NeuroImage: Clinical 4 (2014) 585–592

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Error-related functional connectivity of the thalamus in cocaine dependence

Sheng Zhang [a,*], Sien Hu [a], Sarah R. Bednarski [a], Emily Erdman [a], Chiang-shan R. Li [a,b,c]

[a] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519, USA
[b] Inter-departmental Neuroscience Program, Yale University, New Haven, CT 06520, USA
[c] Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520, USA

ARTICLE INFO

Article history:
Received 21 November 2013
Received in revised form 13 January 2014
Accepted 26 January 2014
Available online 7 February 2014

Keywords:
Cocaine
Thalamus
vmPFC
Cognitive control
fMRI
PPI

ABSTRACT

Error processing is a critical component of cognitive control, an executive function that has been widely implicated in substance misuse. In previous studies we showed that error related activations of the thalamus predicted relapse to drug use in cocaine addicted individuals (Luo et al., 2013). Here, we investigated whether the error-related functional connectivity of the thalamus is altered in cocaine dependent patients (PCD, n = 54) as compared to demographically matched healthy individuals (HC, n = 54). The results of a generalized psychophysiological interaction analysis showed negative thalamic connectivity with the ventral medial prefrontal cortex (vmPFC), in the area of perigenual and subgenual anterior cingulate cortex, in HC but not PCD ($p < 0.05$, corrected, two-sample t test). This difference in functional connectivity was not observed for task-residual signals, suggesting that it is specific to task-related processes during cognitive control. Further, the thalamic-vmPFC connectivity is positively correlated with the amount of cocaine use in the prior month for female but not for male PCD. These findings add to recent literature and provide additional evidence for circuit-level biomarkers of cocaine dependence.

1. Introduction

Cocaine dependence is a chronic relapsing disorder. A host of findings implicate deficits in cognitive control as a critical factor contributing to continued drug use in dependent individuals (de Wit, 2009; Everitt et al., 2008; Garavan and Hester, 2007; Li and Sinha, 2008; Porrino et al., 2007). In particular, imaging studies have examined the neural basis of such deficits and described altered cerebral activations during a variety of cognitive challenges (Goldstein et al., 2007, 2009; Hanlon et al., 2009, 2011; Hester and Garavan, 2004; Kaufman et al., 2003; Moeller et al., 2005).

Our previous work combined functional magnetic resonance imaging (fMRI) and a stop signal task to characterize changes in cerebral activations during cognitive control in cocaine dependent patients (Bednarski et al., 2011; Li et al., 2006a, 2008a, 2010b). In a longitudinal study, decreased error-related activation of the thalamus predicted relapse and an earlier time to relapse (Luo et al., 2013). The latter finding is consistent with the effects of psychostimulants on error-related processes (Garavan and Hester, 2007; Li et al., 2010b; Wardle et al., 2012) and altered error processing and error-related learning in individuals addicted to cocaine (Franken et al., 2007; Hester et al., 2007; Li et al., 2006a, 2010a; Madoz-Gurpide et al., 2011; Sokhadze et al., 2008; Vadhan et al., 2008). Together, error-related thalamic activities may be a potential biomarker for cocaine dependence.

As part of the frontal-striato-thalamic circuits, the thalamus is critically involved in motor, cognitive, and affective control (Aglioti, 1997; Haber and Calzavara, 2009; Strick et al., 1995). Many preclinical and clinical studies support a role of the thalamus in saliency processing and performance monitoring (Bellebaum et al., 2005; Blakemore et al., 1998; Diamond and Ahissar, 2007; Mitchell et al., 2007; Monchi et al., 2001; Sommer and Wurtz, 2004; Urbain and Deschenes, 2007; Wagner et al., 2006). For instance, a recent work suggested a mechanism whereby thalamic signals to the striatum may shift the cortical processes of action selection (Ding et al., 2010a,b). Our recent imaging studies have also highlighted the thalamus as a key structure in the neural circuits mediating error-related cognitive control (Hendrick et al., 2010; Ide and Li, 2011a,b; Zhang and Li, 2012a). Understanding the functional connectivities of the thalamus during salient events – such as an error – may further elucidate the circuit level deficits in cocaine dependence.

In the current study, we examined whether and how the functional connectivity of the thalamus is altered during error processing in cocaine dependent patients, as compared to demographically matched

* Corresponding author at: Connecticut Mental Health Center S103, 34 Park Street, New Haven, CT 06519, USA. Tel.: +1 203 974 7310; fax: +1 203 974 7076.
E-mail address: sheng.zhang@yale.edu (S. Zhang).

http://dx.doi.org/10.1016/j.nicl.2014.01.015

healthy individuals, using psychophysiological interaction (PPI, see the Materials and methods section). As a control, we removed the task-related signals from the time series and examined low-frequency functional connectivity of the thalamus (Zhang and Li, 2010, 2012b). Thalamus receives heavy noradrenergic inputs from the midbrain and earlier work with positron emission tomography imaging implicated altered noradrenergic signaling in the thalamus of humans and non-human primates (Beveridge et al., 2005; Ding et al., 2010a,b; Macey et al., 2003; Mash et al., 2005). We hope that, by advancing our understanding of thalamic dysfunctions in cocaine dependence, the current study may help linking the molecular and system level mechanisms of this chronic relapsing disorder.

