and posterior midline components of the DMN were reduced in psychopathic individuals compared with control participants. Consistent with these findings, Sethi et al.⁶¹ recently compared prisoners with high levels of psychopathy and non-offender controls using diffusion tensor imaging and found reduced fractional anisotropy (a measure of structural connectivity) in the former group in the dorsal cingulum tract that connects midline posterior and anterior DMN components⁶¹. However, none of these studies controlled for antisocial personality disorder (an adult condition analogous to CD), and so the effects reported, which were strikingly similar to those observed in the current study, could have been due to antisocial behavior in general rather than psychopathy per se.

Third, the DMN effects related to CD were only present when controlling for ADHD symptoms. Indeed, ADHD symptoms were associated with increased connectivity within the aMPFC-PCC subsystem when controlling for CD group status. In addition, ADHD symptoms were positively correlated with aMPFC-retrosplenial cortex connectivity. As well as highlighting the importance of controlling for ADHD symptoms in studies of CD, these findings add to the literature demonstrating ADHD-related alterations in the DMN⁴¹. The

results of previous studies have been inconsistent in this regard. Some have demonstrated DMN hypoconnectivity related to ADHD^{41,62}. Our study, like several others, demonstrated ADHD-related hyperconnectivity⁵⁷. The reason for this variation between studies is unknown, although it has been suggested these differences reflect the frequent inclusion and failure to control for comorbid disorders (most notably CD)⁶³. Our results suggest that ADHD is associated with intra-DMN hyperconnectivity rather than hypoconnectivity, and that comorbid CD or disruptive behavior disorders may have opposing effects on DMN connectivity.

It should be noted that many other psychiatric disorders have been linked to DMN dysfunction (for a review, see⁵⁹), and therefore abnormalities in this network are not specific to CD. While we were able to demonstrate that our findings of hypoconnectivity in the core aMPFC-PCC subsystem were not the result of co-occurring psychiatric disorders, establishing that this DMN impairment is specific to CD is outside the scope of the current paper, given that we did not include any psychiatric control groups. However, it is possible that the nature of the DMN dysfunction in CD is different in nature from that observed in other disorders. For example, schizophrenia appears to be associated with reduced DMN connectivity in all subsystems of the network²⁷, and this has been correlated with subsystem-specific deficits in cognitive processes²⁸. Likewise, in MDD⁶⁴, OCD,⁶⁵ and autistic spectrum disorders⁶⁶, respectively, there is emerging evidence of disorder-specific abnormalities that may be tied to individual subcomponents of the DMN. To our knowledge, no empirical study has directly compared DMN connectivity across a range of clinical groups to test the specificity (or otherwise) of DMN disturbances. This would be an interesting avenue for future research.

In terms of the functional significance of DMN hypoconnectivity in CD, we hypothesize that this deficit may lead to impairments in self-referential processes that are required for empathy and moral decision-making in CD (i.e., judgments about the self and others). While this prediction has not been tested empirically, it may provide an alternative way of understanding the cognitive features of CD⁶⁷. For instance, a difficulty in accessing one's own mental states may hinder self-evaluative thinking that could lead to difficulties in learning from punishment⁶⁷ or impair affective empathy⁶⁸. Beyond social cognition, self-reflection is also an important factor in decision-making given that we frequently have to evaluate a set of possible outcomes before making our choices. Several studies have demonstrated that participants with CD have difficulties in adjusting their behavior following negative reinforcement⁶⁹, show altered sensitivity to gains or losses during choice evaluation⁷⁰, or discount the value of a reward more sharply with the delay of its receipt⁷¹. Collectively, these findings have been interpreted as reflecting a present-orientated mindset and a difficulty in prospection⁷²—the

ability to build mental representations of future events—which is thought to be mediated by the DMN.

The current study had several strengths, including a relatively large sample, detailed assessment of psychiatric symptoms including CD and ADHD, investigation of the impact of ADHD symptoms on DMN connectivity in CD, as well as conservative treatment of fMRI artifacts. However, there were also some limitations that need to be taken into account. First, a direct test of the impact of this pattern of altered DMN connectivity on self-referential cognitive processes was outside the scope of the current study. Nevertheless, there is a wealth of evidence suggesting that synchronization between the PCC and aMPFC occurs during tasks involving self-referential thought^{73,74}. Second, following Andrews-Hanna et al.¹¹, we placed seeds only in the left hemisphere of the brain. This could have limited our ability to detect group differences in the right hemisphere. Third, our analyses of the effects of ADHD symptoms on DMN connectivity would have been strengthened by including individuals with non-comorbid ADHD alone, as the nature of the present sample meant that CD and ADHD symptoms were positively correlated. Fourth, as the analysis was restricted to males, the results of this study may not generalize to female populations. Finally, group differences in IQ could have contributed to the hypo-connectivity findings that we obtained, although because we included IQ as a covariate of no interest and found no significant association between IQ and DMN connectivity, this interpretation seems unlikely.

In summary, as predicted, CD was associated with relatively reduced connectivity between anterior and posterior components of the core hub of the DMN. This effect was only present when controlling for comorbid ADHD symptoms. Furthermore, individual differences in psychopathic traits within the CD group were unrelated to DMN connectivity, and both childhood- and adolescence-onset CD subgroups appeared to show reduced DMN connectivity compared with typically-developing controls. We hypothesize that these group differences in DMN connectivity may contribute to the difficulties seen in CD in terms of empathy and social understanding.

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Legends for Figures:

Figure 1. Functional connectivity (Fisher z-transformed values) as a function of group status: closed circles show the healthy control group, and open circles show the conduct disorder (CD) group. Note: Participants with CD either: a) including participants with probable substance use disorders or b) excluding participants with probable substance use disorders showed reduced default mode network connectivity between the anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex (PCC) compared with healthy controls. Group differences in connectivity are significant at $p < .05$, false discovery rate (FDR) correction for all seed-to-target pairs or at an uncorrected threshold of $p < .01$.

