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ScienceDirect
Psychiatry Research: Neuroimaging 155 (2007) 189–201
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Thalamo-cortical dysfunction in cocaine abusers: Implications in attention and perception

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Received 14 September 2006; received in revised form 8 January 2007; accepted 4 March 2007

Abstract

Cocaine affects sensory perception and attention, but little is known about the neural substrates underlying these effects in the human brain. We used functional magnetic resonance imaging (fMRI) and a sustained visuospatial attention task to assess if the visual attention network is dysfunctional in cocaine abusers ($n=14$) compared to age-, gender-, and education-matched controls ($n=14$). Compared with controls, cocaine abusers showed (1) hypo-activation of the thalamus, which may reflect noradrenergic and/or dopaminergic deficits; (2) hyper-activation in occipital and prefrontal cortices, which may reflect increased visual cortical processing to compensate for inefficient visual thalamic processing; and (3) larger deactivation of parietal and frontal regions possibly to support the larger hemodynamic supply to the hyper-activated brain regions. These findings provide evidence of abnormalities in thalamo-cortical responses in cocaine abusers that are likely to contribute to the impairments in sensory processing and in attention. The development of therapies that diminish these thalamo-cortical deficits could improve the treatment of cocaine addiction.
Published by Elsevier Ireland Ltd.

Keywords: fMRI; PET; Visual attention; Dopamine; Norepinephrine; Addict

1. Introduction

Cocaine increases the release of neurotransmitters (Raiteri et al., 1977; Fozard et al., 1979; Volkow et al., 2000) that regulate the neurocircuitry of attention, and this is likely to underlie cocaine's effects on attention (Kahkonen et al., 2002; Mair et al., 2005). As is true of other stimulant drugs, the acute administration of cocaine can increase attention (Fone and Nutt, 2005), but chronic use has been associated with impairment in sustained attention (Aharonovich et al., 2003, 2006; Goldstein et al., 2004; Jovanovski et al., 2005). This could reflect the deficit in dopaminergic function reported by imaging studies in cocaine abusers (Volkow et al., 1997). Alternatively it could also reflect changes in noradrenergic activity, which though not investigated yet in cocaine abusers have been shown to occur in non-human primates exposed chronically to cocaine (Beveridge et al., 2005).

Cocaine abusers have been shown to have hypo-perfusion (Gollub et al., 1998; Gottschalk and Kosten,

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0925-4927/$ - see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.pscychresns.2007.03.002

2002) and hyper-activation (Lee et al., 2003) in visual cortices. Moreover, the thalamus, the major visual processor in the pathway from the retina to the visual cortex, is also impaired in cocaine abusers (Volkow et al., 1997). Characterization of the neurobiological substrates involved in the attention deficits in cocaine abusers, which are central to cocaine withdrawal and recovery, is therefore of direct relevance to the treatment of cocaine abuse (Aharonovich et al., 2003). Though multiple neuroimaging studies have been done to characterize the neurocircuitry involved in cocaine addiction, these have been mostly focused on reward processing/motivation (Goldstein et al., 2007a,b,c; Goldstein and Volkow, 2002; Volkow et al., 2003) or inhibitory control/executive function (Hester and Garavan, 2004; Hester et al., 2004; Kaufman et al., 2003), and there is no published imaging research on sustained attention nor on perception in cocaine abusing subjects. The purpose of this study was to evaluate the involvement of the thalamus, which underlies the alerting component of attention (Fan et al., 2005), and is a target region for DA axons arising from DA neurons located in the hypothalamus, periaqueductal gray, ventral mesencephalon, and lateral parabrachial nucleus (Sanchez-Gonzalez et al., 2005) and for noradrenergic axons arising from the locus coeruleus (Melchitzky and Lewis, 2001; Remy et al., 2005), in the attentional deficits that occur in cocaine abusers. Note that the DA pathway that innervates the thalamus appears to be distinct from the mesocortical, mesostriatal or mesolimbic DA pathways (Garcia-Cabezas et al., 2007). Moreover, cocaine has been shown to bind to the thalamus in the human brain (Wang et al., 1995), and imaging studies have provided evidence of disrupted thalamic activity in cocaine abusers (Volkow et al., 1997). We therefore hypothesized that thalamic disruption underlies in part the attentional deficits in cocaine abusers.

For this purpose we used functional magnetic resonance imaging (fMRI) and a sustained visuospatial attention (VA) task to evaluate whether disrupted thalamic activation underlies the abnormal hemodynamics of the visual cortex in cocaine abusers (Gottschalk and Kosten, 2002; Lee et al., 2003). The VA task has graded levels of difficulty, engages cortical and sub-cortical regions (thalamus, parahippocampus), and has been recently used to evaluate brain activation in healthy volunteers (Tomasi et al., 2004), HIV patients with mild attentional deficits (Chang et al., 2004), and marijuana users (Chang et al., 2006). We specifically hypothesized that the VA task would produce lower thalamic activation and larger visual cortex activation in cocaine abusing subjects than for controls and that these functional abnormalities would be associated with impaired task performance (accuracy or speed).

