Error-related functional connectivity of the thalamus in cocaine dependence

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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; Porro 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 Aihissar, 2007; Mitchell et al., 2007; Monchi et al., 2001; Sommer and Wurtz, 2004; Urbain and Deschene, 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...
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 (Falk et al., 2002; Karlsogdt 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.

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, 2009a,b; 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 prior 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

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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^   |
| 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^   |
| Years of marijuana use | 9 ± 3.8      | 1.0 ± 1.3   | 0.001   |
| 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.

^ Two-tailed two-sample t test; ^χ2 test.
SSD (or average of the two middle SSDs) of every second run. The critical SSD was computed by taking the mean of all mid-run SSDs. It was reported that, except for experiments with a small number of trials (less than 30), the mid-run estimate was close to the maximum likelihood estimate of $X_{50}$ (50% positive response; i.e., 50% SS in the SST (Wetherill et al., 1966)). The stop signal reaction time (SSRT) was computed by subtracting the critical SSD from the median go trial RT (Logan, 1994).

We computed the fore-period effect as an index of motor preparedness during the SST (Li et al., 2005a, 2006b, 2009b). Briefly, longer fore-period is associated with faster response time (Bertelson and Tisseyre, 1968; Woodrow, 1914). RT was compared between go trials with a fore-period between 3 and 5 s and between 1 and 3 s, and the effect size of RT difference was defined as fore-period effect. It is also known that in a RT task the RT of a correct response is prolonged following an error, compared with other correct responses, and this prolonged RT is thought to reflect error monitoring (Rabbit, 1966). We thus computed the RT difference between the go trials that followed a stop error (SE) and those that followed another go trial, and termed the effect size of this RT difference “post-error slowing” (PES) (Li et al., 2009b).

2.4. Imaging protocol

Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3 T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC–PC line with TR = 300 ms, TE = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60°, field of view = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4 mm and no gap. Functional, blood oxygen level-dependent (BOLD) signals were then acquired with a single-shot gradient echo echoplanar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 2000 ms, TE = 25 ms, bandwidth = 2004 Hz/pixel, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm and no gap.

2.5. Analyses of imaging data

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation. Standard image preprocessing was performed. Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995a). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

We distinguished four trial outcomes: go success (G), go error (F), stop success (SS), and stop error (SE) trials (Fig. 1). A statistical analytical design was constructed for each individual subject, using the general linear model (GLM) with the onsets of go signal in each of these trial types convolved with a canonical hemodynamic response function (HRF) and with its temporal derivative for entry as regressors in the model (Friston et al., 1995b). Realignment parameters in all 6 dimensions were entered in the model. The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. Serial autocorrelation was corrected by a first-degree autoregressive or AR(1) model. The GLM estimated the component of variance that could be explained by each of the regressors.

2.6. Psychophysiological interaction

Psychophysiological interaction (PPI) describes functional connectivity between brain regions contingent on a psychological context (Friston et al., 1997; Gitelman et al., 2002). Here, we examined the PPI of the thalamus, as defined by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), during error processing (SE > SS). We used a generalized form of context-dependent psychophysiological interaction (gPPI, http://brainmap.wisc.edu/PPI/McLaren et al., 2012). Briefly, in gPPI, the hemodynamic responses of G, SS and SE formed the psychological regressors, while in standard PPI, only SE > SS was included in the GLM. The inclusion of task regressors in gPPI reduces the likelihood that the functional connectivity estimates were driven by simple co-activation. The extracted mean time series of the BOLD signal were temporally filtered, mean corrected, and deconvolved to generate the time series of the neural signal for the thalamus mask for each individual subject to compose the physiological variable. These time series of neural signal were then multiplied by the onset times of the SS and SE separately, and re-convolved with the canonical HRF to obtain the interaction term or PPI variable (Gitelman et al., 2003). Finally, the psychological regressors of G, SS, and SE, the physiological variable of the thalamus, and PPI variables of SS and SE were entered as regressors in a whole-brain GLM. gPPI analysis was performed for each individual subject, and the contrast images (i.e., “1” for the PPI regressors of SE and “−1” for the PPI regressors of SS) were used in random-effect group analysis (Penny et al., 2004).

We compared PCD and HC in group whole brain analyses of gPPI. Because PCD and HC differed in many other clinical variables that cannot be controlled for in a covariance analysis (Miller and Chapman, 2001), we compared the two groups with a two-sample t test. We identified the differences at a combined threshold of voxel p < 0.001, uncorrected, and cluster p < 0.05, corrected for family-wise error of multiple comparisons (Barbalat et al., 2013; Friston et al., 1996; Georgescu et al., in press; Momennejad and Haynes, 2013; Takeuchi et al., 2013; Yoon et al., 2013). All voxel activations were presented in MNI coordinates. In region of interest (ROI) analysis, we used MarsBaR (http://marsbar.sourceforge.net/) to derive for each individual subject the effect size of activity change for the ROIs, and correlated the effect sizes with clinical characteristics with Pearson regression. The regressions examined whether the group differences were related to clinical variables and the SSRT.

