Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence

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Deficits in cognitive control are implicated in cocaine dependence. Previously, combining functional magnetic resonance imaging and a stop signal task, we demonstrated altered cognitive control in cocaine-dependent individuals. However, the clinical implications of these cross-sectional findings and, in particular, whether the changes were associated with relapse to drug use, were not clear. In a prospective study, we recruited 97 treatment-seeking individuals with cocaine dependence to perform the stop signal task during functional magnetic resonance imaging and participate in follow-up assessments for 3 months, during which time cocaine use was evaluated with timeline follow back and ascertained by urine toxicology tests. Functional magnetic resonance imaging data were analysed using general linear models as implemented in Statistical Parametric Mapping 8, with the contrast ‘stop error greater than stop success trials’ to index error processing. Using voxelwise analysis with logistic and Cox regressions, we identified brain activations of error processing that predict relapse and time to relapse. In females, decreased error-related activations of the thalamus and dorsal anterior cingulate cortex predicted relapse and an earlier time to relapse. In males, decreased error-related activations of the dorsal anterior cingulate cortex and left insula predicted relapse and an earlier time to relapse. These regional activations were validated with data resampling and predicted relapse with an average area under the curve of 0.849 in receiver operating characteristic analyses. These findings provide direct evidence linking deficits in cognitive control to clinical outcome in a moderate-sized cohort of cocaine-dependent individuals. These results may provide a useful basis for future studies to examine how psychosocial factors interact with cognitive control to determine drug use and to evaluate the efficacy of pharmacological or behavioural treatment in remediating deficits of cognitive control in cocaine addicts.

Keywords: cocaine; relapse; cognitive control; error processing; gender difference
Introduction

A number of interrelated cognitive processes have been thought to influence, directly or indirectly, substance misuse (Ernst and Paulus, 2005). Substance dependence, characterized by a compulsive state of drug seeking, is distinctively captured by a loss in cognitive control (Goldstein and Volkow, 2002; Everitt and Robbins, 2005). In a broad sense, cognitive control can be defined as the ability to change behaviours in a dynamic fashion on the basis of advance information or feedback derived from monitoring ongoing behaviour (Kok et al., 2006). By setting goals, monitoring performance and inhibiting habitual acts, cognitive control allows behavioural flexibility for one to manoeuvre a changing environment and optimize goal-directed actions (Dalley et al., 2004).

Thus, altered cognitive control can lead to a failure in stopping habitual drug use in individuals with substance use disorders and in excessive monitoring and behavioural rituals in obsessive compulsive disorders (Goldstein and Volkow, 2002; Ursu et al., 2003; Fitzgerald et al., 2005; Kalivas and Volkow, 2005).

Error processing is a critical component of cognitive control. More recently, functional imaging studies began to elucidate the neural basis of error processing during cognitive control (Li et al., 2008b, c; Hendrick et al., 2010; Pourtois et al., 2010; Desmet et al., 2011; Ide and Li, 2011a, b; Zhang and Li, 2012). A circuit of the medial frontal cortices, basal ganglia, thalamus, and the cerebellum and its limbic connectivities mediate the cognitive and affective processes of error detection and learning. Psychostimulants influence error-related processes in healthy individuals as well as in cocaine users (Garavan and Hester, 2007; Li et al., 2010b; Wardle et al., 2012). Many studies have implicated altered error processing and error-related learning in individuals addicted to cocaine (Li et al., 2006; Franken et al., 2007; Hester et al., 2007; Sokhadze et al., 2008; Vadhan et al., 2008; Li et al., 2010a; Madoz-Gurpide et al., 2011). On the other hand, no studies have examined whether these error-related processes are related to drug use behaviours prospectively.

We recruited 97 cocaine-dependent patients for functional MRI of the stop signal task, a behavioural paradigm widely used to examine cognitive control. A staircase procedure was employed to elicit errors in the participants, such that we could reliably examine error-related processes. We used regression analyses to investigate how error-related regional brain activations predicted relapse and time to relapse during a 90-day longitudinal follow-up. In particular, males and females show important differences in their drug using behaviours and clinical profiles of substance use disorders (McGue et al., 1997; Brady and Randall, 1999; Sinha and Rounsaville, 2002; Kampov-Polevoy et al., 2004; Derringer et al., 2010). 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 do males, they demonstrate an accelerated transition to addiction (Brady and Randall, 1999; Mann et al., 2005). Male and female cocaine users differ in physiological and neuroendocrine responses to stress and drug cues (Fox et al., 2006). It is possible that altered cognitive control may play a role in mediating these gender differences. Thus, analyses were performed separately for males and females as well as for a combined sample, in order to identify gender-specific predictors of relapse in cocaine addiction.

Materials and methods

Subjects and assessments

Ninety-seven treatment-seeking individuals (37 females) with cocaine dependence between 18 and 55 years of age were recruited from the greater New Haven area through advertisements to participate in the study (Table 1). Cocaine dependence volunteers met criteria for current cocaine dependence, as diagnosed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders fourth edition (First et al., 1995). Recent cocaine use was confirmed by urine toxicology screens upon admission. Participants were drug-free while residing in the Clinical Neuroscience Research Unit, a monitored treatment unit at the Connecticut Mental Health Centre, for 2 to 4 weeks before imaging. Cocaine dependence volunteers were assessed with the Beck Depression Inventory (Beck et al., 1961) and the State-Trait Anxiety Inventory (Speilberger et al., 1970) at admission (Table 1). The average Beck Depression Inventory and State-Trait Anxiety Inventory state and trait 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. 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 a history of or current dependence on another psychoactive substance (except nicotine) and current or past history of psychotic disorders. Pregnant or lactating women were not recruited.