2. Methods

2.1. Subjects

Fourteen healthy chronic cocaine abusers (8 men, 6 women; age = 38.1 ± 10.4 years; education = 13.8 ± 2.6 years; mean ± S.D.), and 14 age-, gender-, and education-matched healthy control subjects (8 men, 6 women; age = 34.6 ± 7.9 years—$P = 0.31$ for group differences in age, two-sample t-test; education = 15.1 ± 2.3 years—$P = 0.11$ for group difference in education, two-sample t-test) participated in this study. These participants were recruited from advertisements on public bulletin boards, in local newspapers, and by word-of-mouth. Each subject provided a written informed consent approved by the Institutional Review Board at the Brookhaven National Laboratory. All subjects were carefully screened to ensure that they fulfilled study criteria. The inclusion criteria for both groups were: age 18 years or older, ability to read and speak English fluently; and right-hand dominance. Subjects were excluded if they had any confounding chronic medical or neuropsychiatric illnesses, contraindicated metallic objects in the body, poor vision (worse than 20/80 without use of glasses and unable to wear contact lenses), or claustrophobia. Additionally, control subjects were excluded if they had history of drug dependence or positive urine toxicology screen on the day of the study. Cocaine abusers were evaluated with the Structured Clinical Interview for DSM-IV Axis I Disorders [research version (First et al., 1996; Ventura et al., 1998) — Patient Edition (SCID-I/P)]. Cocaine abusers were included in the study if they had a DSM-IV diagnosis for Cocaine Dependence or Abuse, and at least a 12-month (3.5 g/week) history of cocaine use (predominantly by smoked route); they were excluded if they had a positive urine toxicology screen for amphetamines, marijuana, benzodiazepines, or opiates on the day of the study. Six of the cocaine subjects had a positive urine toxicology screen for cocaine on the day of the study; they reported use of cocaine one ($n = 2$), 2 ($n = 1$), or 3 ($n = 3$) days before the study. The urine toxicology screen was negative for the remaining eight cocaine subjects; they reported use of cocaine more than 30 days prior the study. Six cocaine subjects were non-smokers and eight cocaine subjects were current cigarette smokers (mean daily use = 9 ± 7 cigarettes). Eleven control subjects were non-smokers and three

control subjects were current cigarette smokers (mean daily use = 11 ± 6 cigarettes); the difference in cigarette smoking status between the groups was not significant ($P = 0.12$; Fisher's exact test).

2.2. VA paradigm

Subjects performed a set of non-verbal VA tasks, which involved mental tracking of moving balls (Chang et al., 2004; Culham et al., 1998; Jovicich et al., 2001; Tomasi et al., 2004) and had a blocked design. The task blocks were 60 s long and composed of five "TRACK" and respond periods. During these periods, 2, 3, or 4 out of 10 target balls were briefly highlighted, and then all balls started to move; the subjects' task was to fixate on the center cross and track the target balls as they moved randomly across the display (12° of the central visual field) with instantaneous angular speed of 3°/s. The 10 balls moved in a simulated Brownian motion, and collided with, but did not penetrate, each other. At the end of "TRACK" periods, the balls stopped moving and a new set of balls was highlighted; the subjects' task was to press a button if these balls were the same as the target set. Button press events were used to record performance

Table 1
Talairach coordinates of brain areas showing effects of cocaine abuse on BOLD-fMRI signals for the VA task (2-, 3-, and 4-ball tasks conjunctively) and their statistical significance

Brain region	Side	[mm]			*z*-scores		
		x	y	z	Control	Cocaine	Cocaine>Control
cdACG; BA32	C	−6	18	42	5.4*	4.8 *	NS
rACG; BA32	C	−18	42	−3	NS	−8.5 *	−6.7 *
ACG; BA24	C	−12	15	30	NS	−3.5 *	−3.1 *
IFG; BA47	L	−33	21	−3	4.1 *⦿	3.1 *⦿	NS
	R	33	21	0	4.1 *	2.7 *	NS
MFG; BA6	L	−30	6	54	7.9 *	9.6 *	2.8 *
	R	27	6	54	5.9 *	8.6 *	3.2 *
MFG; BA9	L	−45	6	24	7.2 *⦿	7.4 *⦿	NS
	R	42	12	27	3.3 *	7.6 *	4.0 *
MDTHA	L	−6	−15	3	6.0 *	NS	−2.7 *
	R	6	−15	3	4.4 *	2.6 *	NS
LGTHA	L	−21	−21	−3	4.1 *	−2.7 *	−4.7 *
LC	L	−3	−36	−12	NS	−4.1 *	−2.8 *
INS; BA13	L	−39	−12	6	−8.8 *	−7.8 *	NS
	R	39	−12	12	−6.9 *	−8.1 *	NS
HIP	R	33	−33	−6	NS	−6.0 *	−3.8 *
AMY	L	−21	−6	−18	NS	NS	2.7
PHG; BA30	L	−15	−48	3	−8.3 *	−6.2 *	NS
	R	15	−48	3	−6.1 *	−4.0 *	NS
PreCUN; BA7	C	−9	−48	45	NS	−2.5 *	−4.2 *
PreCUN; BA19	L	−33	−69	39	7.0 *	−7.8 *	−9.7 *
PreCUN; BA31	C	3	−63	24	−11.5 *	−10.8 *	NS
CG; BA24	C	−6	−6	42	−8.0 *	−8.3 *	NS
PCL; BA6	C	−6	−33	63	NS	−5.2 *	−4.3 ▽
IPC; BA40	L	−39	−48	57	10.8 *⦿	9.5 *⦿	NS
	R	27	−45	57	10.0 *⦿	9.2 *⦿	NS
SPC; BA7	L	−24	−60	60	10.6 *	8.1 *	NS
	R	12	−60	60	11.2 *	10.2 *	NS
LG; BA18	L	−18	−75	−9	NS ▣	10.7 * ▣	8.9 *
	R	9	−78	3	NS ▣	3.0 * ▣ ◁	3.0 *
FusG; BA37	L	−39	−57	−12	NS ▣	2.7 * ▣	NS
BA19/37	L	−42	−63	−12	8.7 *	9.9 *	NS
	R	42	−63	−12	5.5 *	7.2 *	NS
Cerebellum	C	0	−75	−33	6.1 *	8.1 *	NS

