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Default mode network activity in male adolescents with conduct and substance use disorder☆

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ABSTRACT

Background: Adolescents with conduct disorder (CD) and substance use disorders (SUD) experience difficulty evaluating and regulating their behavior in anticipation of future consequences. Given the role of the brain's default mode network (DMN) in self-reflection and future thought, this study investigates whether DMN is altered in adolescents with CD and SUD, relative to controls.
Methods: Twenty adolescent males with CD and SUD and 20 male controls of similar ages underwent functional magnetic resonance imaging as they completed a risk-taking decision task. We used independent component analysis as a data-driven approach to identify the DMN spatial component in individual subjects. DMN activity was then compared between groups.
Results: Compared to controls, patients showed reduced activity in superior, medial and middle frontal gyrus (Brodmann area (BA) 10), retrosplenial cortex (BA 30) and lingual gyrus (BA 18), and bilateral middle temporal gryus (BA 21/22) – DMN regions thought to support self-referential evaluation, memory, foresight, and perspective taking. Furthermore, this pattern of reduced activity in patients remained robust after adjusting for the effects of depression and attention-deficit hyperactivity disorder (ADHD). Conversely, when not adjusting for effects of depression and ADHD, patients demonstrated greater DMN activity than controls solely in the cuneus (BA 19).
Conclusions: Collectively, these results suggest that comorbid CD and SUD in adolescents is characterized by atypical activity in brain regions thought to play an important role in introspective processing. These functional imbalances in brain networks may provide further insight into the neural underpinnings of conduct and substance use disorders.

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

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1. Introduction

1.1. Conduct and substance use disorder vulnerability

Conduct disorder (CD) and substance use disorder (SUD; DSM-IV, APA, 2000) are strongly comorbid (Disney et al., 1999) and prevalent in youth (Nock et al., 2006), with characteristics that reflect a failure of restraint and inhibition (Crowley et al., 2006; Crowley and Gelhorn, 2010). That failure could result from an inability to engage effectively in introspective processing; this trait may be identifiable by evaluating brain activation in the default mode network (DMN; Whitfield-Gabrieli and Ford, 2012). Therefore, we studied male adolescents in treatment for CD and SUD, seeking functional abnormalities in regions within DMN.

CD and SUD are comorbid manifestations of an underlying liability known as behavioral disinhibition (Kendler et al., 2011) that is highly heritable (i.e., heritability = ~0.8; Young et al., 2000). Adolescents with CD/SUD have functional and structural deficits in several critical regions of the decision-making network including those important for monitoring conflicting choices, emotional decision-making, and inhibition (Crowley et al., 2010; Dalwani et al., 2011). In addition to impairments in executive function, youth with CD/SUD and adults with antisocial phenotype, demonstrate atypical self-reflective, and self-evaluative behavior (Sharp, 2008; Fonagy and Target, 1997). However, we find no functional MRI data on this vulnerable CD/SUD population evaluating the specific DMN.

Children with CD, who lack self-reflection, may experience difficulties in adjusting their behavior based on past outcomes (Delfos, 2004). Individuals who lack the ability to reflect on the negative consequences of immoral actions may become predisposed to rule-breaking antisocial behavior (Raine and Yang, 2006). Adolescents with CD lack in episodic memory (Fairchild et al., 2011), an attribute needed to guide future thoughtful behavior by remembering one's past actions (Schacter et al., 2012).

The antisocial behavior characteristic of CD suggests impairments in social cognition or "theory of mind" (i.e., thinking about others or what others are thinking; Sharp, 2008). Research suggests that theory of mind is an important contributor to the development of antisocial behavior as it is a prerequisite to empathic responding, which facilitates the inhibition of antisocial behavior (Happé and Frith, 1996; Sharp, 2006, 2008). In sum, lack of self-reflection, introspection, internal mentation, theory of mind, and episodic memory are attributes that may lead to lack of remorse or guilt, callousness, and antisocial behavior – traits highly characteristic of CD/SUD youth.

1.2. Role of the default mode network (DMN)

The brain's DMN plays an important role in self-evaluative processing, social perspective-taking, episodic memory, internal mentation and future thought/foresight (Whitfield-Gabrieli and Ford, 2012; Andrews-Hanna, 2012). Though these processes can differentiate youths with CD/SUD from the general youth population, the DMN has yet to be explored in this patient population.

The DMN is a "functionally connected" network and is comprised of the following regions: medial prefrontal cortex (MPFC), medial and lateral parietal cortex, and temporal lobe (Greicius et al., 2003). DMN can be studied in fMRI paradigms that combine periods of rest and active stimuli (Sharp et al., 2011). Cognitively demanding tasks with short periods of rest or periods with low cognitive load, strongly recruit DMN, a high-level network, which shows increased blood oxygenated level dependent (BOLD) signal activation during periods of rest and reduced activation during periods of high cognitive demand (Buckner et al., 2008).

