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Increased error-related thalamic activity during early compared to late cocaine abstinence

Chiang-shan R. Li[a,b,c,*], Xi Luo[a,d], Rajita Sinha[a], Bruce J. Rounsaville[a,e], Kathleen M. Carroll[a,e], Robert T. Malison[a], Yu-Shin Ding[f,g], Sheng Zhang[a], Jaime S. Ide[a]

[a] Department of Psychiatry, Yale University, New Haven, CT 06519 USA
[b] Department of Neurobiology, Yale University, New Haven, CT 06520 USA
[c] Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06520 USA
[d] Department of Statistics, Yale University, New Haven, CT 06519 USA
[e] VA Connecticut Healthcare System, West Haven, CT 06516 USA
[f] Department of Diagnostic Radiology, Yale University, New Haven, CT 06519 USA
[g] Positron Emission Tomography Center, Yale University, New Haven, CT 06519 USA

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ABSTRACT

Altered cognitive control is implicated in the shaping of cocaine dependence. One of the key component processes of cognitive control is error monitoring. Our previous imaging work highlighted greater activity in distinct cortical and subcortical regions including the dorsal anterior cingulate cortex (dACC), thalamus and insula when participants committed an error during the stop signal task (Li et al., 2008b). Importantly, dACC, thalamic and insular activity has been associated with drug craving. One hypothesis is that the intense interoceptive activity during craving prevents these cerebral structures from adequately registering error and/or monitoring performance. Alternatively, the dACC, thalamus and insula show abnormally heightened responses to performance errors, suggesting that excessive responses to salient stimuli such as drug cues could precipitate craving. The two hypotheses would each predict decreased and increased activity during stop error (SE) as compared to stop success (SS) trials in the SST. Here we showed that cocaine dependent patients (PCD) experienced greater subjective feeling of loss of control and cocaine craving during early (average of day 6) compared to late (average of day 18) abstinence. Furthermore, compared to PCD during late abstinence, PCD scanned during early abstinence showed increased thalamic as well as insular but not dACC responses to errors (SE > SS). These findings support the hypothesis that heightened thalamic reactivity to salient stimuli co-occur with cocaine craving and loss of self control.

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1. Introduction

Error processing is an important component process of cognitive control (Taylor et al., 2007). By detecting errors we modify ongoing behavior and establish new contingencies. Failure to register errors has been implicated in a number of psychiatric conditions including substance misuse (Garavan and Stout, 2005). For instance, we observed that, compared to healthy control participants, patients with cocaine dependence (PCD) demonstrated decreased post-error behavioral adjustment during the stop signal task (SST), suggesting impaired performance monitoring (Li et al., 2006b). Other investigators have employed different behavioral tasks and highlighted various aspects of altered error-related measures in substance abusing individuals (Franken et al., 2007; Garavan and Hester, 2007; Hester et al., 2007; Paulus et al., 2008; Verdejo-García et al., 2007; Yeung et al., 2007). It has also been theorized in computational modeling that altered error processing contributes to compulsory drug use in addiction (Reddish, 2004; Reddish and Johnson, 2007).

In our functional magnetic resonance imaging (fMRI) studies of the SST, we described a distinct pattern of activation in the dorsal anterior cingulate cortex (dACC), thalamus, and insula during error processing (Li et al., 2008b). Importantly, these cerebral structures are also implicated in mediating drug craving (see Koob and Volkow, 2010; Li and Sinha, 2008 for a review). For instance, structures including the ventral tegmental area, thalamus, ACC, insula, and amygdala demonstrated greater activation during fMRI in response to marijuana as compared to neutral cue in abstinent marijuana users (Filbey et al., 2009). Following up on their earlier studies of mesolimbic responses to cigarette cues, Franklin

* Corresponding author at: Connecticut Mental Health Center, S103 Department of Psychiatry, Yale University School of Medicine 34 Park Street New Haven, CT 06519 USA. Tel.: +1 203 974 7354; fax: +1 203 974 7076.
E-mail address: chiang-shan.li@yale.edu (C.-s.R. Li).

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et al. (2009) investigated the effects of a dopamine transporter polymorphism on cue elicited activation in brain regions including the ventral striatum/pallidum, anterior cingulate and insula. With perfusion MRI, Wang et al. (2007) demonstrated an association between abstinence induced craving and increased cerebral blood flow in the orbitofrontal cortex (OFC), ACC, ventral striatum, thalamus, amygdala, and insula, in cigarette smokers. A positive association between the severity of nicotine dependence and cue reactivity in the OFC and ACC was also observed by McClernon et al., 2008. In a pharmacological fMRI study, Hermann and co-workers showed decreased cue–as compared to control–induced activation in the thalamus after administration of an atypical dopamine receptor blocker in abstinent alcohol dependent patients. Overall, these along with many other studies support the role of a network of cerebral structures in mediating drug and alcohol craving (Duncan et al., 2007; Feldstein et al., in press; Grüsser et al., 2004; Hermann et al., 2006; King et al., 2010; McClernon et al., 2009; Risinger et al., 2005; Rose et al., 2007; Weinstein et al., in press).

