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Deficits in default mode network activity preceding error in cocaine dependent individuals

Sarah R. Bednarski[1], **Sheng Zhang**[1], **Kwang-Ik Hong**[1], **Rajita Sinha**[1], **Bruce J. Rounsaville**[1,4], and **Chiang-shan R. Li**[1,2,3,*]

[1]Department of Psychiatry, Yale University, New Haven, Connecticut 06519

[2]Department of Neurobiology, Yale University, New Haven, Connecticut 06519

[3]Interdepartmental Neuroscience Program, Yale University, New Haven, Connecticut 06519

[4]VA Connecticut Healthcare Systems, West Haven, Connecticut 06516

Abstract

Background—Cocaine dependence is associated with cognitive deficits and altered task-related cerebral activation in cognitive performance (see Li and Sinha, 2008, for a review). Relatively little is known whether these individuals are also impaired in regional brain activation of the default mode network (DMN). We demonstrated previously that greater activation of the default brain regions precedes errors in a stop signal task performed by healthy controls (SST, Li et al., 2007). We seek to determine whether individuals with cocaine dependence are impaired in DMN activity, specifically activity preceding error, as compared to the healthy people. We also examine the relation to years of cocaine use.

Methods—Individuals with cocaine dependence (CD, n=23) and demographics-matched healthy controls (HC, n=27) performed a SST that employed a tracking procedure to adjust the difficulty of stop trials and elicit errors approximately half of the time. Blood oxygenation level dependent (BOLD) signals of go trials preceding stop error as compared to those preceding stop success trials were extracted with generalized linear models using Statistical Parametric Mapping.

Results—HC showed activation of bilateral precuneus and posterior cingulate cortices and ventromedial prefrontal cortex (vmPFC) preceding errors during the SST. In contrast, despite indistinguishable stop signal performance, CD did not show these error predicting activations. Furthermore, the effect size of error-preceding vmPFC activation was inversely correlated with years of cocaine use.

*Address correspondence to: Dr. Chiang-shan Ray Li, Connecticut Mental Health Center, S112, Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06519, Phone: 203-974-7354, FAX: 203-974-7076, chiang-shan.li@yale.edu.

Contributors

Sarah R. Bednarski collected and analyzed the data, and wrote the manuscript. Kwang-Ik Hong and Sheng Zhang analyzed the data. Chiang-shan R. Li designed the study, analyzed and interpreted the data, and wrote the manuscript. Rajita Sinha and Bruce J. Rounsaville participated in the interpretation of the data and writing of the manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Conclusions—These findings indicate DMN deficits and could potentially add to our understanding of the effects of chronic cocaine use on cerebral functions in cocaine dependence. Work to further clarify potential changes in functional connectivity and gray matter volume is warranted to understand the relevance of DMN to the pathology of cocaine misuse.

Keywords

attention; attentional lapse; default circuit; prefrontal; neuroimaging

1. Introduction

Past neuroimaging work has distinguished “default” activity generated during resting state from cerebral activity associated with cognitive task performance (Shulman et al., 1997; Raichle et al., 2001, 2007; Grecius et al., 2003; Grecius and Menon 2004; Vincent et al., 2007; Pfefferbaum et al., 2010). This neurological baseline seen in the resting brain can be described by the default mode network (DMN) (Raichle et al., 2001). In general, a cognitive task typically increases activation in the task-oriented network, meanwhile decreasing activation in the DMN (Raichle et al., 2001; Greicius et al., 2003). Dysfunctions of the DMN were noted in a wide variety of neurological and psychiatric conditions, including Alzheimer’s disease, attention deficit hyperactivity disorder, anxiety, and depression (Grecius et al., 2004; Rombouts et al., 2005; Wang et al., 2006; Sorg et al., 2007; Baliki et al., 2008; Uddin et al., 2008; Broyd et al., 2009; Bush 2010).