Relevant to SUD, atypical DMN has been reported in heroin-addicted adults (Ma et al., 2011), in prenatally cocaine-exposed adolescents (Li et al., 2011) and in alcoholic adults (Chanraud et al., 2011) in either resting-state functional MRI (fMRI), or in tasks needing cognitive involvement or during tasks with both. DMN alterations have been observed in individuals with major depression, attention-deficit hyperactivity disorder (ADHD), and other psychiatric disorders (Broyd et al., 2009), some of which are comorbid with CD/SUD. DMN has a strong overlap with brain areas involved in social cognition (Andrews-Hanna, 2012; Schilbach et al., 2008). Tang et al. (2013) recently showed decreased functional connectivity between regions of DMN and attention networks in antisocial personality disorder (ASPD) adults. The same study using data-driven classifier based on machine learning showed that the DMN made a sizeable contribution in discriminating ASPD from control subjects.

By showing improvement in aberrant functional connectivity, changes in DMN may help establish efficacy for treatment of psychiatric disorders (Tregellas et al., 2011; Tanabe et al., 2011). The DMN is a robust non-invasive biomarker, and a potential phenotype for molecular genetic studies and for brain pathology (Biswal et al., 2010; Glahn et al., 2010), distinguishes patients from controls (Broyd et al., 2009), and detects neuropathophysiological diseases (e.g., Koch et al., 2012), all of which could be applied to CD/SUD.

1.3. Study objectives

Given the relevance of the DMN for CD/SUD, we sought to evaluate DMN activity in male CD/SUD adolescents compared to non-affected controls on a rapid-event fMRI decision-outcome risk-taking paradigm. To identify the DMN, we used independent component analysis (ICA), a multivariate-based (i.e., all voxels analyzed at the same time) data-driven approach that separates independent components (brain networks) from a mixture (fMRI signal; McKeown et al., 1998). We predicted that DMN activity in male CD/SUD adolescents compared to controls would differ in the main DMN areas (medial prefrontal and parietal cortex, lateral parietal and temporal cortex).

2. Methods

We utilized this dataset previously to examine patient–control differences in fMRI signal change during risky and cautious decisions and their consequences and showed widespread hypoactivation in male CD/SUD adolescents compared to controls in several critical regions of the decision-making network (see Crowley et al., 2010).

2.1. Sample and inclusion/exclusion criteria

This study includes 20 patients (18 right-handed) and 20 controls (19 right-handed). All subjects were males, ages 14–18 years, with IQ ≥ 80 as estimated from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Inclusion criteria for controls were no CD nor SUD (DSM-IV, APA, 2000) except nicotine, no court convictions, no substance related arrests or treatment or school-expulsions, and no obvious psychosis or physical illness. Inclusion criteria for patients were enrollment in our university-based treatment program for serious CD and SUD; presence of serious conduct problems including symptoms of CD (e.g., theft, weapon fights) and at least one non-nicotine SUD diagnosis. Exclusion criteria for patients included psychosis, current high risk of suicide, violence, or fire-setting.

Both patients and controls were excluded if they or their parents lacked sufficient English skills for assenting or consenting or if they had non-prescribed substances present in urine (see Supplementary Material Section S1.a[8]) or saliva tested about 7 days before, and immediately before, scanning. Other exclusion criteria include marked claustrophobia, orthodontic braces, color blindness, contraindications to MR scanning (embedded metal, pacemakers, cochlear implants, etc.), history of head injury with loss of consciousness for more than 15 min, history of significant neurological illness or neurosurgery or a serious general medical disorder.

[8] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

2.2. Functional MRI paradigm: "Colorado Balloon Game"

While in the MRI, subjects played a rapid-event fMRI paradigm known as the "Colorado Balloon Game", consisting of trials with an active choice (risky/cautious) called "decision trials" with outcomes (wins/loss if risky; minimal compensation if cautious) and trials where the game directs the subject's response called "directed trials". The task included brief periods of rest and directed trials provided longer periods of minimal cognitive load (see Crowley et al. (2010) for detailed description of the task, its timing and payoff pattern).

2.3. Image acquisition

After training in a mock scanner, subjects performed the fMRI task in a 3T General Electric MRI scanner. The task consists of 3 sessions of 30 paired decision and directed trials. The echo-planar imaging (EPI) acquisition parameters were: TR = 2000 ms, TE = 26 ms, flip angle = 70°, FOV = 220 mm^2, 64^2 matrix, 36 slices, 4 mm thick, no gap, angled parallel to the planum sphenoidale. More details on image acquisition are provided in Supplementary Material Section S2[9].

2.4. ICA analyses

The EPI data were preprocessed using motion correction, co-registration to respective high-resolution structural image, normalization to the pediatric template in MNI space and smoothing with a 6 mm full-width-half-maximum gaussian kernel. Group ICA (using GIFT; http://mialab.mrn.org/software/gift/index.html) was then conducted on the preprocessed data separately on each group (Calhoun et al., 2008). Using the infomax algorithm (Bell and Sejnowski, 1995), we derived independent spatial networks activated during the task e.g. decision network, DMN, etc. with their respective temporal information (time course). Each subject's DMN component was identified as the component with the highest spatial correlation to a standard DMN mask (Pickatlas; http://fmri.wfubmc.edu/software/PickAtlas). Previous studies have utilized similar procedures (e.g., Tregellas et al., 2011). Supplementary Material Section S3[10] provides a detailed description of the ICA method.