Sample size: 14 cocaine abusers and 14 matched healthy control subjects. Random-effects analyses. Symbols: (*), and (▽) are cluster-level corrected $P_{corr} < 0.001$ and $P_{corr} < 0.05$, respectively; (⦿) VA-load effect with $P_{corr} < 0.05$; (▣) Positive correlation of BOLD signals and RT during the 4-ball tracking task; (◁) Negative correlation of differential BOLD signals (4-balls − 2-balls) and differential performance accuracy (4 balls − 2 balls); Pearson correlation coefficient $|r| > 0.5$.

accuracy (the difference between right/hits and wrong/false alarm events) and reaction times (RT) during the fMRI tasks. After a 0.5-s delay, the original target balls were then re-highlighted to re-focus the subjects' attention on these balls. The control blocks were 60 s long and composed of five "DO NOT TRACK" periods. During these periods all 10 balls moved and stopped in the same manner as during "TRACK" periods; however, no balls were highlighted, and subjects were instructed not to track the balls, instead to view them passively; the use of this resting condition allowed us to minimize the confounding effect of visual input activation. The order of VA-load conditions (2-, 3-, and 4-ball conditions) was randomized for each subject to minimize order effects. Subjects performed a training session of a shortened version of the paradigm outside of the scanner to ensure that they understood and were able to perform this task. The task specifically activates attention-related brain regions comprising parietal and occipital cortices, and DA modulated regions (thalamus, prefrontal cortex, and the cerebellum); similar activation patterns were observed in studies of sustained attention (Fassbender et al., 2004; Lawrence et al., 2003), selective attention (de Fockert et al., 2001; Le et al., 1998), visual search (Leonards et al., 2000), object recognition (Adler et al., 2001), attention to visual motion (Buchel et al., 1998), and orienting visual attention (Arrington et al., 2000). This visual attention paradigm requires sustained attention and visual indexing, a pure attentional process that allows tagging a small number of visual objects in the visual field for fast access of subsequent attentional processing (Pylyshyn and Storm, 1988), and has minimal working memory requirements (Tomasi et al., 2006a) because there is no time delay between the last moving frame and the subsequent ball highlight.

The stimuli were presented to the subjects on MRI-compatible LCD goggles connected to a personal computer. The display software was synchronized precisely with the MRI acquisition using a trigger pulse.

2.3. Data acquisition

Subjects underwent fMRI in a 4 T whole-body Varian/Siemens MRI scanner using a T2*-weighted single-shot gradient–echo planar imaging sequence (TE/TR = 25/3000 ms, 4 mm slice thickness, 1 mm gap, typically 33 coronal slices, 48 × 64 matrix size, 4.1 × 3.1 mm in-plane resolution, 90° flip angle, 124 time points, sound pressure level of acoustic noise = 92 dB) to map the blood oxygenation level dependent (BOLD) responses in the whole brain. Padding was used to minimize motion. The sound pressure level of scanner noise at the subjects' ears was reduced through the use of earplugs (28 dB; Aearo Ear TaperFit 2; Aearo Company) and headphones (30 dB; Commander XG MRI Audio System, Resonance Technology inc.) to minimize the interference effect of scanner noise on attentional processing (Tomasi et al., 2005).

Anatomical images were collected using a T1-weighted 3D-MDEFT sequence (Lee et al., 1995) (TE/TR = 7/15 ms, 0.94 × 0.94 × 3 mm spatial resolution, axial orientation, 256 readout and 192 × 48 phase-encoding steps, 8 min scan time) and a modified T2-weighted Hyperecho sequence (Hennig and Scheffler, 2001) (TE/TR = 42/10000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm in-plane resolution, 5 mm thickness, 1 mm gap, 2 min scan time), and reviewed to rule out gross brain morphological abnormalities.

2.4. Data processing

The first four volumes in the time series were discarded to avoid non-equilibrium effects in the fMRI signal. Subsequent analyses were performed with the statistical parametric mapping package SPM2 (Wellcome Department of Cognitive Neurology, London UK). A six-parameter rigid body transformation was

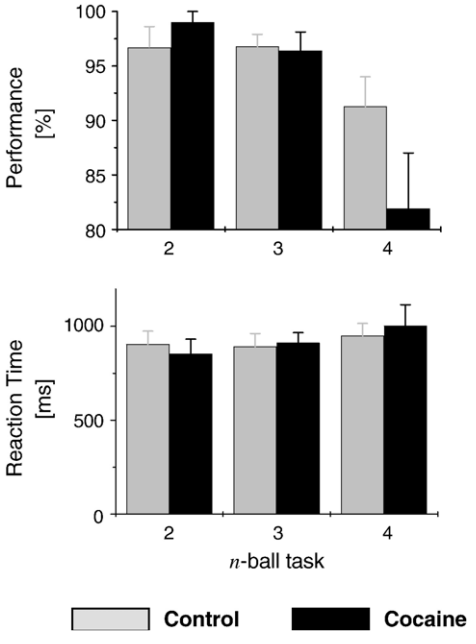

Fig. 1. Average performance accuracy and reaction times during fMRI. Sample size: 14 cocaine abusers and 14 controls. Error bars are standard errors.