Imaging studies of cocaine dependent individuals have largely focused on task-evoked activity. In particular, numerous studies have described frontal cortical and subcortical dysfunctions in individuals with cocaine or other psychostimulant use disorders (Aron and Paulus 2007; Everitt et al., 2007; Garavan and Hester 2007; Hanlon et al., 2009, and in press; Li and Sinha 2008; Porrino et al., 2007; Wesley et al., 2011). For instance, Goldstein and colleagues utilized a sustained attention task to show that while practice is associated with altered activation in the posterior cerebral regions in healthy individuals, it is associated with changes of activation in frontal brain regions in cocaine dependent individuals (Goldstein et al., 2007). In another study, hypoactivation of the dorsal anterior cingulate cortex to an emotionally salient stimulus is associated with the current frequency of cocaine use (Goldstein et al., 2009). Our previous study of the stop signal task demonstrated decreased medial superior frontal and anterior cingulate cortical activation during inhibitory control (Li et al., 2008c) and altered thalamic processing of errors in association with loss of self control (Li et al., 2010a) in abstinent cocaine dependent individuals. These studies elicit a difference, and likely deficit, in response to cognitive tasks in the cocaine-dependent brain. On the other hand, little is known whether the DMN is also dysfunctional in these individuals. The current study addressed this question.

We built upon our previous findings from the stop signal task that areas within the DMN, including the ventromedial prefrontal cortex, posterior cingulate cortex, and precuneus, were significantly more active in go trials preceding a stop error as compared to those preceding a stop success in healthy participants, thereby marking the DMN as an inherent mechanism for “error prediction” (Li et al., 2007). A recent study which pooled data from five stop signal task experiments in healthy populations also found an increase in DMN activity prior to error commission (Congdon et al., 2010). An fMRI study of the Flanker task used independent component analysis to examine the hemodynamic response prior to an error. Results showed a decreased deactivation in the DMN combined with a decrease in task network activation up to six seconds preceding an erroneous vs. correct trial (Eichele et al., 2008). In a fourth report, the DMN is more active, or decreasingly deactivated, during error laden trials in an attention task requiring identification of a target surrounded by congruent

or incongruent distracter stimuli (Weissman et al., 2006). Overall, these results indicate a dynamic range of activation in the DMN, which could influence mental state and cognitive performance. Here we seek to determine whether individuals with cocaine dependence are impaired in DMN activity as compared to the healthy people. Specifically, by contrasting go trials preceding a stop error and those preceding a stop success trial, we examined whether error-preceding activity in the DMN during the stop signal task was altered in cocaine dependent individuals and whether this altered activity was related to years of cocaine use. On the basis of our previous work, we hypothesized that cocaine dependent volunteers, as compared to healthy controls, would show less activation preceding errors in the posterior cingulate cortex/precuneus and the perigenual anterior cingulate cortex.

2. Methods

2.1. Subjects

Twenty-three abstinent individuals with cocaine dependence (CD) and 27 demographics matched healthy control (HC) volunteers were recruited from the greater New Haven area through advertisements and word-of-mouth to participate in the study (Table 1). CD volunteers met criteria for current cocaine dependence, as diagnosed by the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). Recent cocaine use was confirmed by urine toxicology screens upon admission. They were drug-free while staying in a monitored treatment unit for two weeks prior to the current fMRI study. CD volunteers were assessed with Beck Depression Inventory (BDI) at admission and once every week during their inpatient stay. The average (mean±SD) BDI scores were 17.9±10.2 at admission and 6.7±6.0 after two weeks, consistent with those reported previously for this population (Rubin et al., 2007; Falck et al., 2002; López and Becoña, 2007). They were also assessed with State-Trait Anxiety Inventory (STAI) at admission. The average STAI scores of 45.2±13.8 for trait and 39.8±12.7 for state were within the range reported previously for CD (Karlsgodt et al., 2003; Rubin et al., 2007). None of the CD volunteers had BDI or STAI scores indicating clinical depressive or anxiety disorders. 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. Individuals with current depressive or anxiety symptoms requiring treatment or currently being treated for these symptoms were excluded as well. The data of 11 HC volunteers came from the cohort of our earlier study (Li et al., 2007) and the majority (18) of the HC volunteers did not undergo SCID or a urine toxicology test. 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.