2.5. Group comparisons and covariates

The *z*-score for every voxel was estimated by normalizing each voxel's intensity with respect to intensity of all the voxels in the DMN component. We use "DMN activity" to refer to the intensity (*z*-score) of the DMN signal. We first examined the pattern of DMN activation by conducting a whole-brain voxel-wise analysis using one-sample *t*-tests on the DMN component (spatial maps) for controls and patients separately. The DMN maps were compared between groups on a voxel-wise basis with a second-level ANCOVA in SPM5 adjusting for age and IQ. Statistical maps were set at a cluster-level threshold of $p < 0.05$ (97 voxels), corrected for multiple comparisons with family-wise error using AlphaSim Monte-Carlo simulations (Ward, 2000) and a voxel-level threshold of $p < 0.005$. Inclusive masking of the main effect ($p < 0.05$) was applied to ensure results reflected only DMN differences.

2.6. Rationale for using age and IQ as covariates

Age-dependent effects on DMN have been demonstrated before (Pyka et al., 2009) and in large meta-analytic studies (Biswal et al., 2010; Allen et al., 2011). Also, given the age-related brain development in these adolescent years (14–18 years; Lenroot et al., 2007; Giedd et al., 2009) we co-varied age. Intelligence may be associated with strength of connectivity in DMN (Ming et al., 2009), hence we also controlled for IQ.

2.7. Steps to validate DMN

We validated whether we correctly identified the DMN component. First, given the event-related design, we verified that DMN was active during periods of rest by evaluating the pattern of temporal activation of our DMN component (see Supplementary Fig. S3[11]). Second, parameterizing DMN time courses using multiple regression analyses we obtained association estimates (beta weights) between the DMN time course and the phases of the fMRI paradigm [i.e., risky decision, cautious decision, reward, loss, collect (after active decision), risky directed, cautious directed, reward, loss, collect (after directed instructions)]. These beta weights represented the degree of synchrony between DMN time course and the canonical hemodynamic response model, indicating whether or not the network represented in the component was engaged during that task phase (Supplementary Fig. S4a and b[12]). Third, we used spectral analyses to demonstrate that our DMN component was activated at low frequency (note: typical signature of DMN activity represents low-frequency BOLD fMRI signal changes; 0.012–0.1 Hz) in the resting brain (see Supplementary Fig. S5[13]). Details of these analyses are included in Supplementary Material Section S4[14].

2.8. Examining patient DMN activity with abstinence and task performance

In exploratory analyses, we examined within patients the association between DMN activity with length of abstinence (days) from substances (see Supplementary Fig. S6[15]) and separately the relationship between task performance (risk-taking, i.e., number of risky presses) and DMN activity using multiple regression analyses after adjusting for age and IQ (see Supplementary Fig. S7 and Supplementary Material Section S5[16]).

2.9. Secondary analyses

We conducted whole-brain analyses to examine group differences controlling for ADHD and depression. These disorders are more common in youths with CD/SUD than the general population (Crowley et al., 2001). We also separately examined three potential confounds by re-analyzing our data after excluding 3 left-handed subjects (2 patients, 1 control), and excluding 7 recent tobacco smokers (6 patients, 1 control), and excluding subjects taking prescribed medication (6 patients, 4 controls) around the time of scanning. Description of prescribed medications by subjects can be found in Supplementary Section S1.b. Similar to our primary analyses, secondary analyses were adjusted for age and IQ.

3. Results

Demographics, and diagnostic patient–control sample comparisons are included in Table 1. As expected, patients differed significantly on various clinical measures including severity of ADHD, depression, IQ and SES.

3.1. Single group analyses on DMN

DMN activity was observed in both controls and patients in the [*x*, *y*, *z*] co-ordinates reported in Supplementary Table S1 and Figs. S1 and S2[17]). Group results were identical before and after running a bootstrapping procedure that runs group ICA repeatedly for fixed number of iterations (ICASSO, see Supplementary Material Section S3[18]), suggesting reliability in component selection (Average stability index for all the components: controls: mean ± SD = .977 ± .007; patients: mean ± SD = 978 ± .005).

3.2. Group comparison on DMN, adjusting for age and IQ

3.2.1. Contrast: controls > patients. Whole-brain voxel-wise group comparison showed significantly less activation in patients in frontal regions within the DMN, including bilateral superior, middle and medial frontal gyrus (BA10) and in other DMN regions such as bilateral middle temporal gyrus (BA21) and the retrosplenial cortex (BA30; Fig. 1 and Table 2).