2.7. Task-residual functional connectivity

To examine whether altered thalamic functional connectivity is specific to error processing, we performed a functional connectivity analysis on the “task residual data” — the time series that remained after removal of task-related signals (Zhang and Li, 2010, 2012b). Briefly, task-residual time series was obtained by removing task-related activity with the GLM. Previous studies suggested a linear superposition of task activity and spontaneous BOLD fluctuations and assumed that, if task-induced variance was adequately removed (Arfanakis et al., 2000; Fox et al., 2006a,b), the remaining residual signal should represent the spontaneous signals (Fair et al., 2007). Additional preprocessing was applied to the task-residual data to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al., 2007; Fox et al., 2005; Fox and Raichle, 2007; Rombouts et al., 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and the whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.
Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al., 2001). Thus, we applied a temporal band-pass filter (0.009Hz < f < 0.08 Hz) to the time course in order to obtain low-frequency fluctuations (Fair et al., 2007; Fox et al., 2005; Fox and Raichle, 2007; Lowe et al., 1998).

The BOLD time courses were averaged spatially over the same thalamic mask. For individual subjects, we computed the correlation coefficient between the averaged time course of the mask and the time courses of all other brain voxels. To assess and compare the task-residual “correlograms,” we converted these image maps, which were not normally distributed, to z score maps by Fisher’s z transform (Berry and Mielke, 2000; Charles et al., 2004; Jenkins and Watts, 1968): \( z = 0.5 \log_e[(1 + r)/(1 - r)] \). The z score maps were used in group random effect analyses.

### 3. Results

#### 3.1. Behavioral performance

Table 2 shows behavioral measures of the stop signal task. Both PCD and HC participants succeeded in about half of the stop trials, indicating success of the staircase procedure in tracking their performance. Across subjects, there were 261 ± 38 G trials, 19 ± 30 F trials, 49 ± 5 SS trials, and 46 ± 5 SE trials for PCD and 281 ± 15 G trials, 4 ± 5 F trials, 48 ± 5 SS trials, and 44 ± 6 SE trials for HC. Compared to HC, PCD showed prolonged (p = 0.02; two-tailed two-sample t test) stop signal reaction time (SSRT) and lower go response rate (p = 0.003), in accord with our previous reports (Li et al., 2006a, 2008a). The two groups were otherwise not different in behavioral performance.

#### 3.2. Thalamic error-related connectivities

In gPPI, we identified brain regions that were functionally connected with the thalamus with whole brain analyses. PCD subjects showed positive PPI with the dorsal lateral prefrontal cortex (dLPFC, \( x = -18, y = 5, z = 54, \) voxel Z = 5.35, 2700 mm\(^3\)), while HC subjects showed negative PPI with the ventromedial prefrontal cortex (vmPFC, \( x = 6, y = 44, z = -11, \) voxel Z = 4.50, 6858 mm\(^3\)) at a threshold of \( p < 0.001 \) uncorrected and cluster-level threshold of \( p < 0.05 \). We used the same thalamic mask for both PCD and HC. PCD showed greater positive PPI with the thalamus with whole brain analyses. PCD subjects showed positive PPI (p = 0.09, r = 0.28) in PCD but not HC (p = 0.60), and the slopes of the regression lines showed a trend difference between PCD and HC (p = 0.09; Zar, 1999). That is, greater vmPFC connectivity was associated with inferior response inhibition in PCD. The vmPFC connectivity was not correlated to days of cocaine use in the month prior to admission (p = 0.44), daily amount of cocaine use (in grams) in the month prior to admission (p = 0.94), or years of cocaine use (p = 0.35), across all PCD’s. The effect size also did not correlate with years of alcohol use (p = 0.89), years of marijuana use (p = 0.86), BDQ score (p = 0.46), STAI state anxiety score (p = 0.69), STAI trait anxiety score (p = 0.95), or cocaine craving as assessed by CCO (p = 0.62) in PCD. There appears to be a trend for a negative correlation to days of abstinence prior to scan (p = 0.07, r = −0.25), without considering the issue of multiple comparisons. We then reran the regression analysis between thalamus-vmPFC connectivity strength and SSRT with days of abstinence as a covariate, and the result remained significant (p = 0.04, r = 0.34).