2.2. Behavioral task

The behavioral 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 via button press was recorded with a fiber-optic button box (Current Designs, Philadelphia, PA). We employed a simple reaction time task in this stop-signal paradigm (Li et al., 2006; 2009; Logan and Cowan 1984). 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 and the remainder were stop trials. In a stop trial, an additional "X," the "stop" signal, appeared after 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 (SSD), the duration of time in which 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 SSD increased by 67 ms; conversely, if they failed, the SSD decreased by 67 ms (Levitt 1970). There was an inter-trial-interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up in a small number of trials. Prior to the fMRI 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 one to two minute 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. With the staircase procedure we anticipated that the subjects succeeded in withholding their response in approximately half of the stop trials.

2.3. Imaging protocol

We employed a 3T scanner (Siemens Trio) and a circularly-polarized head coil (with one element and no acceleration) for the current study. Conventional T_1-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 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 = 4mm and no gap. Functional, blood oxygenation 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 = 2,000 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 = 4mm and no gap. Three hundred images were acquired in each run for a total of 4 runs.

2.4. Data analysis and statistics

Data were analyzed with Statistical Parametric Mapping (SPM5, 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. 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 each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Ashburner and Friston 1999; Friston et al., 1995a). Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

Four main types of trial outcome were first distinguished: go success (G), go error (F), stop success (SS), and stop error (SE) trial (Fig. 1a). For the evaluation of "pre-stop" processes, G trials were further divided into those that preceded a G (pre-G), SS (pre-SS), and SE (pre-SE) trial (Fig. 1b). 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 the temporal derivative of the canonical HRF entered as regressors in the model (Friston et al., 1995b). Realignment parameters in all 6 dimensions were also entered in the model. CD and HC

volunteers did not differ in the extent (mean± standard deviation) of translational (CD: 0.35 ± 0.59 mm vs. HC: 0.32 ± 0.57 mm; p=0.376, two-sample t test) or rotational (0.16 ± 0.40° vs. 0.18 ± 0.42°; p=0.516) head motion. The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. Serial autocorrelation of the time series was corrected by a first-degree autoregressive or AR (1) model (Della-Maggiore et al., 2002; Friston et al., 2000). The GLM estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we constructed the following statistical contrast for the individual subjects: pre-SE vs. pre-SS. The *con* or contrast (difference in β) images taken from the first-level analysis were used for the second-level group statistics (random effect analysis; Penny and Holmes 2004), including a one-sample t test each for CD and HC groups and a two-sample t test comparing CD and HC. Brain regions were identified using an atlas (Mai et al., 2003). In region of interest (ROI) analysis, we used MarsBaR (Brett et al., 2002; http://marsbar.sourceforge.net/) to derive the effect size of activity change for the ROIs in each individual subject. All voxel activations are presented in MNI coordinates.

3. Results

3.1. General behavioral performance

Table 2 shows stop signal performance. Both CD and HC participants succeeded in about half of the stop trials, indicating the successful utility of the staircase procedure in tracking subject performance. CD and HC did not differ in any aspects of the stop signal performance.

3.2. Neural activity preceding SE vs. SS trials

At a threshold of $p<0.005$, uncorrected, and 50 voxels in extent of activation, HC but not CD showed greater activation in the perigenual and subgenual anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC)/precuneus during pre-SE compared to pre-SS go trials (Fig. 2a, Table 3). Direct comparison with a two-sample t test showed greater error predicting activation (pre-SE > pre-SS) in the ventromedial prefrontal cortex and posterior cingulate cortex/precuneus (Fig. 2b, Table 3). Fig. 3 showed the two-sample t test results in axial sections of the brain. In contrast, no brain regions showed greater error-preceding activation in CD, compared to HC.

In addition to voxel-wise whole brain activation, we also performed small volume correction based on the coordinates obtained in our earlier work (Li et al., 2007): spheres with 15 mm in radius centered on PCC/precuneus (x=−16, y=−60, z=32), perigenual ACC (x=4, y=32, z=4), and transverse frontopolar gyrus (x=4, y=52, z=24). Both the PCC/precuneus and perigenual ACC masks identified the same peaks with the former being significant at $p<0.05$, corrected for family-wise error of multiple comparisons.