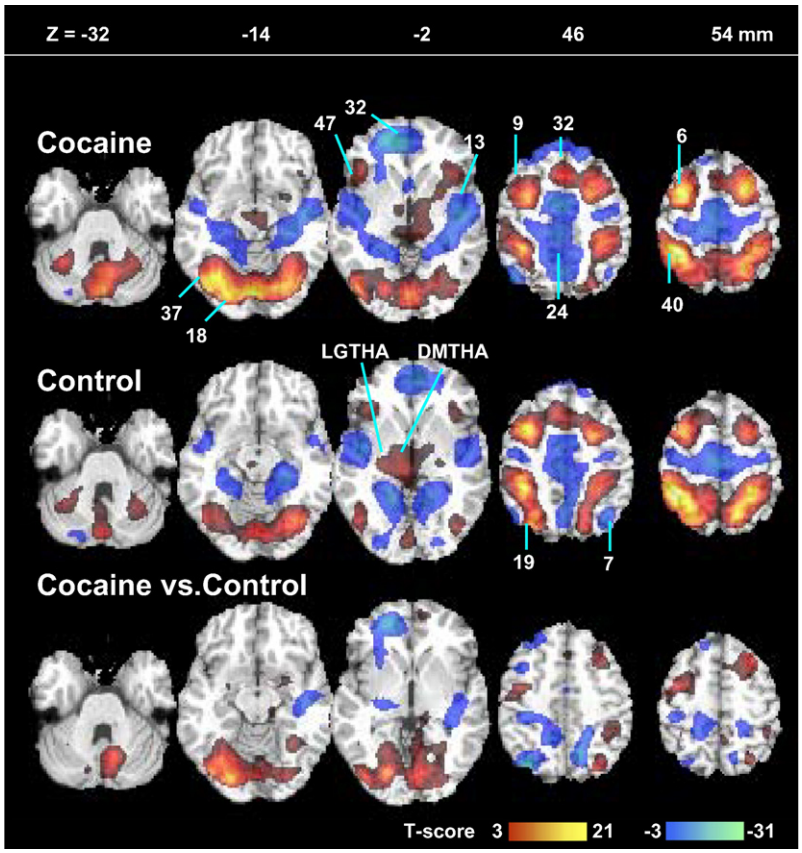

Fig. 2. Statistical maps of the average BOLD signal across conditions (2-, 3-, and 4-ball tracking tasks) for 14 cocaine abusers (upper panel), 14 control subjects (middle panel), and for the differential activation between the groups (bottom panel). White labels (top) indicate the *z*-coordinate of each axial slice in mm in the Talairach frame of reference. White numbers and blue arrows indicate the BAs. Random-effects analyses (two-way repeated measures ANOVA). Red–yellow and blue–green color bars show the *t*-score windows for activation and deactivation, respectively.

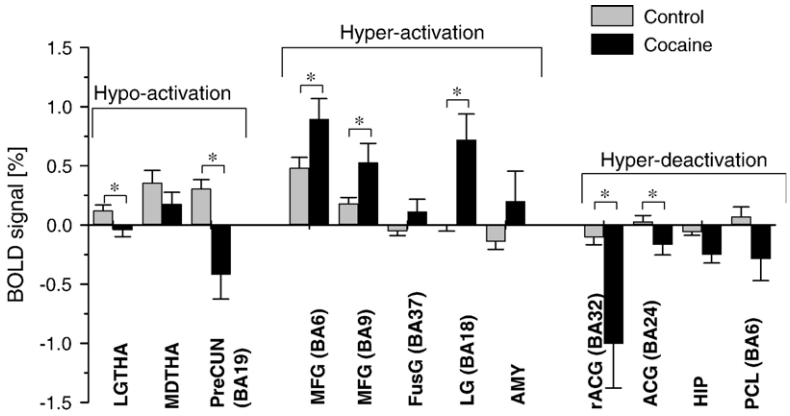

Fig. 3. Average BOLD signals at specific ROIs (Table 1) during VA (2-, 3-, and 4-ball conditions combined) for 14 controls (gray) and 14 cocaine (black) subjects. (*) Differential effects between control and cocaine subjects were statistically significant ($P<0.05$). ROI volume=27 voxels (0.73 cc). Error bars are standard errors.

used for image realignment, to correct for head motion. Head motion was less than 1-mm translation and 1°-rotation for all scans. The linear correlation between realignment parameters and the stimulus time course was not different across groups; it was lower than 0.29 for 88% of the scans and ranged from 0.3 to 0.6 for the remaining scans. The realigned datasets were normalized to the standard brain (Talairach) using a 12-parameter affine transformation (Ashburner et al., 1997), and a voxel size of $3\times3\times3$ mm^3. An 8-mm full-width-half-maximum Gaussian kernel was used to smooth the data. A general linear model (Friston et al., 1995) was used to calculate the activation maps for each trial. We used a blocked analysis based on a box-car design convolved with the canonical hemodynamic response function (HRF), and low-pass (HRF) and high-pass (cut-off frequency: 1/256 Hz) filters.