[9] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[10] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[11] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[12] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
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[16] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[17] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[18] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

Table 1
Comparison of characteristics of patients and controls.[a]

	Controls ($n=20$)	Patients ($n=20$)	Test statistic	p-Value
Demographics				
Age (mean(SD))	16.5 (1.6)	16.5 (1.0)	$t=0.003$	0.99
Race				
Caucasian (n)	15	12	$\chi^2=1.03$	0.31
Non-Caucasian (n)	5	8		
Education				
Highest-grade comp. (mean(SD))	9.70 (1.69)	9.15 (0.98)	M-W-U = 158.5	0.25
Ever repeated grade (n)	1	6	Fisher's exact	0.09
Clinical measures				
IQ full-scale (SD)	104.9 (9.0)	97.3 (8.9)	$t=2.67$	0.01
Carroll Rating Scale (SD)	4.1 (3.8)	8.5 (6.7)	M-W-U = 106.5	0.01
Attention deficit hyperactivity problems t-score[b]	53.5 (4.5)	58.3 (8.2)	$t=2.28$	0.002
Impulsivity, aggression and conduct disorder				
Eysenck Impulsivity Scale (SD)	6.7 (4.5)	11.9 (6.0)	$t=6.84$	0.004
Aggression score	0.5 (1.1)	5.7 (3.2)	M-W-U = 40.5	<0.001
Lifetime CD diagnosis (n)	1	19	$\chi^2=36.1$	<0.001
Substance use disorders (SUD)				
SUD symptoms across drugs (SD)	0.2 (0.67)	12.4 (7.2)	M-W-U = 2.0	<0.001
Alcohol abuse	0	8	Fisher's exact	<0.004
Alcohol dependence	0	8	Fisher's exact	<0.004
Amphetamine dependence	0	2	Fisher's exact	NS
Cannabis abuse	0	7	Fisher's exact	<0.009
Cannabis dependence	0	10	$\chi^2=13.33$	0.0003
Club drugs abuse	0	3	Fisher's exact	NS
Club drugs dependence	0	4	Fisher's exact	NS
Cocaine abuse	0	2	Fisher's exact	NS
Cocaine dependence	0	2	Fisher's exact	NS
Hallucinogen abuse	0	2	Fisher's exact	NS
Hallucinogen dependence	0	1	Fisher's exact	NS
Tobacco dependence	1	13	$\chi^2=15.82$	<0.0001

SD = standard deviation; IQ = intelligence quotient measured by the two subtests from the Wechsler Abbreviated Scale of Intelligence; Carroll Rating Scale score of ≥10 is suggestive of clinical depression; CD diagnosis = at least three lifetime DSM-IV conduct disorder symptoms; n = count (total number); SUD = substance use disorder; t = t-value for the t-test; χ^2 = Chi-square test (without the Yates' continuity correction); M-W-U = Mann–Whitney-U.

[a] Groups were compared based on appropriate statistical tests based on normality.

[b] For attention deficit hyperactivity problem t-score missing Child Behavioral CheckList (Achenbach, 1991a) score for one patient was replaced by Youth Self Report score (Achenbach, 1991b) IQ reported in Crowley et al. (2010) has two typos that have been addressed in this manuscript (i) Patient IQ score instead of 97.1(9.3) is 97.3(8.9) and (ii) the IQ full-scale t-score is IQ full-scale.

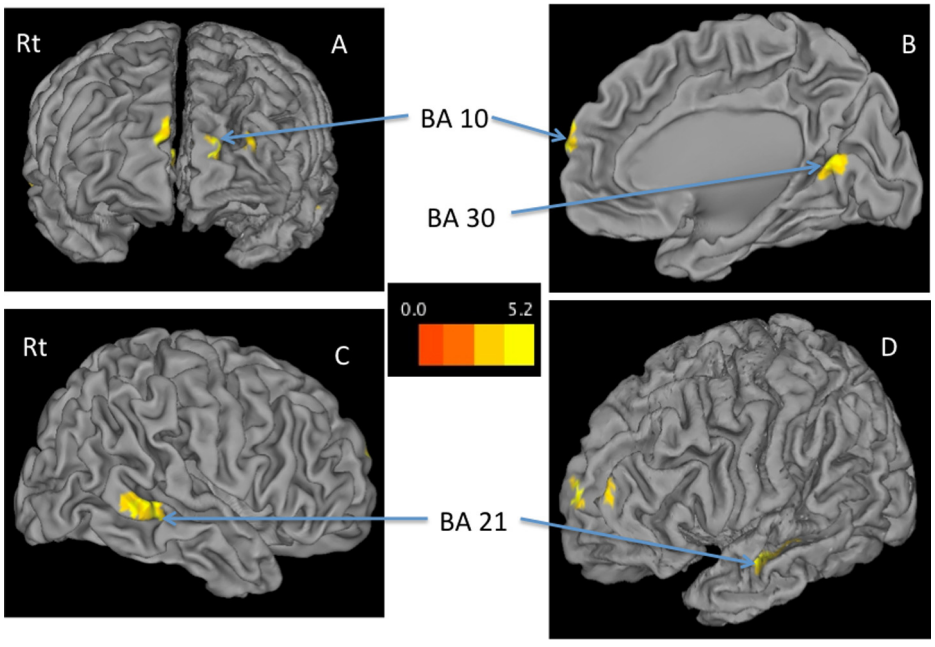

Fig. 1. Control > patient DMN activity. Statistical map set at a family-wise error corrected cluster-level threshold of $p < 0.05$ and overlaid on 3-D SPM template using CARET. (A) Frontal view in radiological convention (Rt = right); (B) right medial surface; (C) right lateral surface; (D) left lateral surface; BA = Brodmann area. Controls showed more activity than patients in superior and middle frontal gyrus (BA10), retrosplenial cortex (BA30), lingual gyrus (BA18) and middle temporal gyrus (BA21,22)

