



Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence

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ABSTRACT

Background: Individuals with drug addictions report increased willingness to approach rewards. Approach behaviors are thought to involve executive control processes and are more strongly represented in the left compared to right prefrontal cortex. A direct link between approach tendencies and left hemisphere activity has not been shown in the resting brain. We hypothesized that compared to controls, substance dependent individuals (SDI) would have greater left hemisphere activity in the left executive control network (ECN) at rest.

Methods: Twenty-five SDI and 25 controls completed a Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) questionnaire and underwent a resting-state fMRI scan. Group independent component analysis was performed. We used template matching to identify the left and right ECN separately and compared the corresponding components across groups. Across group, BAS scores were correlated with signal fluctuations in the left ECN and BIS scores with right ECN.

Results: BAS scores were higher in SDI compared to controls ($p < .003$) and correlated with signal fluctuation in the left ECN. SDI showed significantly more activity than controls in the left prefrontal cortex of the left ECN. Conversely, SDI showed less activity than controls in the right prefrontal cortex of the right ECN.

Conclusions: Results from this study suggest that approach tendencies are related to the left ECN, even during rest. Higher resting-state signal in the left ECN may play a role in heightened approach tendencies that contribute to drug-seeking behavior.

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1. Introduction

Personality traits such as impulsivity, sensation-seeking, and heightened willingness to approach rewarding events may predispose individuals to initiate drug use (Hanson et al., 2008; Teichman et al., 1989). Gray's theory of personality proposes two opposing constructs affecting motivation: the behavioral activation system (BAS) and the behavioral inhibition system (BIS) (Gray, 1987). The BAS is sensitive to positive or appetitive outcomes (i.e., approach), while the BIS inhibits behavior that may lead to negative or aversive outcomes (i.e., avoidance) (Carver and White, 1994). Carver and White (1994) developed a psychometric instrument to measure such traits: the BIS/BAS scales. This measure has repeatedly shown differences between healthy individuals and those with

psychological disorders. For example, individuals with substance abuse or dependence disorders (Franken et al., 2006; Knyazev, 2004; Simons et al., 2009; van Toor et al., 2011), score higher than controls on BAS, suggesting that these individuals are more likely to approach what they deem to be rewarding, even if those rewards are associated with negative consequences (e.g., seeking drugs because they lead to a "high" even though it can lead to loss of friend or a job). In contrast, individuals with anxiety disorders (Johnson et al., 2003; Torrubia and Tobena, 1984), depression (Johnson et al., 2003), and anorexia nervosa (Harrison et al., 2010) score higher than controls on BIS, suggesting that these individuals are motivated to avoid negative outcomes (e.g., not eating food to avoid gaining weight). Together, these studies suggest that personality differences in the tendency to approach rewards or the tendency to avoid negative outcomes may be linked to vulnerabilities for specific psychopathologies such as substance dependence.

Functional neuroimaging investigations into the neural correlates of approach behaviors have mainly implicated the striatum and left dorsolateral prefrontal cortex (DLPFC; Barros-Loscertales

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et al., 2006b, 2010; Spielberg et al., 2011) where those of avoidance behaviors suggest that right DLPFC, hippocampal formation, amygdala, and anterior cingulate are involved (Amodio et al., 2008; Barros-Loscertales et al., 2006a; Spielberg et al., 2011; Torrubia and Tobena, 1984). While the DLPFC is involved in both approach and avoidance, these studies suggest hemispheric asymmetry with the left DLPFC more strongly associated with approach and the right DLPFC with avoidance (Heller, 1993; Spielberg et al., 2011).

The neural correlates of the approach and avoidance systems have been predominantly studied using task-based fMRI. Here we extend these studies by examining the relationship between these traits and resting-state brain activity in substance dependent individuals (SDI). The term “activity” used here refers to the strength or amplitude of the signal corresponding to the spatially independent network of interest. Recognizing that the meaning of the term may differ depending on the context (i.e., task-based or non-task based) “activity” is preferred over “connectivity” because the latter is often, although not exclusively, used in the context of seed-based analyses.

Several resting-state networks have been identified, the most extensively studied being the Default Mode Network (DMN), shown to deactivate during task performance and activate during internal mentation (Broyd et al., 2009; Raichle et al., 2001; Vincent et al., 2008). Another resting-state network which might be viewed as particularly pertinent to the field of substance dependence is the executive control network (ECN), thought to be involved in goal-directed behavior and cognitive control (Seeley et al., 2007; Spreng et al., 2010; Sutherland et al., 2012; Vincent et al., 2008). The enhanced motivation to seek and take drugs combined with an inability to inhibit drug-related behaviors are thought to represent a failure of executive control (Barros-Loscertales et al., 2011; Goldstein and Volkow, 2002; Volkow et al., 2011). We propose that the executive control resting-state network allows an investigation of neural mechanisms of approach and avoidance in SDI. Like the approach and avoidance systems, the ECN has been shown to have separable right and left hemisphere components (Damoiseaux et al., 2006; Habas et al., 2009; Seeley et al., 2007; Shirer et al., 2012). Since the approach system is associated with the left DLPFC and SDI typically demonstrate increased willingness to approach rewards, we hypothesized that SDI would have greater activity than controls in the left ECN. Second, we hypothesized that across all subjects approach ratings would be associated with higher left ECN and BIS with higher right ECN activity.