On the Clinical Neuroscience Research Unit, cocaine dependence volunteers received treatment that consisted of daily individual psychotherapy, regular substance abuse group therapy, social work services, family meetings when appropriate, and outpatient treatment planning. The daily routine was highly regimented, with >80% of waking time scheduled. Visitation at the Clinical Neuroscience Research Unit is restricted and monitored.

The Human Investigation Committee at Yale University School of Medicine approved all study procedures, and all subjects provided written informed consent prior to study participation.

Longitudinal clinical follow-up

The procedures of longitudinal follow-up were similar to those described in a recent study (Rando et al., 2011). On discharge from the inpatient unit, all participants with cocaine dependence were given appointments for follow-up interviews at 14, 30, 60 and 90 days after discharge. Reminders were sent the week before each appointment. Cocaine use was assessed at each appointment using the timeline follow-back method (Sobell and Sobell, 1992) on the Substance Use...
Table 1: Demographics and clinical characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Non-relapsors</th>
<th>Relapsors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 17)</td>
<td>Females (n = 10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0 ± 7.3</td>
<td>41.5 ± 8.9</td>
</tr>
<tr>
<td>Race (EA/AA/Others)</td>
<td>2/14/1</td>
<td>2/7/1</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.1 ± 1.2</td>
<td>12.6 ± 1.0</td>
</tr>
<tr>
<td>Cigarette smokers (n, %)</td>
<td>14 (82%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Years of cocaine use</td>
<td>17.1 ± 9.2</td>
<td>18.5 ± 10.6</td>
</tr>
<tr>
<td>Years of alcohol use</td>
<td>15.1 ± 9.1</td>
<td>11.7 ± 8.2</td>
</tr>
<tr>
<td>Years of cannabis use</td>
<td>8.2 ± 4.9</td>
<td>6.0 ± 5.0</td>
</tr>
<tr>
<td>Prior month cocaine (days)</td>
<td>12.5 ± 9.1</td>
<td>16.4 ± 9.7</td>
</tr>
<tr>
<td>Prior month cocaine (g)</td>
<td>9.9 ± 14.0</td>
<td>13.3 ± 17.2</td>
</tr>
<tr>
<td>Prior month alcohol (days)</td>
<td>13.8 ± 11.0</td>
<td>12.0 ± 11.1</td>
</tr>
<tr>
<td>Prior month alcohol (g)</td>
<td>17.4 ± 6.4</td>
<td>16.5 ± 5.8</td>
</tr>
<tr>
<td>BDI score</td>
<td>13.5 ± 10.2</td>
<td>15.3 ± 11.9</td>
</tr>
<tr>
<td>STAI state score</td>
<td>40.1 ± 9.2</td>
<td>41.9 ± 8.9</td>
</tr>
<tr>
<td>STAI trait score</td>
<td>45.4 ± 12.0</td>
<td>48.0 ± 12.5</td>
</tr>
<tr>
<td>Life time depression (n, %)</td>
<td>5 (29%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Life time PTSD (n, %)</td>
<td>4 (24%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

Prior month cocaine/alcohol = days of cocaine/alcohol use in the month before admission; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory; PTSD = post-traumatic stress disorder; AA = African American; EA = European American.

Calendar (Maisto et al., 1982; Miller and Del Boca, 1994), an instrument that has been validated in drug-abusing samples and widely used in assessing cocaine use outcomes in treatment research. Urine samples were also obtained at each follow-up appointment for toxicology tests to confirm subjective reports. In addition, patients provided permission to contact individuals close to them who had knowledge of their drug use, to obtain collateral information in the event that the patients were lost to follow-up. Relapse was defined as any use of cocaine. Of the 103 patients who completed the MRI scan, six patients (5.8%) did not complete follow-up and were not included in the relapse analyses. Of the remaining 37 female and 60 male participants with cocaine dependence, 27 and 53 relapsed, respectively, suggesting a trend toward greater relapse rate in males than females (P < 0.061, Fischer’s exact test, two-sided).

Behavioural task

The behavioural task ran from the commercial software ‘Presentation’ (NeuroBehavioral Systems; http://www.neurobs.com/). Visual stimuli were front projected to a screen situated in front of the scanner, and manual response by a button press was recorded with a fibre-optic button box (Current Designs). We used a simple reaction time task in this stop-signal paradigm (Logan and Cowan, 1984; Chao et al., 2009; Li et al., 2009). 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) anywhere between 1 and 5 s, the dot turned into a circle. The subjects were instructed to quickly press a button at the ‘go’ signal but not before. 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. Approximately three-quarters of all trials were ‘go’ trials. The remaining one-quarter were ‘stop’ trials. In a ‘stop’ trial, an additional ‘X’, the ‘stop’ signal, appeared and replaced 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 signal delay, the duration of time that the go signal remained on the screen prior to the appearance of the stop signal, started at 200 ms and varied from one stop trial to the next according to a staircase procedure: if the subject succeeded in withholding the response, the stop signal delay decreased by 64 ms (Levitt, 1971). There was an intertrial interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could occur in a small number of trials. Before the functional MRI study each subject had a practice session outside the scanner. In the scanner, each subject completed four 10-min runs of the task with a 1 to 2 min break in between runs. Depending on the actual stimulus timing (trial varied in fore-period duration) and speed of response, the total number of trials varied slightly across subjects in an experiment. On average, there were ~105 trials in each run, with a total of 420 trials collected for each subject. With the staircase procedure, we anticipated that the subjects succeeded in withholding their response in approximately half of the stop trials.