Table 2
Regions in which group significantly differed in default mode network.[A,B]

Controls > patients							Patients > controls						
Structure	BA or side[C]	Cluster size	Maximum activation[D]				Structure	BA or side[C]	Cluster size	Maximum activation[D]			
			x	*y*	*z*	*t*				*x*	*y*	*z*	*t*
Sup. Fr. Gy.[E]	R,L 10	191[E]	−10	68	14	5.4	Cuneus	L 19	128	−18	−90	36	4.6
Mid. Fr. Gy.[E]	L 10		−30	60	12	2.8	Cuneus	R 19	171	14	−88	34	3.9
Med. Fr. Gy.[E]	L 10		−6	66	10	2.9							
Retrospl. cortex[E]	R,L 30	262[E]	−2	−68	6	4.0							
Lingual Gy.[E]	R,L 18		8	−64	4	4.2							
Mid. temp. Gy.[E]	R 21	178[E]	58	−46	−2	6.0							
Mid. temp. Gy.[E]	R 22		66	−46	4	3.8							
Mid. temp. Gy.	L 21	129	−54	−6	−18	5.1							
Total activated voxels		760							299				

Abbreviations: BA: Brodmann area; Fr: frontal; Gy: gyrus; Med: medial; Mid: middle; Retrospl: retrosplenial; Sup: superior; Temp: temporal.
[A] Procedure for determining significance: whole brain cluster-wise family-wise error correction ($p_{corr} < 0.05$).
[B] Analyses procedure examined: ANCOVA (adjusted for age and IQ).
[C] If bilateral, the larger maximum is shown.
[D] Montreal Neurological Institute coordinates, mm from anterior commissure.
[E] Regions bearing comprise one activated cluster.

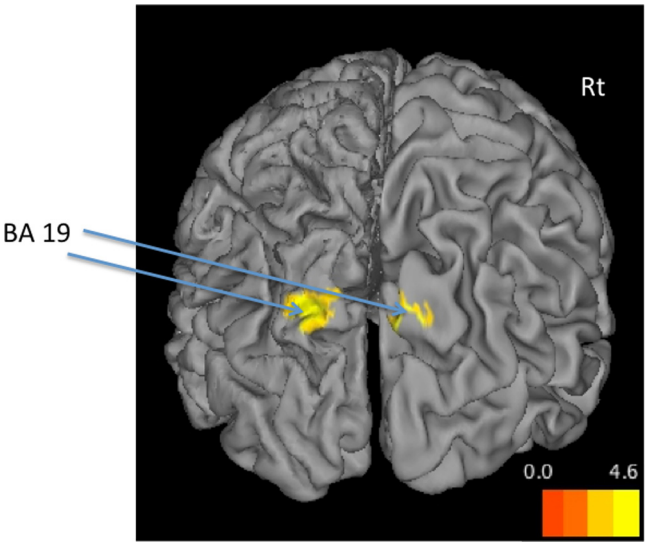

Fig. 2. Patient > control DMN activity. Statistical map set at a family-wise error corrected cluster-level threshold of $p < 0.05$ and overlaid on 3-D SPM template using CARET. The figure shows the back view of the surface (Rt = right); BA: Brodmann area. Patients showed more activity than controls in the cuneus region (BA19).

3.2.2. Contrast: patients > controls. As shown in Table 2 and Fig. 2, patients showed significantly increased activation in the bilateral cuneus near BA19, extending into the posterior precuneus.

Figs. 3 and 4 illustrate the activity of all subjects in the regions with patient–control difference.

3.3. Within patient DMN activity vs. abstinence and task performance

Exploratory analyses show that longer period of abstinence was associated with increased DMN activity in two regions (clusters): left superior, middle and medial frontal gyrus (BA9,10) ($t = 4.8$, df = 16, $r = 0.77$) and right superior, medial frontal gyrus (BA10) and anterior cingulate (BA32) ($t = 6.2$, df = 16, $r = 0.84$). Lower DMN activity was associated with greater risk-taking in one region (cluster): cuneus and lingual gyrus (BA18), precuneus (BA30) and posterior cingulate (BA31) ($t = -4.24$, df = 18, $r = -0.71$) (see Supplementary Material Section S5 and Supplementary Figs. S6 and S7[19]).

3.4. Examining effect of potential confounders

After adjusting for ADHD and depression scores, patients still demonstrated significantly reduced activity compared to controls within a similar set of regions as observed in Fig. 1 (see results on SPM's glass brain in Supplementary Fig. S8[20]). But no regions exhibited significantly increased activation in patients compared to controls. Even after excluding smokers, left handers, and medicated subjects there was still a similar patterns of greater DMN activity in controls vs. patients (see Supplementary Fig. S8[21]).

4. Discussion

Our primary goal was to identify and compare DMN activity in male CD/SUD adolescents and controls when engaged in a rapid-event fMRI task that involved decision-making, outcomes, short periods of rest (fixations) and relatively longer periods of minimal cognitive load (directed trials).