In an exploratory analysis, we examined the correlations separately for female and male PCD. In women but not men, thalamic connectivity with the vmPFC was positively correlated with the amount of cocaine use in the month prior to admission (p = 0.002 and r = 0.65 for women; p = 0.61 for men) but not with any other clinical variables (all p's > 0.1). This correlation of vmPFC connectivity with the amount of cocaine use in female PCD was significant even when we considered a total of 20 comparisons with a corrected p of 0.05/20 = 0.0025.

### 4. Discussions

#### 4.1. Thalamic-vmPFC connectivity during error-related cognitive control

While healthy control individuals (HC) showed a negative thalamic functional connectivity with the ventromedial prefrontal cortex (vmPFC) during errors, cocaine dependent individuals (PCD) exhibit a positive (albeit non-significant in whole brain analysis) connectivity. As a result, compared to HC, PCD increased in error-related thalamic connectivity with the vmPFC. The extent of thalamic-vmPFC connectivity is positively correlated with the stop signal reaction time across all PCD’s. This connectivity is also positively correlated with the amount of drug use in the month prior to admission for female but not for male PCD. These results highlighted a few interesting issues to discuss in the below.

Dysfunction of the vmPFC is implicated in chronic pain (Apkarian et al., 2011; Lane and Wager, 2009), depression (Drevets et al., 1997), anxiety (Etkin and Wager, 2007), as well as drug addiction (Goldstein and Volkow, 2011). Many functional imaging studies of drug abusers showed vmPFC responses to drug cues (Bonson et al., 2002; Brody et al., 2002, 2004; Daglish et al., 2001; Goldstein and Volkow, 2011; Grusser et al., 2004; Killts et al., 2004; Myrick et al., 2004; Peters et al., 2009; Sell et al., 2000; Tapert et al., 2004; Wang et al., 1999). For instance, a meta-analysis of studies of cue-induced drug craving

### 3.3. Correlation with stop signal reaction time (SSRT) and clinical variables

We derived the effect size of thalamic interaction with the vmPFC for individual participants. Compared to a zero mean, vmPFC showed significant positive PPI for PCD (p < 0.05) while negative PPI for HC (p < 0.001) as shown in Fig. 2D. Pearson regression showed that, across subjects, the effect size was positively correlated to SSRT (p = 0.04, r = 0.28) in PCD but not HC (p = 0.60), and the slopes of the regression lines showed a trend difference between PCD and HC (p = 0.09; Zar, 1999). That is, greater vmPFC connectivity was associated with inferior response inhibition in PCD. The vmPFC connectivity was not correlated to days of cocaine use in the month prior to admission (p = 0.44), daily amount of cocaine use (in grams) in the month prior to admission (p = 0.94), or years of cocaine use (p = 0.35), across all PCD’s. The effect size also did not correlate with years of alcohol use (p = 0.89), years of marijuana use (p = 0.86), BDQ score (p = 0.46), STAI state anxiety score (p = 0.69), STAI trait anxiety score (p = 0.95), or cocaine craving as assessed by CCO (p = 0.62) in PCD. There appears to be a trend for a negative correlation to days of abstinence prior to scan (p = 0.07, r = −0.25), without considering the issue of multiple comparisons. We then reran the regression analysis between thalamus-vmPFC connectivity strength and SSRT with days of abstinence as a covariate, and the result remained significant (p = 0.04, r = 0.34).

In an exploratory analysis, we examined the correlations separately for female and male PCD. In women but not men, thalamic connectivity with the vmPFC was positively correlated with the amount of cocaine use in the month prior to admission (p = 0.002 and r = 0.65 for women; p = 0.61 for men) but not with any other clinical variables (all p's > 0.1). This correlation of vmPFC connectivity with the amount of cocaine use in female PCD was significant even when we considered a total of 20 comparisons with a corrected p of 0.05/20 = 0.0025.

### Table 2

| SSRT (ms) | FP effect (effect size) | Median go RT (ms) | % go | % stop | PES (effect size) |
|-----------|-------------------------|-------------------|------|--------|-----------------|
| PCD (n = 54) | 241 ± 49 | 1.84 ± 1.65 | 601 ± 110 | 942 ± 10.2 | 530 ± 3.8 | 1.28 ± 1.74 |
| HC (n = 54) | 220 ± 39 | 2.01 ± 1.44 | 627 ± 129 | 98.4 ± 2.4 | 533 ± 3.7 | 1.49 ± 1.59 |
| p-Value* | 0.02 | 0.56 | 0.27 | 0.003 | 0.64 | 0.52 |

Note: All values are mean ± standard deviation; PCD: individuals with cocaine dependence; HC: healthy controls; SSRT: stop signal reaction time; FP: fore-period; RT: reaction time; % go: percentage of go response trials; % stop: percentage of stop success trials; PES: post-error slowing.