Imaging protocol

We used a 3 T Scanner (Siemens Trio) and a circularly-polarized head coil (with one element and no acceleration) for the current study. Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization. Anatomical images of the functional slice
locations were next obtained with spin echo imaging in the axial plane parallel to the anterior commissure-posterior commissure line with repetition time = 300 ms, echo time = 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 oxygenation level-dependent signals were then acquired with a single-shot gradient echo planar imaging sequence. Thirty-two axial slices parallel to the anterior commissure-posterior commissure line covering the whole brain were acquired with repetition time = 2000 ms, echo time = 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. Three hundred images were acquired in each run for a total of four runs.

Preprocessing of imaging data

Data were preprocessed with Statistical Parametric Mapping (Wellcome Department of Imaging Neuroscience, University College London, UK). Images from the first five repetition times at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radiofrequency pulsing and relaxation. Images of each individual subject were 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 to a Montreal Neurological Institute echo planar imaging template with affine registration followed by non-linear transformation (Friston et al., 1995; Ashburner and Friston, 1999). Finally, images were smoothed with a Gaussian kernel of 8 mm at full-width at half-maximum.

Four main types of trial outcome were distinguished: go success, go error, stop success, and stop error. A statistical analytical design was constructed for each individual subject using the general linear model with the onsets of go signal in each of these trial types convolved with a canonical haemodynamic response function and with the temporal derivative of the canonical haemodynamic response function entered as regressors in the model (Friston et al., 1994a). Realignment parameters in all six dimensions were also entered in the model. The data were high-pass filtered (1/128Hz cut-off) to remove low-frequency signal drifts. Serial autocorrelation of the time series was corrected by a first-degree autoregressive or AR (1) model (Friston et al., 2002). The general linear model estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we constructed a statistical contrast of ‘stop error > stop success’ to examine error processing for each individual subject (Logan and Cowan, 1984). The ‘con’ or contrast (difference in β) images taken from the first-level analysis were then used for the second-level group statistics (random effects analysis; Penny et al., 2003), including a one-sample t-test to identify error-activated regions as well as logistic and Cox regressions. Brain regions were identified using an atlas (Mai et al., 2003). In region of interest analyses, we used MarsBar (http://marsbar.sourceforge.net/) (Brett et al., 2002) to derive the effect size of change activity for the regions of interest in each individual subject. All voxel activations were noted in Montreal Neurological Institute coordinates.

Because a contrast of ‘stop error > stop success’ may involve greater stop error or less stop success related activations, we also examined the contrasts ‘stop error > go success’ and ‘stop success > go success’ in predicting relapse in additional models. The results would help disambiguate the effects of stop success and stop error related activations and facilitate interpretation of the results. Furthermore, although the primary focus of this study was error processing, we examined the effects of ‘stop success > stop error’, which reflects attentional monitoring and inhibitory control, a construct that has also been implicated in substance misuse, including cocaine (Li et al., 2008a).

Neural predictors of relapse: logistic regression

To capture initial relapse to cocaine use, relapse was examined using a dichotomous variable to reflect any level of cocaine use since discharge from the inpatient unit. We used logistic regression to examine error-related regional brain activations that predicted relapse to cocaine use during follow-up. Only voxels with significant activation in a one-sample t-test (P < 0.05, corrected for family-wise error of multiple comparisons, based on the Gaussian Random Field Theory) (Friston et al., 1993, 1994b) were retained for further analysis.

To predict the relapse status by each voxel, we employed a logistic regression model for each voxel i as follows,

\[
\logit(p_i) = \alpha_i + \beta_i X_i \tag{1}
\]

where \(p_i\) is the probability of relapse for the ith subject, and \(X_i\) is the T value of the jth voxel from subject. The logistic Model (1) was implemented by the Matlab function ‘glmfit’, with coefficient \(\beta_i\) characterizing the association between the voxel signal and relapse status. Specifically, the odds ratio for relapse was inflated by a multiple of \(\exp(\beta_i)\) if the activation pattern \(X_i\) increased by 1 unit. Its statistical significance was evaluated by correcting for multiple comparisons using a simulation procedure as implemented in Analysis of Functional NeuroImages (http://afni.nimh.nih.gov/afni).

We assessed Model (1) separately for male and female subjects with cocaine dependence. Notably, in contrast to previous studies that predicted outcome using region of interest analyses (Langleben et al., 2005; Paulus et al., 2005b; Rando et al., 2011), our logistic model was voxel-based, with the spatial pattern of regional findings fully determined by our prediction goal.

After identifying functional regions of interest as determined by the voxel-wise \(\beta_i\)’s in Model (1), we averaged the signals \(X_i\) within each region of interest to perform model refitting and validation. This helped reduce the number of models to report and validate, improve the signal-to-noise ratio, and allow us to interpret relapse prediction based on the region of interest instead of each voxel.

The accuracy of dichotomous prediction was assessed using receiver operating characteristic analysis, with the area under the curve indicating prediction accuracy (Macmillan and Creelman, 2005). Area under the curve considers both sensitivity and specificity and is a threshold-independent measure of the prediction performance.