Figure 2. Increased functional connectivity (Fisher z-transformed values) as a function of attention-deficit/hyperactivity disorder (ADHD) symptoms: closed circles show the healthy control group, and open circles show the conduct disorder (CD) group. Note: After controlling for group status, participants with high levels of ADHD symptoms show hyper-connectivity between the anterior medial prefrontal cortex (aMPFC) seed and two components of the default mode network (DMN): the posterior cingulate cortex (PCC) and the retrosplenial cortex (Rsp). Correlations between ADHD symptoms and connectivity are significant at $p < .05$, false discovery rate (FDR) correction for all seed-to-target pairs.

Table 1: *Default Mode Network Regions of Interest and Their Respective Montreal Neurological Institute (MNI) Coordinates*

Subsystem	Region	Abbreviation	MNI coordinates		
			X	Y	Z
Posterior cingulate- anterior medial prefrontal cortex core	Posterior cingulate cortex	PCC	-8	-56	26
	Anterior medial prefrontal cortex	aMPFC	-6	52	-2
Dorsomedial prefrontal cortex Subsystem	Dorsomedial prefrontal cortex	dMPFC	0	52	26
	Temporal parietal junction	TPJ	-54	-54	28
	Lateral temporal cortex	LTC	-60	-24	-18
	Temporal pole	TP	-50	14	-40
Medial temporal lobe (MTL) Subsystem	Ventral medial prefrontal cortex	vMPFC	0	26	-18
	Posterior inferior parietal lobule	pIPL	-44	-74	32
	Retrosplenial cortex	Rsp	-14	-52	8
	Parahippocampal cortex	PHC	-28	-40	-12
	Hippocampal formation	HF	-22	-20	-26

Table 2. *Demographic and Clinical Characteristics of the Sample.*

	CD Group (n=28)	Control Group (n=28)	<i>t-test</i>
Age (months)	198.38 (17.57)	196.45 (14.27)	.46
IQ	92.66 (10.15)	103.34 (10.22)	4.00*
Handedness	25R; 3L	25R; 3L	
ADHD symptoms ^a	7.93 (4.45)	0.69 (1.42)	8.34*
Psychopathic traits ^b	122.34 (22.00)	101.31 (15.79)	14.24*

Note. Values in parentheses show standard deviation. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder.

^aADHD symptoms derived from the ADHD supplement of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version.

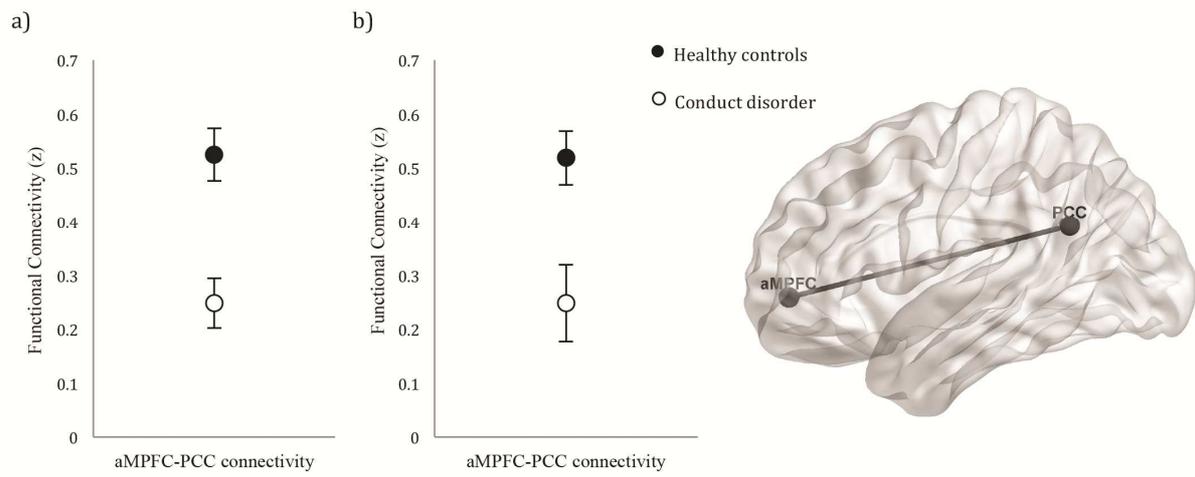
^bPsychopathic traits measured using the total score on the Youth Psychopathic traits Inventory.

* $p < .05$

Table S1: *Default Mode Network Connectivity Differences Observed When Controlling for Potential Confounding Factors*

Contrast	Connectivity	<i>t</i>	<i>P</i> _(uncorrected)
Main effects of CD group status, adjusting for age, IQ, and ADHD symptoms. Sixteen participants with probable SUDs (as assessed using the problem severity scale of the PESQ) excluded.	aMPFC-PCC	2.75	.009
	aMPFC-LTC	3.01	.004
Main effects of CD group status, adjusting for age, IQ, and ADHD symptoms. Seven participants with comorbid ADHD excluded.	aMPFC-PCC	3.57	.0008
Main effects of CD group status, adjusting for age, IQ, and ADHD symptoms. Six left-handed participants excluded.	aMPFC-PCC	3.13	.003

Note: ADHD = attention-deficit/hyperactivity disorder; aMPFC = anterior medial prefrontal cortex; CD = conduct disorder; LTC = lateral temporal cortex; PCC = posterior cingulate cortex; PESQ = Personal Experiences Screening Questionnaire (an indicator of risk for substance use disorders); SUDs = substance use disorders.



ACCEPTED MANUSCRIPT