*p-Value based on 2-tailed 2-sample t test.
demonstrated that activity in vmPFC is more likely to be elicited by drug cues in situations in which there is a perceived opportunity to engage in drug use in the near future (Wilson et al., 2004). Thus, increased thalamic-vmPFC connectivity supports excessive saliency-elicited activities in a circuit that may mediate drug craving and subsequent drug use behaviors.

An additional vmPFC function has to do with cognitive control. For instance, in an fMRI study of dieters engaged in real-life decisions about food consumption, Hare and colleagues reported greater activation in the left middle frontal cortex in individuals who exercised self-control, choosing healthy over tasty food (Hare et al., 2009). Interestingly, the activation of the left frontal regions showed a negative psychophysiological interaction with the vmPFC, in the same area as observed in the current study. In a pharmacological fMRI study of the stop signal task, methylphenidate elicited a decrease in vmPFC activations along with improved inhibitory control in cocaine dependent patients (Li et al., 2010b). Notably, the vmPFC is part of the “default mode” network, which shows greater activation during resting as compared with behaviorally engaging conditions (Buckner et al., 2008; Fox et al., 2005). Thus, consistent with these previous reports, the current finding of a positive correlation between the vmPFC connectivity and SSRT suggests compromised vmPFC function and inhibitory control in PCD.

Together, these findings suggest that increased thalamic-vmPFC connectivity may be associated with diminished saliency-elicited self control in chronic cocaine users, consistent with an integral role of this circuitry in interference resolution (Hare et al., 2009; Hermann et al., 2009; Lamm and Lewis, 2010; Roy et al., 2012; Stern et al., 2011; Tabibnia et al., 2008) and the extinction of cocaine seeking (Peters et al., 2013).

4.2. Gender differences in thalamic-vmPFC connectivity

Female but not male PCD showed positive correlation between the thalamic-vmPFC connectivity and the amount of drug use in the month prior to admission. Previous studies suggested that males and females show important differences in their drug using behaviors and clinical profiles of substance use disorder (Brady and Randall, 1999; Derringer et al., 2010; Kampov-Polevoy et al., 2004; McGue et al., 1997; Sinha and Rounsaville, 2002). For instance, males use illicit substances more frequently and in greater quantities than females (Berkowitz and Perkins, 1987; Thomas, 1995). Although female substance users typically begin using substances later than males do, they demonstrate an accelerated transition to addiction (Berkowitz and Perkins, 1987; Thomas, 1995). Although female substance users typically begin using substances later than males do, they demonstrate an accelerated transition to addiction (Berkowitz and Perkins, 1987; Thomas, 1995). Furthermore, imaging studies also supported gender differences in the influence of cocaine use on cerebral responses (Adinoff et al., 2001, 2006; Andersen et al., 2012; Ernst et al., 2000; Li et al., 2005b,c; Levin et al., 1994; Luo et al., 2013; Tucker et al., 2004; Volkow et al., 2011). Volkow et al. (2011) showed that decreased thalamo-cortical activation during exposure to cocaine cues was associated with vulnerability to relapse in female but not male cocaine users. Our finding adds to this growing literature by showing that thalamic-vmPFC connectivity is likely more vulnerable to recent cocaine use in women.
4.3. Limitations of the study and conclusions

There are a number of issues to consider for the current findings. First, PCD differed from HC in terms of nicotine, alcohol, as well as marijuana use, and potentially other substances that were not assessed. Therefore, we cannot rule out the possibility that the current findings may be attributed to the use of these other substances and/or an interaction between cocaine and these other substances. Second, the thalamus comprises several subnuclei that are each distinct in cortical/subcortical connectivities and functions. Thus, the current findings do not address heterogeneity of thalamic functions or how chronic cocaine use may influence these distinct thalamic connectivities differently. Finally, chronic cocaine use is known to influence gray matter volumes (Ide et al., 2014). Future study with a larger sample size will examine the interaction of these functional and structural changes in cocaine addiction.

In summary, psychophysiological interaction during error processing demonstrates altered connectivity between the thalamus and vmPFC, which may be related to drug craving and impaired cognitive control in cocaine dependence (Colzato et al., 2007). These findings complement recent studies of task-related and resting state functional as well as structural connectivity that provide circuit-level biomarkers of cocaine dependence (Gu et al., 2010; Lane et al., 2010; Tomasi et al., 2010; Urbano et al., 2009).

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