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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.