Using linear regression, we correlated the effect size of error-predicting activation of the vmPFC and posterior cingulate cortex/precuneus with years of cocaine use across the 23 CD. The results showed that the effect size of vmPFC ($R^2=0.332$, $p<0.005$, Fig. 4) but not posterior cingulate cortex/precuneus ($R^2=0.016$, $p>0.5$) was inversely correlated with years of cocaine use.

4. Discussion

The main finding of this study indicates a lack of moment-to-moment DMN fluctuation in CD as compared to HC. The contrast made here is of identical go trials preceding an unanticipated stop trial with an error versus with a success. In other words, CD do not

demonstrate a neural signature of impending error as seen in HC. This difference between the populations cannot be attributed to performance differences because there are none.

The contrast of pre-SE and pre-SS trials did not address any specific task outcomes such as response inhibition or post-error slowing as was the focus of our previous work (Li et al., 2006; 2008a; 2008b). Rather, both pre-SE and pre-SS are go trials, with the difference being that the pre-SE precedes a stop error and the pre-SS precedes a stop success trial. In HC, the activity of DMN can be used to differentiate between these two trial conditions. That is, in accord with many previous studies of the DMN (summarized in Congdon et al., 2010), the activity of DMN goes down when participants are more alert (less prone to errors), while at other moments the activity of the DMN goes up when they are less alert (more prone to errors). Thus, our data (current and Li et al., 2007) suggest that if a stop trial occurs at the time when the immediately preceding activity of the DMN goes down, then participants are more likely to succeed in stopping than when the activity of the DMN goes up. Our current findings indicate that this fluctuation of DMN activity does not happen in CD individuals. Whether it is a failure to deactivate or activate, the DMN of CD individuals lacks this moment to moment fluctuation in activity.

We demonstrated that this deficit in DMN was linearly correlated with the years of cocaine use in CD. Although the number of years of cocaine use is unlikely the sole indicator of the severity of cocaine dependence, this association is consistent with recent studies showing the modulation of the DMN including vmPFC functional circuitry by catecholaminergic agents (Argyelan et al., 2008; Kelly et al., 2009; Nagano-Saito et al., 2009). For instance, in Parkinson's disease patients performing a motor sequence learning task and a simple movement task, intravenous levodopa abolished learning-related deactivation occurring in the vmPFC (Argyelan et al., 2008).

While the current results characterized dysfunctions of the DMN as a consequence of chronic cocaine use, other studies highlighted the acute effects of psychostimulants on the DMN. For instance, in Positron Emission Tomography (PET) imaging of brain glucose metabolism in healthy adults, Volkow and colleagues showed that methylphenidate, a psychostimulant with neuropharmacological properties similar to cocaine, decreases activation of the DMN during cognitive performance and that this effect is associated with improved performance in those individuals who activated the DMN during the task (Volkow et al., 2008). A more recent study showed that treatment with methylphenidate suppressed activation of the ventral ACC and posterior cingulate cortex in children with attention deficit hyperactivity disorders (Peterson et al., 2009). The authors suggested that methylphenidate may ameliorate mind-wandering by decreasing activity of the DMN. Our recent fMRI study also demonstrated that methylphenidate improved inhibitory control by decreasing vmPFC activation during stop signal inhibition in CD (Li et al., 2010b). In another study combining PET imaging and fMRI, Tomasi and colleagues showed in healthy individuals that the availability of the dopamine transporters (DAT) in the striatum is negatively correlated with the blood oxygenation level dependent signal in the precuneus – an area of the DMN – under increased attentional load in a visuospatial task (Tomasi et al., 2009). The authors suggested that stimulant medications may help improve attention and cognitive performance by blocking DAT and thereby increasing dopaminergic modulation of the DMN. Overall, these findings appeared to converge to suggest a potential impact of psychostimulants on the DMN, consistent with the current findings in cocaine dependent individuals.