Neural predictors of time to relapse: Cox regression

We employed the Cox proportional hazards model to predict time to relapse (Therneau and Grambsch, 2000). The Cox model specified the day-to-relapse time \(y_i\) by the hazard function

\[
h(t) \exp(h_i X_i), \tag{2}
\]

If a participant did not relapse during the 90-day follow-up period, we set \(y_i = 90\) and marked this observation as censored. We used the Matlab function ‘coxphfit’ to estimate the Cox Model (2). Again, the significance of \(h_i\) was corrected for multiple comparisons using...
the same simulation procedure as implemented in Analysis of Functional NeuroImages. We plotted the survival functions of regional activations that predicted time to relapse.

Time-dependent area under the curve of the receiver operating characteristic analyses were used to assess generalizability of the Cox model. We computed the area under the curve for each day between Days 1 and 90 of the follow-up period and plotted the area under the curves against time.

Logistic and Cox regression with clinical covariates

In separate models of logistic and Cox regression, we included years of cocaine use, years of alcohol use, as well as the amount of cocaine and alcohol use in the month before admission, as covariates.

Validation of logistic and Cox regression models

As described above, after identifying functional regions of interest as determined by the voxel-wise $\beta_j$'s in Models (1) and (2), we averaged the signals $X_{ij}$ within each region of interest to validate the results. To assess the reproducibility of our models, we cross validated the results using a 5-fold stratified scheme. At each replication, logistic and Cox proportional hazard models were built using 80% each of the relapsed and non-relapsed subjects. The predicted relapse rate and the true relapse rate of the remaining 20% subjects were assessed statistically over 100 replications.

Results

Stop signal task performance

Table 2 summarizes stop signal performance. We considered differences as statistically significant at $P < 0.01$, as evaluated by two-sided two-sample t-tests, to account for testing for five performance measures. All participants with cocaine dependence succeeded in approximately half of the stop trials, indicating the success of the staircase procedure in tracking subject performance and eliciting errors.

Compared with cocaine-dependent individuals who did not relapse, those who relapsed showed prolonged stop signal reaction time, but the difference did not reach statistical significance ($P > 0.219$), potentially because of the unbalanced sample with a much smaller number of non-relapsing subjects. A group (cocaine dependent relapsor versus non-relapsor) x gender ANOVA also did not reveal any significant gender main effect (all $P > 0.264$) or group x gender interaction effect (all $P > 0.048$). Together, these results indicated that behavioural performance on the stop signal task could not distinguish between cocaine dependence relapsors and non-relapsors.

Neural predictors of relapse and time to relapse

We used logistic and Cox regressions to identify error-related regional activations that predicted cocaine use and time to initial cocaine use, respectively, after cocaine-dependent participants were discharged from the hospital. Error related activations were derived by contrasting stop error and stop success trials as in our previous studies (Li et al., 2008b, 2010a). In cocaine-dependent females, the logistic model showed that decreased activation of the thalamus ($x = -12$, $y = -13$, $z = 7$; 338 voxels, cluster $P < 0.001$, corrected) and dorsal anterior cingulate cortex ($x = -6$, $y = 14$, $z = 43$; 107 voxels, cluster $P < 0.05$, corrected) during error processing predicted relapse (Fig. 1A). In cocaine-dependent females, the Cox model showed that decreased activation of an almost identical area of the thalamus ($x = 0$, $y = -22$, $z = 7$; 112 voxels, cluster $P < 0.05$, corrected) predicted an earlier time to relapse.

To assess the overall influence of these regional activations on relapse, we refitted the logistic and Cox models using the mean T values ($= \text{mean } X_{ij}$) extracted for each of the regions of interest. The results are shown in Table 3. To evaluate the robustness of the findings, we also examined the refitted coefficients of the male model using female region of interest data, and vice versa. None of these latter models yielded significant results. The logistic model characterized the association between voxel activation and relapse status. Specifically, the odds ratio for relapse increased by a multiple of $\exp(\beta_j)$ if the activation pattern $X_{ij}$ increased by 1 unit (Supplementary material). Thus, if average thalamic region of interest activation (T-value) increased by 1 unit, the odds ratio for relapse within 90 days decreased by $1 - \exp(-0.9831) = 62.6\%$.

Table 2 Stop signal task performance

<table>
<thead>
<tr>
<th></th>
<th>Go trial reaction time (ms)</th>
<th>Go response rate</th>
<th>Stop success rate</th>
<th>Post-error slowing (effect size)</th>
<th>Stop signal reaction time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-relapsors, all ($n = 17$)</td>
<td>$612 \pm 138$</td>
<td>96.3 ± 1.7</td>
<td>51.4 ± 4.2</td>
<td>1.06 ± 1.75</td>
<td>$221 \pm 37$</td>
</tr>
<tr>
<td>Non-relapsors, females ($n = 10$)</td>
<td>$582 \pm 133$</td>
<td>96.3 ± 1.7</td>
<td>50.4 ± 4.3</td>
<td>0.78 ± 1.80</td>
<td>$228 \pm 43$</td>
</tr>
<tr>
<td>Non-relapsors, males ($n = 7$)</td>
<td>$654 \pm 144$</td>
<td>96.2 ± 1.8</td>
<td>52.9 ± 3.9</td>
<td>1.45 ± 1.84</td>
<td>$212 \pm 27$</td>
</tr>
<tr>
<td>Relapsors, all ($n = 80$)</td>
<td>$610 \pm 118$</td>
<td>96.0 ± 1.5</td>
<td>53.1 ± 4.0</td>
<td>1.26 ± 1.88</td>
<td>$235 \pm 55$</td>
</tr>
<tr>
<td>Relapsors, females ($n = 27$)</td>
<td>$649 \pm 93$</td>
<td>95.4 ± 0.9</td>
<td>53.1 ± 3.2</td>
<td>1.55 ± 2.48</td>
<td>$243 \pm 61$</td>
</tr>
<tr>
<td>Relapsors, males ($n = 53$)</td>
<td>$590 \pm 125$</td>
<td>96.2 ± 1.7</td>
<td>53.1 ± 4.4</td>
<td>1.11 ± 1.50</td>
<td>$231 \pm 52$</td>
</tr>
</tbody>
</table>