We are particularly interested in the overlapping pattern of regional brain activations during cognitive control and drug craving. In the SST, medial cortical regions including the dACC and subcortical structures including the thalamus and insula showed greater activation during stop errors as compared to stop successes. The same brain regions are also extensively implicated in drug craving. This association is of potential importance to understanding the etiology of drug addiction as deficits in cognitive control and drug craving co-occur in patients with drug addiction (Volkow et al., 2010; see also Baicy and London, 2007; Koob and Volkow, 2010 for a review). Two hypotheses are in place to explain how altered dACC, thalamic and insular activity may be associated with craving and changes in cognitive control. One hypothesis is that the intense interoceptive activity during withdrawal and craving is ill adaptive for these cerebral structures to register error and/or monitor performance. An alternative hypothesis is that the dACC, thalamus and insula shows abnormally heightened responses to performance errors, suggesting that excessive responses to salient stimuli such as drug cues could precipitate craving. The two hypotheses would each predict decreased and increased activity during stop error (SE) as compared to stop success (SS) trials in the SST.

We tested these two hypotheses by comparing error-related regional brain activation in cocaine dependent patients early and late during abstinence, with patients experiencing significantly greater craving and subjective loss of control early during their abstinence.

2. Materials and methods

2.1. Subjects, informed consent and assessment of impulse control

Twenty-six abstinent patients with cocaine dependence (PCD) participated in the 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 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.

Cocaine craving was assessed with the cocaine craving questionnaire, brief version (CCQ-Brief), for all participants on the same day or within days of the scan (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).

In all except 3 PCD's, we also assessed subjective feeling of difficulties in emotion regulation and impulse control using the difficulties in emotion regulation scale in the same week or, in some cases, on the same day of the fMRI (DERS, Gratz and Roemer, 2004). The DERS is a 36-item self-report measure, with each item rated on a 5-point analog scale: 1 = almost never; 2 = sometimes; 3 = about half of the time; 4 = most of the time; 5 = almost always. It has been shown to have high internal consistency, test–retest reliability and construct validity in the general population and in cocaine dependent patients (Fox et al., 2007; Gratz and Roemer, 2004). The total score of DERS ranges from 36 to 180, with higher score indicating greater emotion dysregulation and difficulties in impulse control. Abstinent cocaine patients were found to have persistent problems in impulse control compared to healthy individuals (Fox et al., 2007).

Table 1
Demographics of the subjects.

Subject characteristic	Early ($n = 9$)	Late ($n = 17$)	p value
Days of abstinence before fMRI	5.8 ± 4.7	18.0 ± 2.2	<0.0001[b]
Men/women	5/4	8/9	0.43[a]
Age (years)	36.6 ± 6.2	36.8 ± 6.0	0.93[b]
Ethnicity			
African American	4 (44.4%)	7 (41.2%)	0.54[a]
Caucasian	5 (55.6%)	10 (58.8%)	
Education (years)	11.4 ± 2.2	12.4 ± 1.0	0.16[b]
Average number of days of cocaine use/month prior to admission	19.1 ± 9.5	17.8 ± 8.4	0.72[b]
Average number of years of cocaine use	9.0 ± 5.1	11.7 ± 6.7	0.30[b]
Life time diagnosis of depression	1 (11.1%)	2 (11.8%)	0.71[a]
Life time diagnosis of PTSD	3 (33.3%)	5 (29.4%)	0.51[a]

Note: values are mean ± s.d.
[a] Binomial test.
[b] Two-tailed two-sample test.

2.2. Behavioral task

We employed a simple reaction time (RT) task in this stop signal paradigm (Fig. 1). There were two trial types: "go" and "stop," randomly intermixed. A small dot appeared on the screen to engage attention and eye fixation at the beginning of a go trial. After a randomized time interval (fore-period) anywhere between 1 and 5 s, the dot turned into a circle, prompting 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 the stop trials, 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.

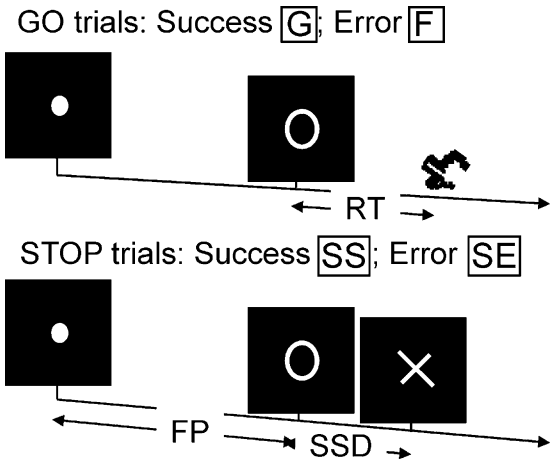

Fig. 1. (a) Stop signal paradigm. In "go" trials (75%) observers responded to the go signal (a circle) and in "stop" trials (25%) they had to withhold the response when they saw the stop signal (an X). In both trials the go signal appeared after a randomized time interval between 1 and 5 s (the fore-period 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.

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