Both groups exhibited typical DMN activation patterns consistent with prior literature in adults (Buckner et al., 2008) and adolescents (Lagioia et al., 2010). As hypothesized, patients exhibited reduced DMN activity compared to controls in several DMN regions (see Fig. 1, Table 2) and this pattern changed minimally (1) after adjusting for ADHD and depression, the common comorbidities in our patients and (2) after separately excluding recent smokers, left handed and medicated subjects (see Supplementary Fig. S8[22]). Conversely, patients only showed more activation than controls in the posterior precuneus/cuneus (Fig. 2) and that difference was no longer significant after adjusting for ADHD and depression or after we excluded recent smokers. However, as a caveat, our approach of excluding subjects to assess possible contributions of confounding variables reduces our power to detect such differences.

[19] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[20] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[21] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[22] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

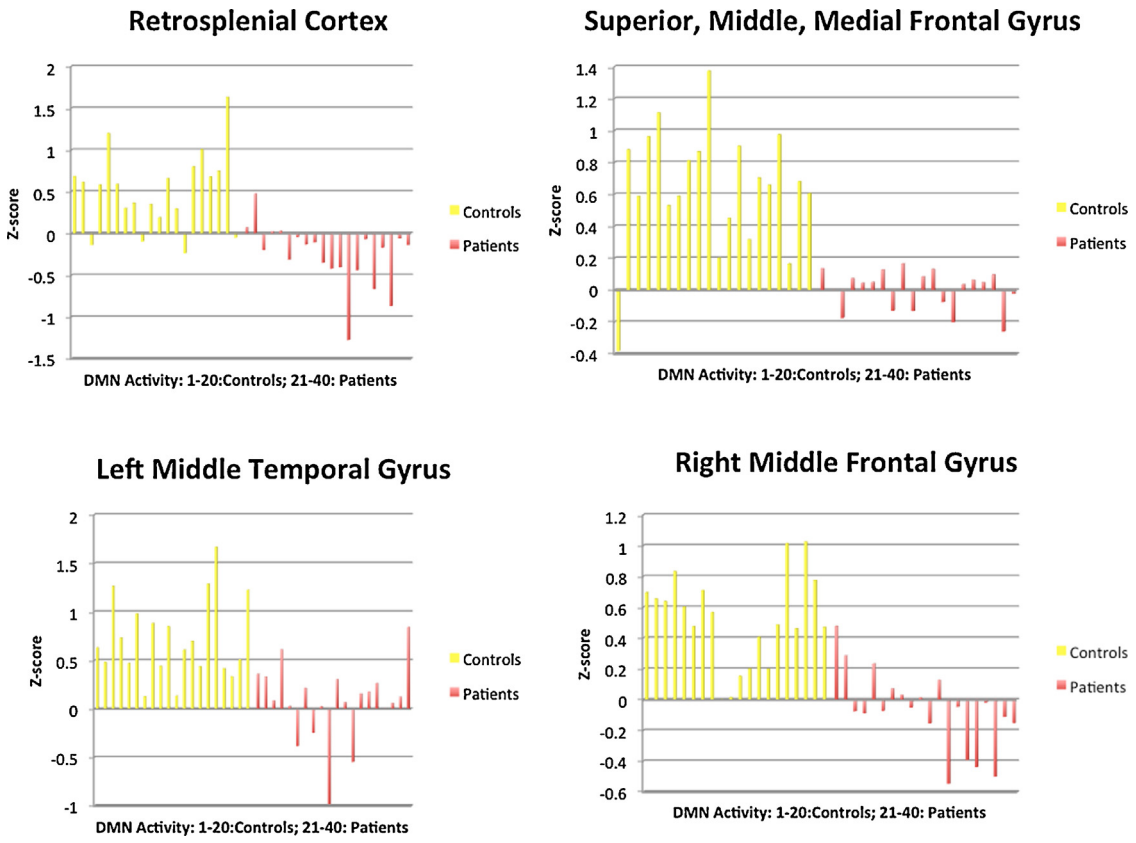

Fig. 3. Individual DMN activity *z*-scores for control > patient. Activity (*z*-scores) in regions where controls show greater DMN activity than patients. The yellow bars represent DMN activity in controls and the red bars represent DMN activity in patients.

4.1. Lower DMN activity in patients vs. controls

4.1.1. Medial prefrontal cortex (MPFC). The DMN plays an important role in internally-directed thought (Buckner et al., 2008), becomes engaged when an individual's mind wanders about thoughts unrelated to the task at hand (Christoff et al., 2009), and activates during experimentally-directed tasks that are of an internally-focused, introspective nature (Andrews-Hanna, 2012). Furthermore, the DMN demonstrates reciprocal relationships with task difficulty during externally-directed tasks (Mason et al., 2007). Pyka et al. (2009) explanation that increased DMN activity following increased cognitive load (in a working-memory paradigm) is due to increased subsequent self-evaluation and reflection of preceding events, supports our proposal that patients may be less likely to engage in self-reflective activity in a conflicting decision paradigm requiring regular cognitive load than their non-affected peers. The anterior MPFC may play a particular role in self-reflective and evaluative thought, as it becomes engaged across a variety of tasks requiring individuals to reference information to one's self or close others (e.g. Northoff et al., 2006; Andrews-Hanna, 2012).