Number in bracket indicates sample size. Post-error slowing (effect size) is computed by a two-sample t-test of reaction time between post-stop error and post-go go trials (Li et al., 2008b). Stop signal reaction time is computed by subtracting the critical stop signal delay from the median go reaction time (Li et al., 2010b). The numbers reported are mean ± SD.
The results of the Cox model suggested that, with average thalamic activation increasing by 1 unit, the hazard rate of relapse decreased by \( \frac{1}{e^{0.2215}} = 19.9\% \) in females.

In cocaine-dependent males, the results of logistic model identified decreased activation of the left insula \((x = 48, y = 5, z = 3; 348\) voxels, cluster \( P < 0.001\), corrected) and dorsal anterior cingulate cortex \((x = -12, y = 26, z = 34; 215\) voxels, cluster \( P < 0.001\), corrected) in predicting relapse (Fig. 1B). On the other hand, the Cox model did not identify a brain region that predicted time to relapse at the corrected \( P < 0.05\) threshold. At a relaxed threshold of \( P < 0.1\), corrected, the Cox model showed that decreased activation of the left insula \((x = -48, y = 14, z = 7; 66\) voxels) and dorsal anterior cingulate cortex \((x = -9, y = 20, z = 37; 15\) voxels) predicted an earlier time to relapse.

Figure 2 showed the survival curves for these areal predictors of relapse in females and males, separately.

Further analyses for the combined sample and gender differences

To evaluate the regions of interest predicting relapse for both males and females, we examined the activations using the logistic and Cox models for all subjects. The logistic model revealed a significant cluster in the dorsal anterior cingulate cortex \((x = 6, y = 11, z = 34; 308\) voxels, cluster \( P < 0.001\), corrected), confirming error-related activity of this medial cortical structure as a gender-shared predictor of relapse.

To further assess gender differences, we expanded the logistic and Cox models by including gender and gender-voxel interaction terms. Importantly, the gender term adjusted for the overall relapse likelihood differences between females and males and the interaction term accounted for the significant slope changes from females to males. The logistic model showed that the voxel coefficients that decreased significantly from females to males were within the thalamus \((x = -15, y = -19, z = 4; 600\) voxels, cluster \( P < 0.001\), corrected) and the voxel coefficients that increased significantly were in the left insula \((x = -42, y = 8, z = 14; 298\) voxels, cluster \( P < 0.005\), corrected). The Cox model
revealed similar findings with significant decrease in signals within the thalamus ($x = 18$, $y = -16$, $z = 13$; 236 voxels, cluster $P < 0.001$, corrected) and increase in signals within the left insula ($x = -39$, $y = 23$, $z = 7$; 111 voxels, cluster $P < 0.05$, corrected), from females to males. These results each confirmed error-related activity of the thalamus and left insula as the gender specific predictors of relapse to cocaine use in cocaine-dependent females and males.

**Results of models accounting for drug use and other clinical covariates**

In separate logistic and Cox models, we accounted for drug use characteristics by including years of cocaine use, years of alcohol use, and the days of cocaine and alcohol use in the month prior to study, amount of cocaine use (g) in the prior month, Beck Depression Inventory score, cocaine craving, and abstinence days. In cocaine-dependent females, the logistic model identified the thalamus ($x = -6$, $y = -10$, $z = 4$; 744 voxels, cluster $P < 0.001$) and, at a relaxed $P$-value of 0.1, dorsal anterior cingulate cortex ($x = 15$, $y = 23$, $z = 37$; 160 voxels); the Cox model identified the thalamus ($x = 18$, $y = -16$, $z = 13$; 1,131 voxels, cluster $P < 0.001$) and dorsal anterior cingulate cortex ($x = 6$, $y = 11$, $z = 37$; 179 voxels, cluster $P < 0.005$). In cocaine-dependent males, the logistic model identified the left insula ($x = -48$, $y = 8$, $z = 2$; 197 voxels, cluster $P < 0.001$) and dorsal anterior cingulate cortex ($x = -3$, $y = 20$, $z = 31$; 139 voxels, cluster $P < 0.01$); the Cox model identified the thalamus ($x = -3$, $y = -16$, $z = 2$; 103 voxels) at $P < 0.1$.

Except for the Cox model in predicting time to relapse in males, these regional findings were all significant at $P < 0.05$, corrected for family-wise error of multiple comparisons, with small volume correction for the regions identified from the first model. Thus, these voxel-wise results were consistent with the model without these additional covariates.