2. Materials and methods

2.1. Participants

Twenty-five drug abstinent SDI were recruited from the University of Colorado Denver's Addiction Research and Treatment Services (ARTS) program, a gender-specific long-term residential treatment program. Drug abstinence was monitored by observation and random urine screens at the treatment center. The mean duration of self-reported abstinence for all drugs was 1.43 years across all SDI participants. The inclusion criterion was dependence on stimulants (methamphetamine, cocaine or crack) according to the *DSM-IV*. Most SDI were also dependent on other drugs, most commonly tobacco, alcohol, and cannabis (Table 1). Twenty-five controls were

recruited from the community through newspaper ads, flyers, a marketing company, and a database of community members interested in participating in research. Controls were excluded if they met criteria for dependence on any drug or alcohol. Nicotine dependence was not exclusionary. Exclusions were history of head trauma with loss of consciousness exceeding 15 min, neurological illness, schizophrenia, bipolar disorder, current major depression (within the last 2 months). Handedness was determined through self-report. All participants provided written informed consent approved by the Colorado Multiple Institutional Review Board.

2.2. Structured interviews

2.2.1. Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM). This computerized structured interview (Cottler et al., 1989, 1995) was administered to characterize the substance dependence diagnoses of SDI and to ensure that controls did not meet criteria for dependence diagnoses on substances other than tobacco. Results from the interview provide *DSM-IV* diagnoses for eleven substances: amphetamines, cocaine, marijuana, alcohol, tobacco, hallucinogens, opioids, inhalants, sedatives, club drugs, and PCP.

2.2.2. Diagnostic Interview Schedule – Version IV (DIS-IV). This computerized structured interview provides diagnostic and symptom information about psychiatric diagnoses according to the *DSM-IV* (Robins et al., 2000). Three modules were administered to exclude participants with schizophrenia, bipolar disorder, or current major depression.

2.3. Questionnaire

2.3.1. Behavioral Inhibition and Activation Scale (BIS/BAS). This 20 item self-report scale measures approach (BAS) and avoidance (BIS) personality traits (Carver and White, 1994). The BAS is divided into three subscales: a persistent pursuit of desired goals (drive), a desire for new rewards and willingness to approach a potentially rewarding event on the spur of the moment (fun-seeking), and a positive response to the occurrence or anticipation of reward (reward responsiveness). A higher score indicates a greater level of that particular trait. BIS is not subdivided, but the questions reference reactions to the anticipation of a punishment.

2.4. MRI acquisition and preprocessing

2.4.1. MRI acquisition. Images were acquired using a 3T whole body MR scanner (General Electric, Milwaukee, WI, USA) with an 8-channel head coil. A high-resolution 3D T1-weighted anatomic scan was collected. One-hundred fifty resting-state functional scans were acquired with the following parameters: TR 2000 ms, TE 30 ms, FOV 220 mm², matrix 64 × 64, voxel size 3.44 mm × 3.44 mm × 4 mm, slice thickness 3 mm, gap 1 mm, interleaved, flip angle 70°. Resting fMRI scan duration was 5 min. Participants were instructed to close their eyes, not think of anything in particular, and not fall asleep. Head motion was minimized using a VacFix head-conforming vacuum cushion (Par Scientific A/S, Odense, Denmark).

2.4.2. MRI data analysis. fMRI data were pre-processed using SPM8 (Wellcome Dept. of Imaging Neuroscience, London, UK) running on Matlab R2011a. The first four images were excluded for saturation effects. Images were realigned to the first volume, normalized to the Montreal Neurological Institute (MNI) space, and spatially smoothed with a 6-mm FWHM Gaussian kernel.

Spatial independent component analysis (ICA) was performed using GIFT software v1.3i (<http://icatb.sourceforge.net>; Calhoun et al., 2001). ICA is a model-free technique that identifies spatially independent sources of blood-oxygen-level-dependent signal variations. ICA is a robust method that can investigate overall brain organization and has been particularly useful in task-free settings. The identified sources, or components, can then be compared across different groups. Group ICA was conducted separately for the SDI and control group, as has been performed previously in the literature (Gao et al., 2009; Sorg et al., 2007; Tregellas et al., 2011). The dimensionality of the data from each subject was reduced using principal component analysis and concatenated into an aggregate data set, then back-reconstructed

Table 1
Drug use for all participants.

Drug	Controls			SDI		
	Number dependent (% of total)	Duration (years)	Last use (years)	Number dependent (% of total)	Duration (years)	Last use (years)
Stimulants	0	–	–	25 (100%)	12.4 (7.9)	4.0 (4.7)
Tobacco	4 (16%)	16.5 (9.9)	3.8 (4.8)	19 (76%)	19.7 (8.9)	0.7 (1.9)
Alcohol	0	–	–	15 (60%)	18.8 (8.7)	2.6 (2.7)
Cannabis	0	–	–	10 (40%)	15.2 (9.5)	3.2 (2.6)
Opioids	0	–	–	6 (24%)	6.2 (6.4)	4.0 (4.7)
Club drugs	0	–	–	3 (12%)	5.7 (3.2)	5.1 (4.1)
Hallucinogens	0	–	–	2 (8%)	8.0 (4.2)	11.0 (4.2)

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