We would also like to emphasize that regions within the DMN are functionally connected as part of the intrinsic activity of brain (Buckner and Vincent, 2007; Raichle and Snyder, 2007). Although the current findings suggested a deficit of certain brain regions within the DMN during an externally imposed task, they did not indicate that the pattern of intrinsic

connectivity was disrupted as a result of cocaine exposure. Future work is needed to examine this issue by analyzing resting state low frequency BOLD signals in CD (Gu et al., 2010).

This study has a few important limitations. First, the majority of our HC volunteers did not undergo a structured psychiatric interview or urine toxicology test. Second, the current results did not specify a causal link between years of cocaine use and deficits of the DMN, despite a positive correlation between the two. There are many clinical factors, including history of abuse of other substances, depression, anxiety, and psychological trauma, which were not accounted for. Furthermore, given that this is a cross-sectional study, other potential variables including mood and sleep at the time of fMRI may also impact the results. An additional issue is that the current findings were obtained with a relatively liberal threshold despite a moderate sample size. Finally, studies have reported changes in cerebral gray matter volumes in cocaine dependence (Lim et al., 2008; Sim et al., 2007; but see also Narayana et al., in press). Although it is unclear how changes in gray matter volume and functional activity are associated, this issue deserves attention in future studies. Taken together, the current results should be considered preliminary and require replication in the future with greater concessions made to the limitations presented.

In conclusion, we show in the current study that cocaine dependence is associated with dysfunction of the default mode network of the cerebral cortex. This finding complements previous work on task-related deficits in cocaine dependence.

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The NIH and the State of Connecticut had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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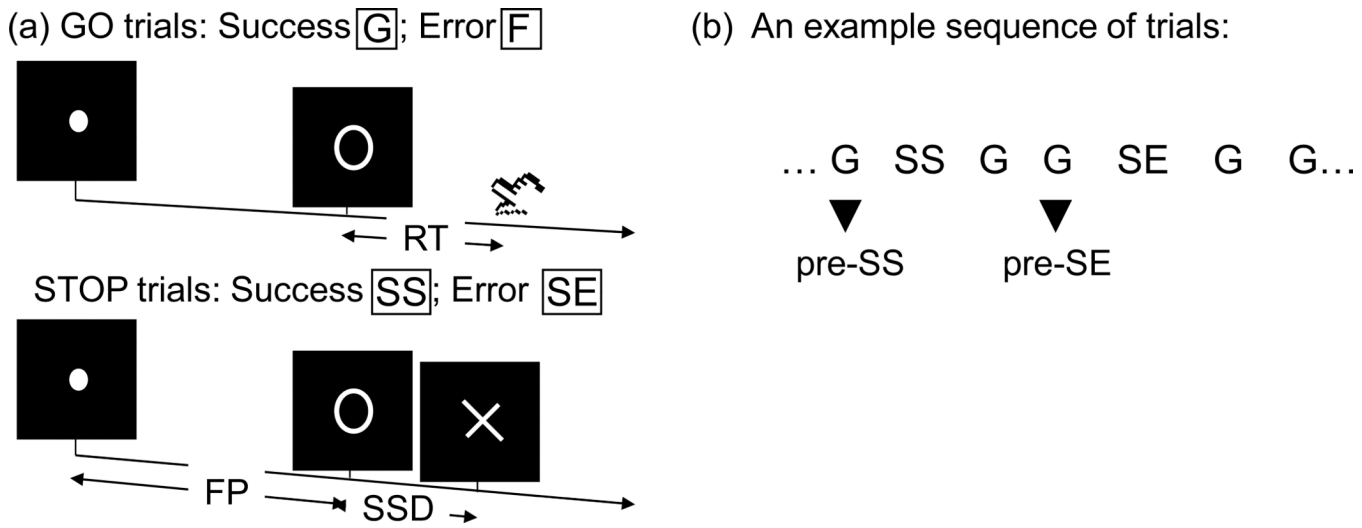

Figure 1.

(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 to 5 s (the fore-period or FP, uniform distribution) 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 and stop error trial, respectively. We distinguished go success (G) and go error (F), and stop success (SS) and stop error (SE) trials during the task. (b) Go successes were further distinguished by their subsequent trial; thus G trials followed by a SS, and SE trial were indicated by pre-SS, and pre-SE trials, respectively.