**Validation of the voxelwise findings**

The results of the logistic model were highly generalizable for both cocaine-dependent females and males. Using receiver operating characteristic analyses, we computed the area under the curve values as an index of prediction accuracy. The results showed an area under the curve of 83% (females, thalamus), 81.7% (females, dorsal anterior cingulate cortex), 89.1% (males, left insula), and 85.9% (males, dorsal anterior cingulate cortex), respectively. We plot the receiver operating characteristic curves in Fig. 3A. Likewise, we computed the time-dependent areas under the curve for each time point of the follow-up. The results showed that the prediction accuracy was largely stable throughout the 90 day follow-up period, with an average prediction accuracy of 76.5% (females, thalamus), 74.6% (females, dorsal anterior cingulate cortex), 77.1% (males, left insula), and 75.2% (males, dorsal anterior cingulate cortex) (Fig. 4).

**Additional validation of the areal activations as a predictor of relapse**

An additional issue is that, in validating the current findings, we used the regions of interest that were identified through an analysis of the entire sample. One could argue that these areal activations are ‘postdictors’ rather than predictors of relapse, because they did not make predictions outside the current cohort. A better validation would be to generate a model solely on the 80% and then test it in a fully independent 20% of the sample. To this end, we performed two additional sets of analyses on the logistic model to further assess the prediction capability of our findings.

The first analysis used a hypothesis-generating approach. We generated logistic models over 100 random samples each for males and females. Participants were randomly split into a training (80%) and validating (20%) data set, stratified by their relapse...
status. We identified regions of interest from the logistic models of training data, and assessed the accuracy of these regions of interest in predicting relapse in the validating data using receiver operating characteristic analysis. Specifically, using only the training data, we first fitted the voxelwise logistic model as described in the 'Materials and methods' section, and identified significant voxels \(P < 0.1\); a more liberal threshold was used because of reduced sample size). At each run, we would have a map of included voxels, and these maps varied across runs. To assess the inclusion frequency, a bootstrap procedure (with 50 bootstrapped samples) was done on each run within the 80% training data. The clusters of voxels included >50% of the bootstrapped samples retained for region of interest analysis (Bunea et al., 2011). The average activations within each identified region of interest were extracted, and logistic models were refitted using each of the mean region of interest activations on the training data only. Finally, the fitted logistic models were used to predict the relapse status of each subject in the validating data. The prediction performance of each region of interest was assessed over 100 random samples using receiver operating characteristics analysis.

The results showed that the area under the curve values of prediction for each region of interest are 59.50% (thalamus, females, \(P < 4.774 \times 10^{-5}\)), 60.99% (dorsal anterior cingulate cortex, females, \(P < 1.727 \times 10^{-6}\)), 68.44% (left insula, males, \(P < 5.361 \times 10^{-11}\)), and 60.83% (dorsal anterior cingulate cortex, males, \(P < 5.584 \times 10^{-4}\)). Thus, the accuracy of these areal activations in predicting relapse was decreased (as expected, because of reduced sample size) but remained statistically significant. These receiver operating characteristic curves are presented in Fig. 3B. Because of the independence of the training and testing data set in each sampling procedure, these area under the curve

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**Figure 3** Accuracy of relapse prediction as computed by the receiver operating characteristic analysis. The area under the curve indexed the accuracy at which each region of interest predicted relapse for females (left: dorsal anterior cingulate cortex and thalamus) and males (right: dorsal anterior cingulate cortex and left insula). (A) Results obtained using the same entire cohort for derivation of regions of interest, an independent 80% for model fitting and the remaining 20% for validation. (B) Results obtained using an independent 80% of the data set for derivation of regions of interest and model fitting, and the remaining 20% for validation. dACC = dorsal anterior cingulate cortex.
values represent the true accuracy of these regional brain activations in predicting relapse in the current cohort of cocaine addicts.

In a second analysis, we assessed the inclusion frequencies of individual voxels over repeated sampling/modelling as described, with the same 50% threshold used in identifying clusters. Again, the average inclusion frequencies were generated using the training data alone. The results revealed these clusters (Supplementary Fig. 1) with the highest percentages of overlap for females: thalamus \((x = 12, y = -16, z = 4); inclusion frequency = 97.07\%\); 506 voxels), dorsal anterior cingulate cortex \((x = -6, y = 14, z = 43); 86.35\%, 310 voxels\), superior temporal gyrus \((x = -57, y = -16, z = 16); 90.71\%, 57 voxels\); and for males: left insula \((x = -48, y = 8, z = -8); 91.8\%, 464 voxels\), dorsal anterior cingulate cortex \((x = -12, y = 20, z = 37); 82.81\%, 414 voxels\), and parahippocampal gyrus \((x = 27, y = -58, z = 10); 74.33\%, 146 voxels\). These findings similarly support these specific areal activations as a relapse predictor in cocaine addicts.

**Results of regression models for other contrasts**

We examined the effects of ‘stop success > stop error’, a contrast that involves attentional monitoring and response inhibition, and the results showed no regional activities predicting relapse at a corrected threshold in either logistic or Cox models.

We also examined the effects of stop ‘error > go success’ and ‘stop success > go success’ in predicting relapse in additional models to disambiguate the psychological constructs involved in ‘stop error > stop success’ in relapse prediction. The results showed that, for the dorsal anterior cingulate cortex, thalamus, and left insula, ‘stop error > go success’ and ‘stop success > go success’ were each associated with negative (as for ‘stop error > stop success’) and positive coefficients in the regressions (Supplementary material). These results suggest that while the contrast ‘stop error > go success’ may predict relapse to some extent, activations during ‘stop success > go success’ in these regions of interest are unlikely to predict relapse (Supplementary material).