2.5. Statistical analyses

The calculated BOLD maps (% signal change) for each trial and subject were included in a two-way repeated measures analysis of variance (ANOVA) model with two groups (A: cocaine abusers and B: controls; or cocaine abusers with A: positive or B: negative urine screen; these separate statistical analyses were conducted for cocaine subjects with positive and negative urine to rule out cocaine acute withdrawal effects), and three conditions (2-, 3-, and 4-ball conditions) in SPM2 using the non-sphericity correction. Linear regression analyses of differential BOLD signals and differential measures of performance (RT or accuracy) between the 2-ball and 4-ball conditions were calculated across subjects voxel-by-voxel in SPM2 to identify brain regions associated with increased RT or decreased accuracy from the lowest (2 balls) to the highest (4 balls) task difficulty. An uncorrected threshold of $P<0.001$ was used to display brain activation. Brain activation clusters were corrected for multiple comparisons using the continuous random field calculation implemented in SPM2. A $P_{corr}<0.05$, corrected for multiple comparisons, was considered significant in the group analysis of brain activation.

2.6. Region-of-interest (ROI) analysis

Functional ROIs with an isotropic volume of 0.73 cc were defined at the cluster centers of brain activation to extract the average BOLD signal from these regions. Specifically, a 9-mm isotropic cubic mask was created and centered at the exact coordinates in Table 1 and was kept fixed across subjects and conditions. The average and standard deviation of BOLD responses in these regions were computed from the SPM2 contrast images using the mask and a custom program written in IDL (Research Systems, Boulder, CO). Additional regression analyses of behavioral measures (RT and accuracy) and BOLD responses were conducted to determine the association of abnormal activation and task performance. Statistical significance for these ROI analyses was defined as $P=0.05$ (uncorrected).

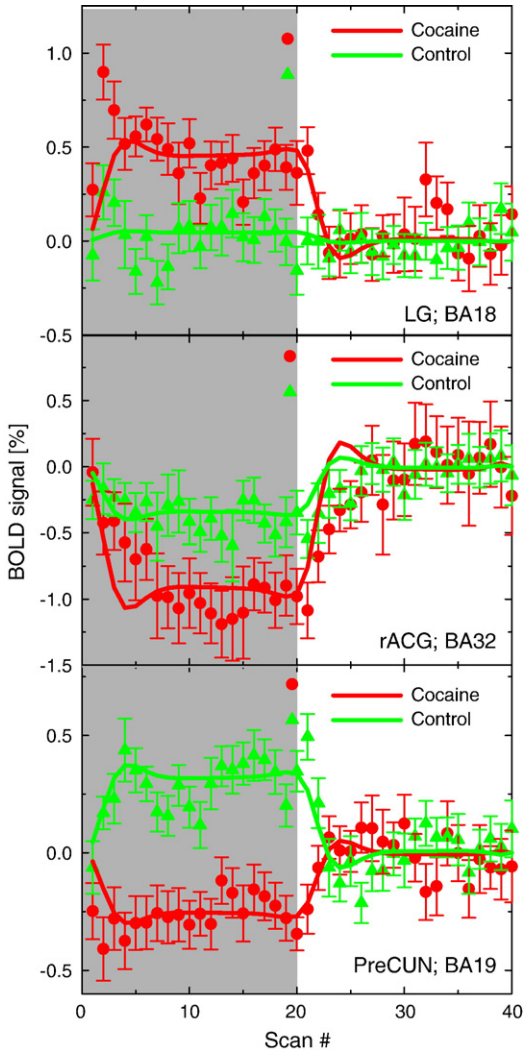

Fig. 4. Average BOLD responses (symbols) across 14 controls (green) and 14 cocaine abusers (red) exemplifying the time courses of the fMRI signals in three ROIs (27 voxels; 0.73 cc; Table 1) and the fitted hemodynamic responses (lines) elicited by the VA task. Light-gray and white periods indicate task and rest blocks, respectively. Error bars are standard errors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Behavioral data

During the fMRI tasks, performance accuracy decreased with the number of tracked balls (visual attention load: $F=17.3$, $P<0.0001$, repeated measures ANOVA) and was similar for cocaine and control subjects for all task conditions (Fig. 1). Performance accuracy was significantly lower for the more demanding condition (4-ball tracking) as compared to the less demanding condition (2-ball tracking) for cocaine subjects and for controls ($P<0.005$ and 0.01, respectively; paired t-test). The load × group interaction effect on performance accuracy was not statistically significant ($F=1.11$, $df=2$, $P=0.34$, repeated measures ANOVA). Performance accuracy during fMRI was not different for cocaine abusers with positive and negative urine results; similarly the load × urine-status interaction effect on performance accuracy was not statistically significant ($F=1.14$, $df=2$, $P>0.12$, repeated measures ANOVA). Reaction time increased with the number of tracked balls ($F=3.73$, $df=2$, $P<0.03$, repeated measures ANOVA) but was not significantly different across groups or conditions. The load × group interaction effect on reaction time was not statistically significant ($F=1.19$, $df=2$, $P=0.31$, repeated measures ANOVA). Reaction time during the 3-ball tracking task was shorter for subjects that had positive-cocaine urine screening than for those that had negative-cocaine urine screening

