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Cocaine dependence and thalamic functional connectivity: a multivariate pattern analysis

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ABSTRACT

Cocaine dependence is associated with deficits in cognitive control. Previous studies demonstrated that chronic cocaine use affects the activity and functional connectivity of the thalamus, a subcortical structure critical for cognitive functioning. However, the thalamus contains nuclei heterogeneous in functions, and it is not known how thalamic subregions contribute to cognitive dysfunctions in cocaine dependence. To address this issue, we used multivariate pattern analysis (MVPA) to examine how functional connectivity of the thalamus distinguishes 100 cocaine-dependent participants (CD) from 100 demographically matched healthy control individuals (HC). We characterized six task-related networks with independent component analysis of fMRI data of a stop signal task and employed MVPA to distinguish CD from HC on the basis of voxel-wise thalamic connectivity to the six independent components. In an unbiased model of distinct training and testing data, the analysis correctly classified 72% of subjects with leave-one-out cross-validation ($p < 0.001$), superior to comparison brain regions with similar voxel counts ($p < 0.004$, two-sample t test). Thalamic voxels that form the basis of classification aggregate in distinct subclusters, suggesting that connectivities of thalamic subnuclei distinguish CD from HC. Further, linear regressions provided suggestive evidence for a correlation of the thalamic connectivities with clinical variables and performance measures on the stop signal task. Together, these findings support thalamic circuit dysfunction in cognitive control as an important neural marker of cocaine dependence.

1. Introduction

Cocaine dependence is a chronic, relapsing disorder (Yuferov et al. 2005). Previous studies have implicated deficits in cognitive control as a critical psychological factor contributing to continued drug use in dependent individuals (de Wit 2009; Garavan and Hester 2007; Li and Sinha 2008; Porrino et al. 2007). Numerous imaging studies described cortical and subcortical dysfunctions in individuals addicted to cocaine or other stimulants (Aron and Paulus 2007; Goldstein et al. 2009; Goldstein et al. 2007; Hanlon et al. 2009; Hanlon et al. 2011; Hester and Garavan 2004; Kaufman et al. 2003; Moeller et al. 2005; Wesley et al. 2011). For instance, chronic cocaine users showed hypo-activation of the thalamus during a visual spatial attention task (Tomasi et al. 2007a). More recently, in a longitudinal study, we showed that decreased error-related activation of the thalamus predicts relapse and time to relapse to drug use in cocaine dependent individuals (Luo et al. 2013).

On the other hand, increased thalamic activations were observed in individuals with cocaine dependence and other addictive disorders when they were exposed to drug cues or situational factors related to drug use (Feldstein Ewing et al. 2010; Filbey et al. 2009; Franklin et al. 2009; Gozzi et al. 2011; Hermann et al. 2006; Jia et al. 2011; McClernon et al. 2009; Rose et al. 2007; Tomasi et al. 2007a; Wang et al. 2007; Weinstein et al. 2010). This seeming inconsistency may relate to functional heterogeneity of the thalamus, with some subregions mediating craving and others subserving control of craving. Understanding how thalamic cortical circuits respond to different psychological constructs and behavioral contexts will help elucidate the multifaceted etiologies of cocaine addiction.

Many studies have demonstrated altered cerebral functional connectivities in cocaine dependence (Cisler et al. 2013; Ding and Lee 2013b; Gu et al. 2010; Kelly et al. 2011; Konova et al. 2013; Li et al.

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2000; Narayanan et al. 2012; Tomasi et al. 2010; Verdejo-Garcia et al. 2012; Wilcox et al. 2011; Zhang et al. 2014). Reduced connectivities were observed in cocaine users between the thalamus and midbrain (Tomasi et al. 2010), putamen and ventral tegmental area (Gu et al. 2010), and anterior cingulate cortex (Verdejo-Garcia et al. 2012). The connectivity between the thalamus and midbrain (Tomasi et al. 2010) and ventral tegmental area (Gu et al. 2010) correlated negatively with the number of years of cocaine use. These studies suggest that cocaine use affects not only the activity but also connectivity of the thalamus. Investigating the functional connectivities of the thalamus may further uncover circuit-level disturbances in cocaine dependence.

Connectivity analysis has delineated functional subclusters of the thalamus in accordance with anatomy (Zhang et al. 2008; Zhang et al. 2010). Multivariate pattern analysis (MVPA), a data-driven technique, can provide new insights into cerebral functional organization (Haxby 2012; Haynes and Rees 2006; Norman et al. 2006; O'Toole et al. 2007; Pereira et al. 2009; Yang et al. 2012). Compared to univariate analyses, MVPA fully utilizes activity patterns across multiple variables and increases sensitivity in differential diagnostics (Norman et al. 2006; Pereira et al. 2009). MVPA has been used to predict behavioral variables and outcomes (Dosenbach et al. 2010), decode cognitive states (Brodersen et al. 2012; Freeman et al. 2011; Hassabis et al. 2009; Haxby et al. 2001; Haynes and Rees 2005; Kamitani and Tong 2005; Lee et al. 2013; Liu et al. 2011; Rissman et al. 2010), and identify patients with depression (Craddock et al. 2009; Fu et al. 2008; Zeng et al. 2012), functional dyspepsia (Liu et al. 2013), autism (Coutanche et al. 2011; Ecker et al., 2010), binge-eating (Weygandt et al. 2012b), mild cognitive impairment/Alzheimer's disease (Cuingnet et al. 2011; Desikan et al. 2009; Fan et al. 2008; Kloppel et al. 2008; Zhou et al. 2010), attention-deficit/hyperactivity disorder (Zhu et al. 2008), and schizophrenia (Ardekani et al. 2011; Shen et al. 2010), in a variety of behavioral contexts. However, to our knowledge, no studies have used MVPA to examine brain activity and connectivity in cocaine addiction.