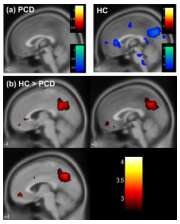

Figure 2.

(a) Brain regions showing greater activation during pre-SE than pre-SS trials (blue) in HC (right panel) but not CD (left panel) in the perigenual and subgenual anterior cingulate cortex and posterior cingulate cortex/precuneus ($p<0.005$, uncorrected). At the same threshold, no brain regions showed greater activation during pre-SS compared to pre-SE trials (red). T statistic for the contrast was shown for a mid-sagittal section ($x=0$) of a mean EPI image. (b) Two sample t-test of the contrast pre-SE > pre-SS showing greater error predicting activation in the ventromedial prefrontal cortex and posterior cingulate cortex/precuneus in HC, as compared to CD ($p<0.005$, uncorrected). T map of the contrast was overlaid on sagittal sections ($x=-4, 0, 4$) of a mean EPI image. Color bars represent voxel T value.

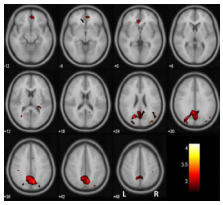

Figure 3.
Brain regions showing greater activation during pre-SE than pre-SS trials in HC, as compared to CD ($p<0.005$, uncorrected). T statistic was overlaid on a mean EPI image in axial sections from $z=-12$ to $z=48$ with adjacent sections 6mm apart. Neurological orientation: Right = right. Color bars represent voxel T value.