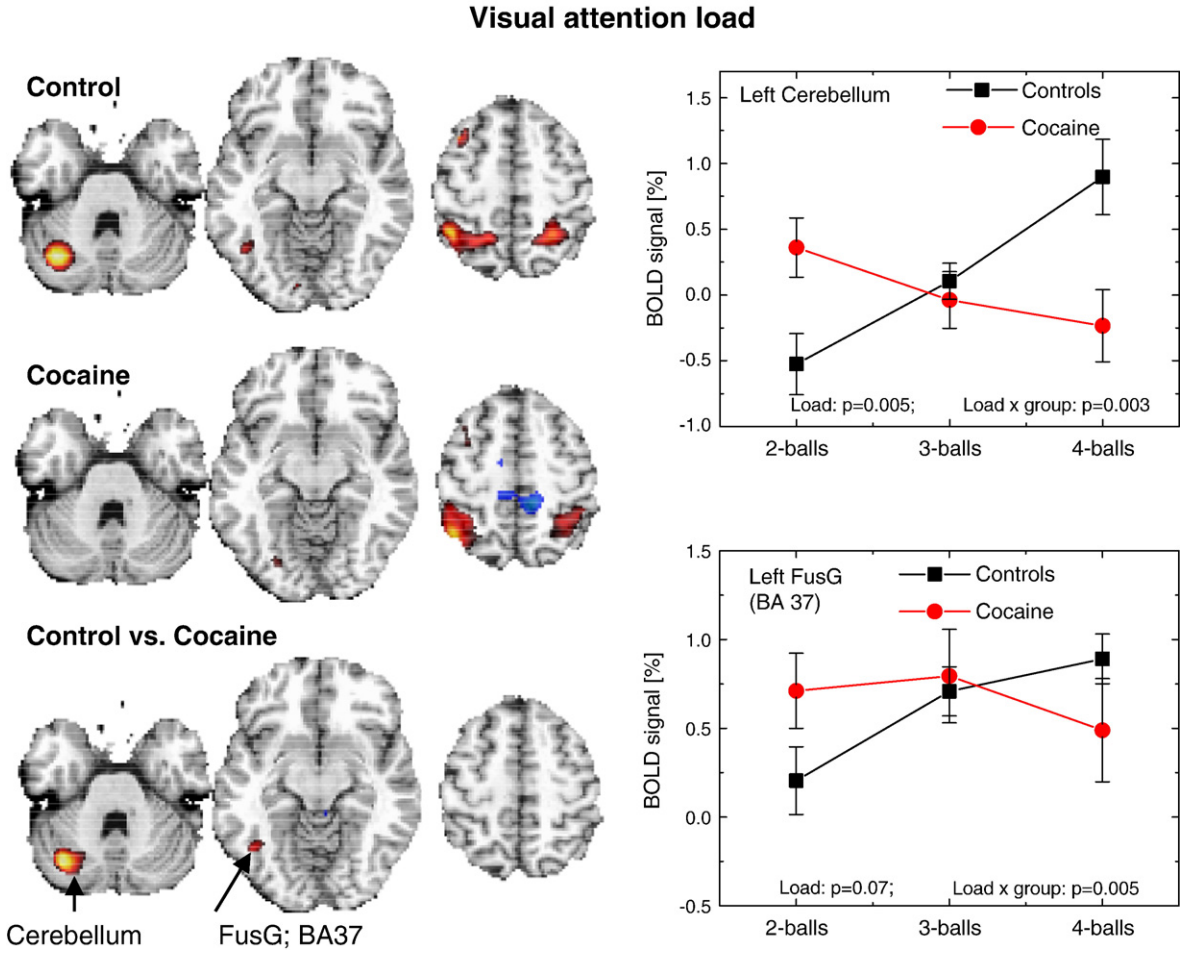

Fig. 5. [Left] Statistical maps of VA-load activation for 14 control subjects (upper panel), 14 cocaine abusers (middle panel), and for the differential VA-load activation between the groups (load × group interaction effect on BOLD responses; bottom panel). Random-effects analyses (two-way repeated measures ANOVA). Red–yellow and blue–green are t-scores for activation and deactivation, respectively. [Right] Scatter plots showing the load × group interaction effect on BOLD responses in left cerebellum (top) and the left FusG (bottom). Error bars are standard errors.

($P<0.02$, two-sample t-test). However, the effect of urine and the load × urine interaction effect on RT were not statistically significant ($F=3.54$, $df=2$, $P>0.09$, repeated measures ANOVA).

3.2. Brain activation

In both groups, the VA task activated a bilateral network (Fig. 2 and Table 1) that included the prefrontal cortex (PFC) [caudal dorsal anterior cingulate [Brodmann area (BA) 32], inferior (IFG; BA47), and middle frontal (MFG; BA6 and 9) gyri], inferior (IPC; BA40) and superior (SPC; BA7) parietal cortices, the medial dorsal body of the thalamus (MDTHA), and the cerebellum, in agreement with our previous studies (Chang et al., 2004; Tomasi et al., 2004); the tasks deactivated the parahippocampal (PHG; BA30) and cingulate (CG; BA24) gyri, the precuneus (PreCUN; BA31), and the insula (INS; BA13), also in agreement with our previous studies (Tomasi et al., 2006b).