Here, we applied MVPA to examine altered thalamic functional connectivity in participants with cocaine dependence (CD). Our earlier work of independent component analysis identified six independent networks of cognitive control from the stop signal task (Zhang and Li 2012). We sought to distinguish CD from healthy controls (HC) with MVPA of voxel-wise thalamic connectivity to these six task-related networks (please see Methods). We posited that, first, thalamic connectivity to these networks should distinguish CD from HC at an accuracy higher than comparison regions with similar volumes (number of voxels). Second, the voxels of which the connectivities to a set of independent components determine the "membership" should aggregate in clusters (as subnuclei) rather than distribute randomly. Thus, we have these specific aims: to investigate whether we could identify CD using only functional connectivity of the thalamus; to examine how the individual voxels of the thalamus distinguish CD from HC with functional connectivities for cognitive control; and to explore the correlation of these connectivities with clinical and performance variables.

2. Materials and methods

2.1. Subjects, informed consent, and assessment

One hundred recently abstinent participants (62 men) with cocaine dependence (CD) and one hundred age- and gender-matched healthy adult (HC) subjects (55 men) participated in this study (Table 1). CD met criteria for current cocaine dependence, as diagnosed by the Structured Clinical Interview for DSM-IV (First et al. 1995). Recent cocaine use was confirmed by urine toxicology screens. They were drug-free while staying in an inpatient unit prior to the current fMRI study. All subjects were physically healthy with no major medical illnesses or current use of prescription medications. None reported having a history of head injury or neurological illness. Other exclusion criteria included dependence on another psychoactive substance (except nicotine) and current or past history of psychotic disorders. Individuals with current depressive or anxiety symptoms requiring treatment or currently being treated for these symptoms were excluded as well. The Human Investigation committee at Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent prior to study participation.

Table 1
Demographics of the subjects.

Subject characteristic	CD (n = 100)	HC (n = 100)	p-Value
Age (years)	40.3 ± 7.4	38.0 ± 10.6	0.08[a]
Gender (M/F)	62/38	55/45	0.39[b]
Years of alcohol use	17 ± 9.0	20 ± 10.2	0.02[a]
Years of Marijuana use	10 ± 4.2	1.0 ± 1.3	0.001[a]
Amount of average monthly cocaine use (gm) in the prior year	16.9 ± 25.8	N/A	N/A
Amount per use in grams	1.0 ± 1.2	N/A	N/A
Days of cocaine use in the prior month	15.1 ± 8.8	N/A	N/A
Years of cocaine use	17.5 ± 8.3	N/A	N/A
Days abstinent prior to scan	18.2 ± 6.1	N/A	N/A

Note: values are mean ± S.D.
[a] Two-tailed two-sample t test.
[b] χ^2 test.

CD's were assessed with the Beck Depression Inventory (Beck et al. 1961) and the State-Trait Anxiety Inventory (Speilberger et al. 1970) at admission. The mean (±SD) BDI (12.2 ± 8.9) and STAI state (36.2 ± 10.7) and trait (40.7 ± 11.2) scores were within the range reported previously for individuals with cocaine dependence (Falck et al. 2002; Karlsgodt et al. 2003; Lopez and Becona 2007; Rubin et al. 2007). Cocaine craving was assessed with the cocaine craving questionnaire, brief version (CCQ-Brief), for all participants every two to three days (Sussner et al. 2006). The CCQ-Brief is a 10-item questionnaire, abbreviated from the CCQ-Now (Tiffany et al. 1993). It is highly correlated with the CCQ-Now and other cocaine craving measures (Sussner et al. 2006). Each item was rated on a scale from 1 to 7, with a higher total score (ranging from 10 to 70) indicating greater craving. CDs averaged CCQ scores of 20.0 ± 7.8 across all assessments and 18.0 ± 5.5 on the day or within 2–3 days of the scan. The majority of CDs received all of these assessments, and subjects with missing data were not included in the correlation analyses (see below).

2.2. Behavioral task and scan procedures

We employed a stop-signal task (SST) as detailed in our previous studies (Duann et al. 2009; Li et al. 2006; Zhang and Li 2012). Briefly, there were two trial types: "go" and "stop," randomly intermixed. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval (fore-period) between 1s and 5s, the dot turned into a circle, prompting the subjects to quickly press a button. The circle vanished at button press or after 1s had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. Three quarters of all trials were go trials. In a stop trial, an additional "X," the "stop" signal, appeared after the go signal. The subjects were instructed to withhold button pressing upon seeing the stop signal. Likewise, a trial terminated at button press or when 1s had elapsed since the appearance of the stop signal. The stop trials constituted the remaining one quarter of the trials. There was an inter-trial-interval of 2 s. The stop signal delay (SSD) started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 64 ms each after a successful and failed stop trial (De Jong et al. 1990; Levitt 1971). Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could appear occasionally. Each subject completed four 10 min runs of the task after a practice session outside the scanner. With the staircase