4.1.2. Retrosplenial cortex. The retrosplenial cortex is part of a "medial temporal lobe (MTL) subsystem" within the DMN, which is thought to play a role in retrieving information from the past to

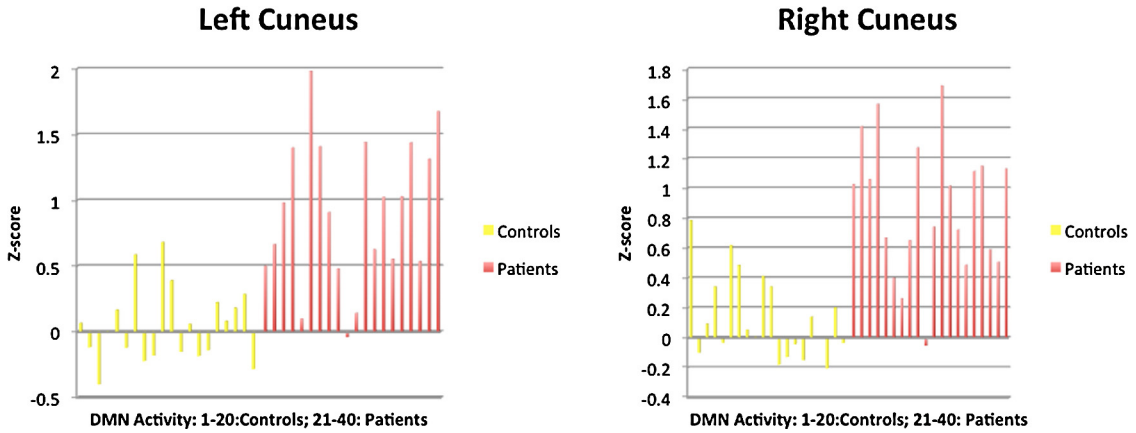

Fig. 4. Individual DMN activity *z*-scores for patient > control. Activity (*z*-scores) in regions where patients show greater DMN activity than controls. The yellow bars represent DMN activity in controls and the red bars represent DMN activity in patients.

construct mental models of what the future might hold (Buckner et al., 2008). This subsystem activates when individuals are instructed to remember their past and imagine their future using imagery-based simulation (Andrews-Hanna et al., 2010b). Furthermore, resting-state functional connectivity between regions within the MTL subsystem correlates with individual differences in spontaneous episodic memories and plans (Andrews-Hanna et al., 2010a). These findings might reflect patients being less able to utilize recollections about past behaviors and consequences when making decisions about future behaviors. This inability to use the past to guide future decisions may reduce their ability to think about the consequences of current drug use, especially in regards to past negative outcomes.

4.1.3. Lateral temporal cortex. DMN regions have also been activated in social cognition (Schilbach et al., 2008). The lateral temporal cortex is part of a "dorsal MPFC (dMPFC) subsystem" that becomes engaged during tasks involving mentalizing or theory of mind (Andrews-Hanna, 2012). The dMPFC subsystem is altered in psychological disorders associated with aberrations in social functions, including autism (Kennedy et al., 2006), schizophrenia and social phobia (Gentili et al., 2009). Alterations in these regions could therefore contribute to antisocial behaviors or tendencies in patients.

4.2. Greater DMN activity in patients vs. controls

When not adjusting for ADHD and depression, patients showed more DMN activity than controls near the bilateral cuneus, with activation overlapping the posterior zone of the precuneus and extending along the visual prestriate cortex into the dorsal lateral occipital region. Though these regions are included in the DMN mask, resting-state functional connectivity and anatomical tracing studies suggest these regions exhibit different patterns of connectivity than MPFC, posterior cingulate and lateral parietal regions (Andrews-Hanna et al., 2010a). Specifically, the posterior precuneus/cuneus connects to extrastriate regions, posterior fusiform, and lateral prestriate cortex (Margulies et al., 2009). Consistent with their pattern of projections, these regions activate during tasks involving visuo-spatial imagery, broad visual attention, and mental imagery associated with episodic memory retrieval (Andrews-Hanna et al., 2010b). After adjusting for ADHD and depression, there were no regions where patients showed significantly more DMN activity than controls. This change in cuneus (BA19) findings could indicate this DMN characteristic is related to these comorbidities (Grimm et al., 2009). For example, Cao et al. (2006) showed increased regional homogeneity (a measure of functional connectivity) in occipital cortex and the cuneus regions and decreased regional homogeneity during resting-state fMRI in various frontal regions in boys (mean age 13.3 years) with ADHD.

4.3. DMN activity in a stimulus-oriented vs. resting-state fMRI paradigm

Group differences may be driven by task-related or task-unrelated alterations in the DMN (Singh and Fawcett, 2008). Other studies have used ICA to extract the DMN component across task periods (Pyka et al., 2009; Li et al., 2011; Esposito et al., 2006). DMN (or intrinsic activity) have been assessed across task performance (Fair et al., 2007; Fox and Raichle, 2007; Garrity et al., 2007; Meda et al., 2009). Smith et al. (2009) compared ICA-defined resting-state networks with fMRI networks showing consistent co-activation during task performance (using the activation maps of experiment included in the online BrainMap database (www.brainmap.org)) and showed remarkable similarity between the task-based and resting-state functional connectivity networks.