The differential activation pattern between the groups demonstrated widespread differences between cocaine abusers and controls (Figs. 2 and 3). This included brain areas that were: (1) activated in controls but activated less or deactivated in cocaine abusers [lateral geniculate body of the thalamus (LGTHA), MDTHA, and the PreCUN BA 19], (2) activated in cocaine abusers more than in controls [MFG, lingual (LG; BA18) and fusiform (FusG; BA37) gyri], and (3) deactivated more in cocaine abusers than in controls [ACG, the left locus coeruleus (LC), and the paracentral lobule (PCL; BA6)]. The average time courses of the fMRI signals in the LG, the rostral anterior cingulate gyrus (rACG; BA32), and the PreCUN in Fig. 4 show the correlation between the stimulus paradigm and signals in regions that demonstrated the largest activation differences between the groups. For cocaine abusers, the correlations were positive in the visual cortex (LG, $r=+0.81$, $P<0.0001$) and negative in the rACG ($r=-0.86$, $P<0.0001$) and parietal cortices specialized in visuospatial processing (PreCUN, $r=-0.82$, $P<0.0001$). For control subjects, the correlations were not significant in the LG ($r=0.10$, $P=0.53$), negative in the rACG ($r=-0.78$, $P<0.0001$) and positive in the PreCUN ($r=0.86$, $P<0.0001$).

3.3. Urine status

These abnormal activations were accentuated in the cocaine subjects with positive urine toxicology screens. Specifically, compared to urine negative cocaine subjects, those with positive urine screens had larger cortical [MFG, precentral gyrus (BA 4 and 6), SPC, IPC, LG] and lower sub-cortical [MDTHA and pulvinar thalamus] activations ($P_{corr}<0.02$; corrected for multiple comparisons), and larger deactivation of the PreCUN, PCG, INS, rACG, ACG, and PCL ($P_{corr}<0.001$); cocaine abusers with negative urine had larger activation in the postcentral gyrus BA3 ($P_{corr}<0.001$) and did not have larger deactivation in any brain region compared to those with positive urine.

3.4. VA-load

Increased VA load (2 balls to 4 balls) produced increased activation (but not deactivations) bilaterally in the IPC and in the left dorsolateral PFC (IFG, and MFG) for both groups (Table 1; Fig. 5). For control subjects VA load additionally activated the posterior lobe of the left cerebellum (tonsil; $P_{corr}<0.001$). Thus, there was an interaction (VA load × group) effect on BOLD responses in the cerebellum ($P_{corr}<0.001$). The VA load × group interaction effect on BOLD responses in the FusG (BA

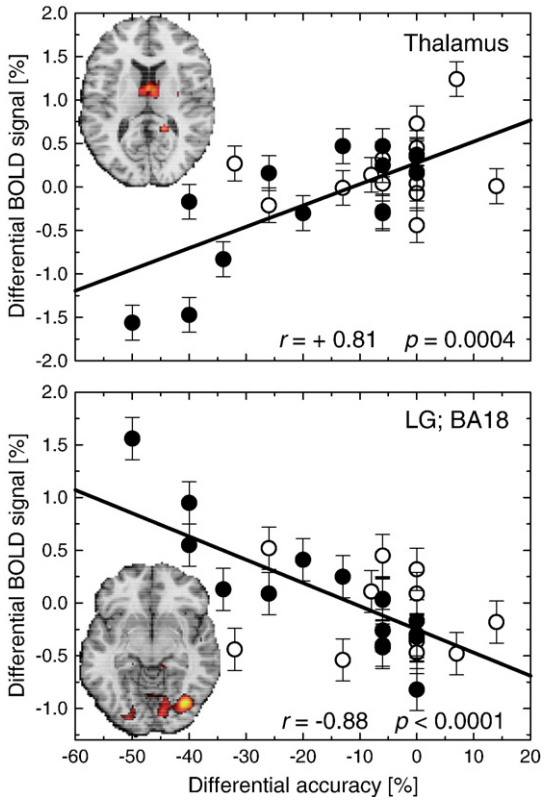

Fig. 6. Linear correlations between differential (4 balls vs. 2 balls) accuracy and BOLD responses in the brain for cocaine abusers (full circles) and controls (open circles. Solid lines are linear fits, and r is the Pearson correlation coefficient. Error bars are standard errors.

37), the human homologous of the monkey MT/V5 area (Born and Bradley, 2005), was statistically significant in the ROI analysis (Fig. 5 Right, $F=5.99$, $df=2$, $P=0.005$; two-way repeated measures ANOVA), but the corresponding VA load × group activation cluster did not survive the SPM2 correction for multiple comparisons ($P_{corr}=0.59$).

3.5. Behavior vs. brain activation

For cocaine abusers but not for control subjects, the BOLD signal change from 2 balls to 4 balls in the anterior thalamus ($P_{corr}=0.02$) and in the LG ($P_{corr}=0.04$) significantly correlated with the corresponding change in performance accuracy. As depicted in Fig. 6, the larger the thalamic and the lower the LG activation decreases, the larger was the decrease in performance accuracy from 2 balls to 4 balls. Furthermore for cocaine and control subjects combined, longer RT during the more demanding 4-ball tracking task was associated with decreased occipital activation in the LG and the FusG ($R<-0.41$, $P<0.03$).

4. Discussion

In the present study we demonstrate that during a visual attention task and compared to healthy matched control subjects, cocaine abusers have widespread differences in the pattern of neural activation and deactivation, including 1) lower thalamic activation, 2) larger activation in the PFC and occipital cortices, and 3) larger deactivation in the anterior CG (BA 32 and 24) and parietal regions. In addition we show that for cocaine abusers but not for controls the thalamic hypo-activation and the occipital hyper-activation are associated with lower performance accuracy.