**Discussion**

**Gender-shared and -specific neural predictors of relapse in cocaine dependence**

The current results identified gender-shared and -specific neural predictors of relapse in cocaine-dependent individuals. Decreased activation of the dorsal anterior cingulate cortex during error processing predicted relapse and an earlier time to relapse in both male and female cocaine-dependent individuals. Additionally, decreased activation of the thalamus and left insula predicted relapse and earlier relapse in cocaine-dependent females and males, respectively. These results are broadly consistent with gender differences in brain structures and functions (Cosgrove et al., 2007) and vulnerability to psychiatric and substance use disorders (Anker and Carroll, 2011; Tunbridge and Harrison, 2011). In particular, these findings provide a direct and specific link of altered error processing to prospective drug use in males and females with cocaine addiction.

Specifically, with thalamic activation increasing by 1 unit, the odds ratio for relapse within 90 days decreases by 62.6\% (logistic regression) and the hazard rate of relapse decreases by 19.9\% (Cox regression) in cocaine-dependent females. In
Regional functions during error processing and cognitive control

Cognitive control comprises multiple processes, of which error processing is a critical component. Error processing allows learning from mistakes and behavioural adjustments. One of the cortical areas that process errors is the dorsal anterior cingulate cortex and its role can be conceptualized under various frameworks of cognitive control (Li et al., 2008c; Hendrick et al., 2010; Ide and Li, 2011a). For instance, recent literature of computational and imaging neuroscience suggests dorsal anterior cingulate cortex in encoding discrepancy or a surprise signal, of which error is a special case [Ide et al., 2013; see also Egner (2011) for an overview]. Of direct relevance to the current results are the many imaging studies implicating hypervigilance and altered functional connectivity of the dorsal anterior cingulate cortex in people with substance use disorders (Bauer, 2002; Bolla et al., 2004; Li et al., 2008a; Sokhadze et al., 2008; Goldstein et al., 2009, 2010; Camchong et al., 2011; Connolly et al., 2012). For instance, individuals with cocaine use disorders showed dorsal anterior cingulate cortex hypervigilance during a reward drug cue task, with the extent of activation modulated by the saliency of the stimuli and correlated with the severity of cocaine use (Goldstein et al., 2009). In particular, recent work by Connolly et al. (2012) showed that long term abstinence is associated with compensatory hyperactivity of the dorsal anterior cingulate cortex during error processing in cocaine-dependent individuals, compared with control participants. The current work with a longitudinal design further extends these cross-sectional findings.

The thalamus is a key structure in the cortical subcortical circuit that processes error information (Hendrick et al., 2010; Ide and Li, 2011a). In a recent study, we used Granger causality analyses to describe a thalamo-medial cortical network in processing error signals during the stop signal task (Ide and Li, 2011a). Error-related negativity potential is reduced in patients with vascular damage to the thalamus (Peterburs et al., 2011), an effect that is likely mediated through thalamic connection to the medial frontal including cingulate cortices (Ide and Li, 2011a; Seifert et al., 2011; Liebermann et al., 2013). By monitoring performance and relaying error signals, thalamus helps maintain perceptual stability (Ostendorf et al., 2010) and allows a shifting of mental set during task switching (Block et al., 2007).

Thalamic dysfunction has also been implicated in stimulant misuse in human and rodent studies (Tomasi et al., 2007; Gu et al., 2010; James et al., 2010; Li et al., 2010a; Moeller et al., 2010; Gozzi et al., 2011; James et al., 2011; Kuo et al., 2011; Volkow et al., 2011). The thalamus showed diminished responses during a working memory task (Tomasi et al., 2007) and functional connectivity of a large circuit of cortical thalamic subcortical regions was altered in chronic cocaine users (Gu et al., 2010). In particular, decreased thalamo-cortical activation during exposure to cocaine cues was associated with vulnerability to relapse in female but not male cocaine users, in accord with the current findings of a gender difference (Volkow et al., 2011). In the stop signal task, females showed greater error-related activation in the thalamus, compared with males, despite indistinguishable behavioural performance including post-error slowing (Li et al., 2009). This gender difference perhaps suggests greater performance monitoring in females, a mechanism that may facilitate abstinence from drug use, according to the current findings.

Through its connections with the prefrontal cortices and limbic regions, the insula is widely implicated in decision making and self control (Critchley, 2005; Paulus et al., 2005a; Preuschoff et al., 2008), which are compromised in cocaine addicts and non-human primates chronically self-administering cocaine (Porro et al., 2004; Li and Sinha, 2008; Hanlon et al., 2010; Porter et al., 2011). Longer duration of cocaine dependence was correlated with greater grey matter volume reduction in orbitofrontal, cingulate and insular cortex (Ersche et al., 2011). Lesions of the insula were implicated in cessation of smoking in humans (Naqvi et al., 2007). Insula also plays an important role in integrating interoceptive information and representing bodily and emotional feelings (Craig, 2011). For instance, lesions of the insula resulted in decreased subjective evaluation of arousal stimuli (Bernton et al., 2011). Notably, compared with females, males showed fewer responses to emotional and stressful stimuli (Kemp et al., 2004; Fukushima and Hiraki, 2006; Wang et al., 2007). In the stop signal task, errors are behaviourally relevant and highly arousing, evoking greater electrodermal responses than stop success or go trials (Zhang et al., 2012). Thus, the gender-specific finding on the insula seems to imply a specific role of arousal (as elicited by negative environmental stimuli such as errors) in facilitating abstinence in males but not females.