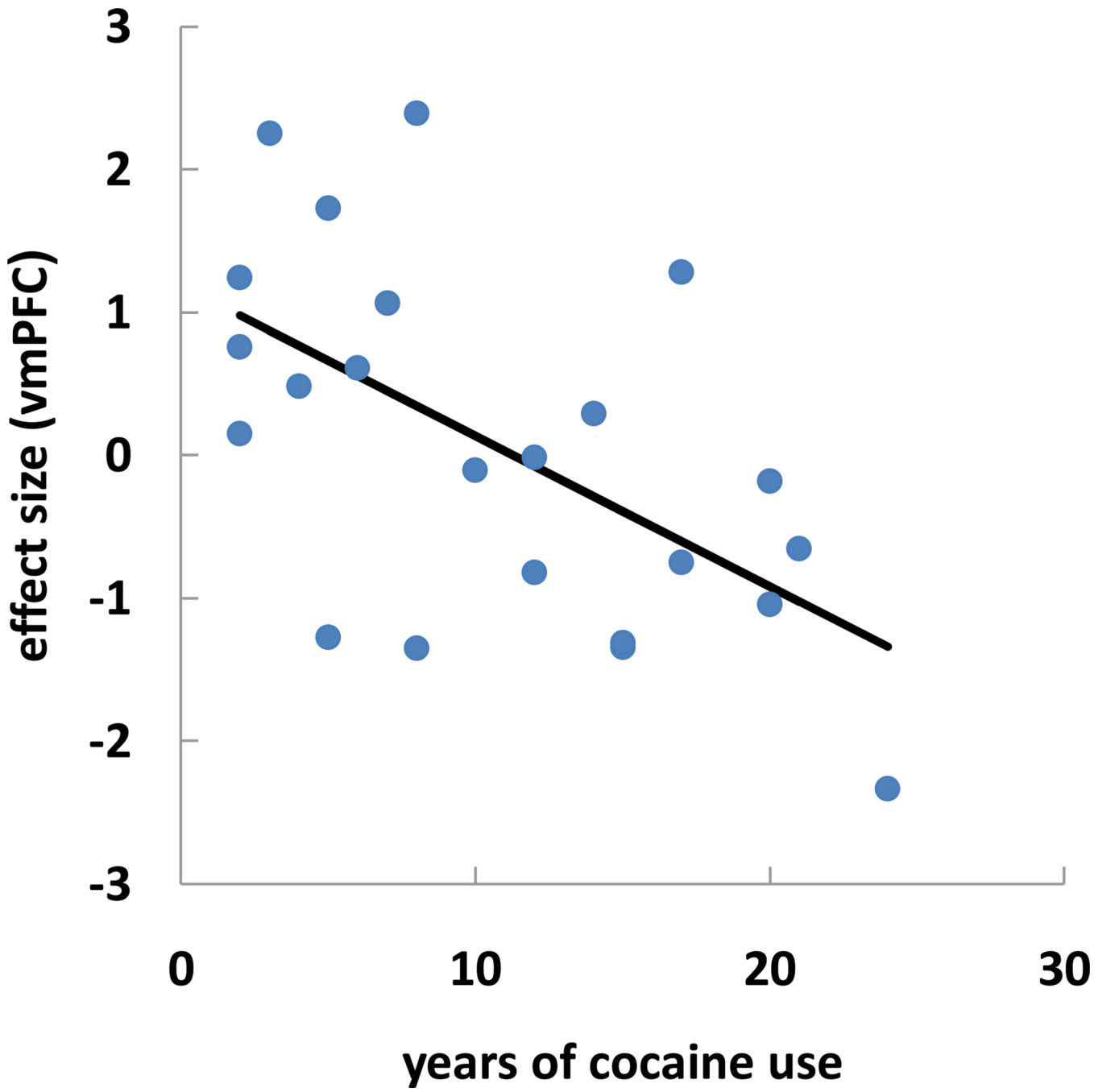

Figure 4.
Effect size correlation of vmPFC (pre-SE > pre-SS) is inversely correlated with years of cocaine use for 23 CD (R^2=0.332, p<0.005, Pearson regression). Each dot represents the data of one subject.

Table 1

Demographics of the subjects.

Subject Characteristics		PCD (n=23)	HC (n=27)	p value
age (years)		36.2 ± 6.3	34.9 ± 6.5	0.49[a]
women/men		12/11	15/12	0.37[b]
ethnicity	African Am.	39.1%	33.3%	0.58[b]
	Caucasian	56.5%	59.2%	
	Hispanic/other	4.3%	7.4%	
education (years)		11.7 ± 1.7	12.6± 1.6	0.08[a]
avg. no. of days with cocaine use (past month)		13.1 ± 7.4	N/A	N/A
avg. no. of yrs. with cocaine use (lifetime)		10.8 ± 6.9	N/A	N/A

Note: values are mean±standard deviation;

[a] 2-sample t test;

[b] $\chi 2$ test.

Table 2

Stop Signal Performance.

	SSRT (ms)	FP effect (effect size)	Median go RT (ms)	%go	%stop	PES (effect size)
PCD (n=23)	200 ± 45	2.05 ± 1.35	546 ± 83	96.5 ± 1.5	51.2 ± 2.0	1.90 ± 1.52
HC (n=27)	196 ± 36	2.25 ± 1.20	537 ± 115	97.2 ± 1.7	50.2 ± 2.7	1.50 ± 1.24
p value*	0.76	0.582	0.747	0.15	0.129	0.309

Note: all values are mean ± standard deviation;

* P value based on 2-tailed 2-sample t test;

CD: individuals with cocaine dependence; HC: healthy controls; SSRT: stop signal reaction time: FP: fore-period; RT: reaction time; %go: percentage of go success trials; %stop: percentage of stop success trials; PES: post-error slowing.

Table 3

Error-preceding regional brain activations: pre-SE go trials > pre-SS go trials.

	Cluster Size (voxels)	Voxel Z Value	MNI Coordinates (mm) X	Y	Z	Side	Identified Region
HC (n=27)	703	4.24	4	−64	12	R	PCC/precuneus
	132	3.23	−4	28	−4	L	perigenual/subgenual ACC
CD (n=23)	None						
HC > PCD	119	3.59	0	32	−20	R/L	ventromedial PFC
	230	3.52	−16	−68	24	L	PCC/precuneus
PCD > HC	None						

Note: p<0.005, uncorrected, and 50 voxels in extent of activation;

PCC: posterior cingulate cortex; ACC: anterior cingulate cortex; PFC: prefrontal cortex.

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