2. Materials and methods

2.1. Subjects, informed consent, and assessment

Fifty-four patients (35 men) with cocaine dependence (PCD) and fifty-four age and gender matched healthy adult (HC) subjects (29 men) participated in this study (Table 1). PCD 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 upon admission. They were drug-free while staying in an inpatient treatment unit prior to the current fMRI study. All subjects were physically healthy with no major medical illnesses or current use of prescription medications. None of them reported having a history of head injury or neurological illness. Other exclusion criteria included dependence on other psychoactive substances (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 the study, and all subjects signed an informed consent prior to participation.

All PCD'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 average Beck Depression Inventory (13.9 ± 7.9) and State–Trait Anxiety Inventory state (40.1 ± 9.7) and trait (41.9 ± 8.9) 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 (Cocaine Craving Questionnaire — Brief), for all participants on the same day or within days of the scan (Sussner et al., 2006). The Cocaine Craving Questionnaire — Brief is a 10-item questionnaire, abbreviated from the Cocaine Craving Questionnaire — Now (Tiffany et al., 1993). It is highly correlated with the Cocaine Craving Questionnaire — 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. PCD's averaged 18.8 ± 7.2 in CCQ score.

Table 1
Demographics of the subjects.

Subject characteristic	PCD (n = 54)	HC (n = 54)	p-Value
Ages (years)	39.8 ± 7.5	37.7 ± 8.4	0.16[a]
Gender (M/F)	35/19	29/25	0.24^
Smokers/non-smokers	45/9	12/42	0.001^
Years of alcohol use	15 ± 8.9	19 ± 9.8	0.01[a]
Years of marijuana use	9 ± 3.8	1.0 ± 1.3	0.001[a]
Amount of monthly cocaine use (g) in the prior year	17.0 ± 26.8	N/A	N/A
Days of cocaine use in the prior month	13.6 ± 8.0	N/A	N/A
Years of cocaine use	17.3 ± 8.0	N/A	N/A
Days abstinent prior to scan	13.8 ± 8.5	N/A	N/A

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

2.2. Behavioral task and scan procedures

We employed a simple reaction time (RT) task in this stop-signal paradigm, as detailed in our previous studies (Chao et al., 2009; Duann et al., 2009; Hu et al., 2012; Hu and Li, 2012; Li et al., 2006b, 2008b,c, 2009a; Fig. 1). 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 1 and 5 s, the dot turned into a circle, prompting the subjects to quickly press a button. The circle vanished at button press or after 1 s 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 told to withhold button press upon seeing the stop signal. Likewise, a trial terminated at button press or when 1 s 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 come up occasionally. Each subject completed four 10-min runs of the task after a practice session outside the scanner. With the staircase procedure we anticipated that the subjects would succeed in withholding their response in approximately 50% of the stop trials.

2.3. Analyses of behavioral data

We computed a critical SSD that represents the time delay between go and stop signals that a subject would need to succeed in 50% of the stop trials (Levitt, 1971). Specifically, SSDs across trials were grouped into runs, with each run defined as a monotonically increasing or decreasing series. We derived a mid-run estimate by taking the middle

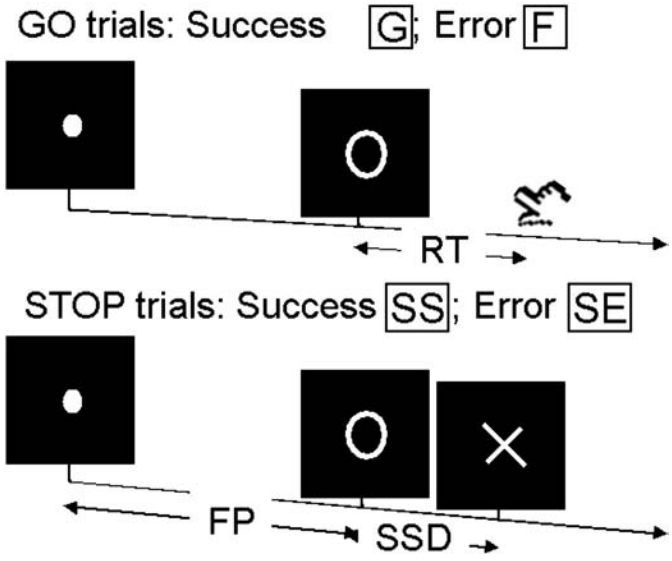

Fig. 1. Stop signal paradigm. In "go" trial (~75%) observers responded to the go signal (a circle) and in "stop" trials (~25%) they had to withhold the response when they saw the stop signal (an X). In both go and stop trials, the go signal appeared after a randomized time interval between 1 and 5 s (the fore-period or FP) following the appearance of the fixation point. The stop signal followed the go signal by a time delay — the stop signal delay (SSD). The SSD was updated according to a staircase procedure, whereby it increased and decreased by 64 ms following a stop success (SS) and stop error (SE) trial, respectively. Four different trial outcomes including go success (G), go error (F), SS and SE were distinguished to characterize participants' behavioral performance and model regional brain activations.