Together, these previous studies strongly indicate the role of the dorsal anterior cingulate cortex, thalamus and the insula in cognitive control and drug addiction. In support of this broad literature, we demonstrated that error-related activities of these structures predicted relapse in cocaine dependence.

Inhibitory control and cocaine misuse

Relappers and non-relappers did not differ in the stop signal reaction time, nor were there activations related to inhibitory control significantly predicting relapse. These findings seemed in accord with recent work by Whelan et al. (2012), who showed that adolescents with drug use and those without did not differ in the stop signal reaction time, suggesting that stop signal reaction time is most likely not a predictor of drug use in adolescents. On the other hand, adolescents with high illegal drug use (five or more life time uses) appeared to have prolonged stop signal reaction time, compared with those with no or low illegal drug use [see Supplementary Table 8 of Whelan et al. (2012)]. These, along
with previous studies in cocaine or methamphetamine dependent individuals (Monterosso et al., 2005; Li et al., 2006, 2010b), suggest that deficits in inhibitory control as indexed by stop signal reaction time probably reflect a consequence of chronic drug exposure but do not, as a single factor, predispose individuals to illicit drug use.

Methodological considerations

In contrast to logistic regressions, a two-sample t-test failed to provide a predictive model for the relapse status. Furthermore, two-sample t-test is vulnerable to the small sample size and unbalanced design (Penny et al., 2003). In addition to these advantages enjoyed by the logistic model, Cox regression allows flexibility of predicting the time (days) to relapse, which serves as a continuous measure of the tendency to relapse. Moreover, the Cox model considers censored data points due to our limited follow-up period, whereas the two-sample t-test lacks such an important feature. These considerations suggest that examination of inter-subject variability within the patient population, particularly in a longitudinal context, is an important approach to understanding the neuropathology of mental illnesses.

Limitations of the study

A few important limitations of the study need to be discussed. First, the present cohort involved individuals who averaged 17 years of cocaine use and were all relapers in the past. Thus, individuals who did not relapse at 3 months would most likely relapse to cocaine use with a longer follow-up period. These considerations suggest that the present cohort may not be ideal to examine neural predictors of relapse given neuroplastic adaptations as a result of chronic cocaine exposure and a probable lack of variance in cognitive control in such a long-term addicted group (e.g. there was no difference in stop signal reaction time between relapers and non-relapers). A related issue is that, despite a moderate sample size, the small number of non-relapers may limit the power of the study to detect predictors of relapse in domains of cognitive control other than error processing. Second, on the basis of the current findings, we cannot ascertain whether the error-processing deficits are a result of chronic cocaine use or cause individuals to engage in cocaine misuse. We feel that they most likely reflect a combination of both factors; chronic cocaine use leads to deficits in cognitive control, which in turn perpetuates continued, habitual use of cocaine. To distinguish these possibilities, one would have to directly control for cocaine exposure. For instance, Ersche et al. (2011) demonstrated abnormalities in fronto-striatal brain systems in stimulant-dependent individuals. Furthermore, such abnormalities were present in their biological siblings who have no history of chronic drug abuse, suggesting a causal role of fronto-striatal functioning including self control in cocaine misuse (Ersche et al., 2012). Third, although current use of, or a history of abuse of, or dependence on other illicit substances is an exclusion criterion and participants denied use of other illicit substances, we did not screen for club drugs or other stimulants such as methylphenidate or methedrone in urine tests. Thus, the potential impact of these other drugs on current findings needs to be evaluated in future work. Fourth, in assessing cocaine use during follow-up, we adhered strictly to the methods involved in the timeline follow-back method, including use of a personal calendar and confirmation with collateral information. However, inherent to studies that use timeline follow-back is the uncertainty and potential unreliability of subjective report. Fifth, we identified gender specific predictors of relapse but their relationship to gender differences in the clinical profiles of cocaine and other substance use disorders need to be ascertained in future studies. Finally, although we have used various approaches to validate these error-related areal activations as a relapse predictor in cocaine addiction, the results will need to be tested and confirmed in an independent cohort.

Conclusion

We demonstrate that diminished brain activations during error processing are related prospectively to drug use in cocaine addicts. Decreased activation in the dorsal anterior cingulate cortex represents a gender shared predictor of relapse, while decreased activation of the thalamus and left insula each predicts relapse in females and males.

Acknowledgements

We thank the medical and nursing staff at the Clinical Neuroscience Research Unit, Connecticut Mental Health Center, and Connecticut Department of Mental Health and Addiction Services for their inpatient care. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Drug Abuse, National Center for Research Resources or the National Institutes of Health.

Funding

This work was supported by National Institutes of Health [R01-DA023248 to C.L., K02-DA026990 to C.L., P50-DA16556 to R.S., P01-AA019072 to X.L., P30-AI042853 to X.L.]; the State of Connecticut; and a Brown University faculty startup fund to X.L.

Supplementary material

Supplementary material is available at Brain online.

References

Anker JJ, Carroll ME. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. Curr Top Behav Neurosci 2011; 8: 73–96.


Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. Ann N Y Acad Sci 2011; 1225: 72–82.


Ide JS, Li C-SR. A cerebellar thalamic cortical circuit for error-related cognitive control. Neuroimage 2011a; 54: 455–64.


James MH, Charnley JL, Flynn JR, Smith DW, Dayas CV. Propensity to ‘relapse’ following exposure to cocaine cues is associated with the recruitment of specific thalamic and epithalamic nuclei. Neuroscience 2011; 199: 235–42.


Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer Verlag; 2000.