To investigate this issue, we extracted the spectral power information of the DMN component for every subject (see Supplementary Material Section S4.c[23]). Consistent with prior ICA studies that examine DMN activity in the absence of an overt task (i.e., at rest), the DMN component in our study exhibited the highest spectral power in the low-frequency bin (0–0.04 Hz) for both groups (Supplementary Fig. S5[24]). However, the average time course of the DMN component (see Supplementary Material Section S4.a[25]) also suggests higher activity for both groups during fixation trials and during less cognitively demanding periods such as following directions versus making decisions (Supplementary Fig. S3[26]). We also conducted multiple regression analyses fitting the DMN time course with various phases of the task [i.e., risky decision, cautious decision, reward, loss, collect (after active decision), risky directed, cautious directed, reward, loss, collect (after directed instructions)] and the beta estimates clearly suggest that the DMN activity for both groups and all conditions consistently showed higher DMN activity during directed (or inactive) phase, where subjects are mostly following simple instructions, compared to the decision (or active) phase, where subjects are more cognitively involved (see Supplementary Material Section S4.b and Supplementary Fig. S4a and b[27]). Thus, it is possible that group changes in DMN activity are driven by a combination of low-frequency fluctuations unrelated to the task as well as changes induced by the task itself. Future studies examining group differences in DMN activity during a pure resting-state paradigm may help differentiate these possibilities.

4.4. Relation of DMN in patient with abstinence and task performance

DMN activity in frontal cortex (i.e., superior, middle, medial frontal gyrus and anterior cingulate) showed a positive association with abstinence from substances. Improved DMN activity with treatment has been shown before (Tregellas et al., 2011; Tanabe et al., 2011).

DMN activity in posterior cingulate, lingual gyrus, cuneus and precuneus showed a negative association with greater risk-taking. Clearly, these exploratory analyses highlight the importance of studying DMN, which could be a clinical phenotype for patients with CD/SUD. However, these exploratory analyses do not suggest causality and more work needs to be done with a larger sample to understand the intricacies of DMN functioning.

4.5. Relation between DMN and the decision-network

We previously reported in this sample hypoactivation in various critical regions of the decision-making network in patients compared to controls (Crowley et al., 2010) and in this study we report hypoactivation in the DMN in patients compared to controls. Together, these findings suggest that patients show impaired brain activity during decision-making and inhibition and diminished activity during self-evaluation, introspection and retrieval of memory from past actions. Tang et al. (2013) recently showed poor functional connectivity between DMN

[23] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[24] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[25] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[26] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[27] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

and attention networks in subjects with antisocial personality disorder (age = 20.52 ± 1.37years) compared with controls (age = 21.67 ± 2.54years). More work is needed to address functional connectivity between different networks in adolescent CD/SUD patients.

4.6. Clinical implications

DMN is a robust non-invasive biomarker, and a potential phenotype for molecular genetic studies and for brain pathology (Biswal et al., 2010; Glahn et al., 2010), distinguishes patients from controls (Broyd et al., 2009), is associated with risk-taking in our task and detects neuropathophysiological diseases (e.g., Koch et al., 2012). DMN may be sensitive to abstinence and showed improvement by therapeutic intervention (Tregellas et al., 2011; Tanabe et al., 2011). Tang et al. (2013) using a data-driven classifier method based on machine learning, recently showed that the DMN made a sizeable contribution in discriminating ASPD from control subjects.

These studies support the clinical importance of studying DMN in CD/SUD adolescents. Furthermore, by studying DMN during a task we answer an important clinical question of whether other brain networks such as DMN also differ along with decision networks (Crowley et al., 2010) during a decision-making task.

4.7. Strengths and limitations

Results from this male-only study cannot be generalized to female adolescents. Our cross-sectional study cannot determine whether differences in DMN activity between patients and controls predate the onset of substance abuse or resulted from repeated exposure to illicit substances, alcohol and nicotine. However, in our sample no youth had currently used either nicotine or other drugs for at least a week before scanning and in some cases for up to two months. Finally, it is important to understand the nature of DMN alterations in patients and controls during effortful tasks and during the resting-state. DMN interaction with other resting-state networks and other networks responsible for cognitive and executive control such as attention and inhibitory networks could highlight certain other aspects of neural disorganization in patients. These efforts may eventually lead to candidate sites for possible therapeutic intervention.

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Contributors

Authors Crowley, Banich, and Sakai are responsible for study design and in decisions involving patient sample, inclusion and exclusion criteria; authors Dalwani and Raymond were responsible in overseeing the MRI procedures, and data collection; authors Dalwani and Tregellas were responsible for data analyses procedures and running ICA analyses, author Dalwani wrote the first draft and author Andrews-Hanna assisted in overall manuscript and constructed some sections in the discussion; authors Dalwani and Mikulich-Gilbertson were responsible for statistical analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Crowley received travel support from the American Psychiatric Association to participate in revising the Diagnostic and Statistical Manual of Mental Disorders (DSMV). Dr. Sakai received reimbursement in 2012 for completing a policy review for the WellPoint Office of Medical Policy & Technology Assessment (OMPTA), WellPoint, Inc., Thousand Oaks, CA. He also serves as a board member of the ARTS Foundation. The other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2013.10.009.

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