4.1. Thalamic hypo-activation

Brain activation in the thalamus (MDTHA and LGTHA) was lower in cocaine abusers than in controls (Table 1, Figs. 2 and 3). The thalamus, a major processor of visual, auditory, and somatosensory information, is essential for the alerting component of attention (Fan et al., 2005) including that for spatial attention (Christian et al., 2006). The DMTHA receives inputs from primary and secondary auditory cortices and is important for the detection of the relative intensity and duration of sounds. The LGTHA is located in the major pathway from the retina to the visual cortex and is the primary processor of visuospatial information in the central nervous system (Horvath, 1998). The LGTHA is innervated by norepinephrine (NE) containing fibers (Kromer and Moore, 1980), and is regulated by NE (Rogawski and Aghajanian, 1980a,b) and DA (Govindaiah and Cox, 2005; Munsch et al., 2005; Zhao et al., 2001). Since cocaine binds to NE and DA transporters (Raiteri et al., 1977), thereby increasing extracellular NE and DA (Beveridge et al., 2005; Ritz et al., 1987; Tanda et al., 1997), our current finding of reduced thalamic recruitment during a visual attention challenge in the cocaine addicted subjects may reflect a dysfunctional NE and DA regulation of the DMTHA and LGTHA that may have limited the capacity of these auditory and visual processors in the cocaine abusers compared to controls (Table 1; Figs. 2 and 3). These current results are consistent with our previous studies that documented reduced DA release (Volkow et al., 1997) and reduced activation (Kubler et al., 2005) in the thalamus in cocaine abusers.

4.2. Visual cortex hyper-activation

The VA task produced stronger activation of the visual cortex (LG) in the cocaine abusers compared to control subjects. Hyper-activation of the LG may reflect larger recruitment of the visual attention network to support sustained visual processing (Tomasi et al., 2006b) possibly to compensate for the inefficient sensory processing in the thalamus.

4.3. PFC hyper-activation

Previous fMRI studies on attentional (GO-NOGO) tasks found reduced activation in the superior PFC in cocaine abusers (Hester and Garavan, 2004; Kaufman et al., 2003). The VA task, however, elicited larger activation in the superior and dorsolateral PFC for the cocaine abusers than for control subjects (Table 1). Similarly, neuroimaging studies on Parkinson's disease have shown larger PFC activation in hypodopaminergic conditions (Cools et al., 2002; Mattay et al., 2002). The dopaminergic system supports cognitive performance via direct as well as indirect (striato-cortical) inputs to the PFC (Gaspar, 1992; Goldman-Rakic et al., 2000). Since DA is necessary for intact cognitive performance (Nieoullon, 2002) and cocaine abusers have abnormalities in brain DA D2 receptor availability and in DA release (Volkow et al., 1997), it is possible that the PFC hyper-activation during the current VA task reflects the cocaine abusers' increased recruitment of cortical regulatory resources (e.g., effort) to compensate for the impaired DA regulation of cognitive function.

4.4. Hyper-deactivation

The cocaine abusers deactivated the rACG more than the control subjects. Competing neural processes such as those produced by attention to introspective or emotional factors (i.e. anxiety during fMRI) might have been partially inhibited during task periods to minimize interference during cognitive task performance (Tomasi et al., 2006b). During rest periods, however, neural processing in the rACG might have been enhanced due to greater awareness of the confined MR scanner environment. FMRI studies on emotional pain modulation have shown that anxiety about pain activates the ACG, and PET studies on anticipatory anxiety found that activation at the ACG correlates linearly with the anxiety ratings, suggesting that its activation might reflect a combined effect of attentional demands and emotional reaction (Simpson et al., 2001). Thus, the larger rACG deactivation in the cocaine abusers, compared to control subjects, may reflect greater suppression of emotional responses that are task-irrelevant (Tomasi et al., 2006b). This interpretation is consistent with a recent study where we showed the same rACG region to be associated with performance accuracy by cocaine abusers on a newly developed emotional drug-related task (Goldstein et al., 2007b).

The locus coeruleus, which is the main source of noradrenergic innervation of the cortex and the thalamus (Mulders and Robertson, 2001; Rogawski and Aghajanian, 1980b), was also deactivated during the VA task in the cocaine abusers but not in control subjects. There is evidence from studies in laboratory animals that noradrenergic activity in the PFC can modulate the attention to external stimuli by altering the firing rate of noradrenergic neurons in the locus coeruleus (Devilbiss and Waterhouse, 2004). There is also evidence from imaging studies in humans that NE is involved in the functional integration of attentional circuits (Coull et al., 1999). Thus, NE in addition to DA is likely to contribute to the abnormal thalamo-cortical activation in the cocaine abusers. Also some of these abnormalities may reflect activation of noradrenergic pathways during withdrawal (Kelley et al., 2005).

4.5. Attention

Most of the pharmacological strategies for the treatment of cocaine addiction have focused on medications that decrease the reinforcing effects of cocaine, enhance the reinforcing effects of non-drug reinforcers, interfere with conditioned responses, inhibit craving and/or inhibit drug or stress-induced relapse (Vocci et al., 2005). However, no treatment strategies target fundamental cognitive elements such as attention in cocaine abusers. Attention is thought to have three independent components: "alerting" (Coull et al., 1996), "orienting" (Corbetta et al., 2000; Kastner et al., 1999), and executive control (Botvinick et al., 1999; MacDonald et al., 2000). There is evidence from fMRI that "alerting" is associated with thalamic activation, "orienting" with MFG activation, and executive control with caudal ACG activation (Fan et al., 2005). Thus, all regions associated with the three components of attention were disrupted in the cocaine abusers in the present study. Inasmuch as impaired cognition negatively affects treatment outcomes in cocaine abusers (Aharonovich et al., 2006), the findings from this study support the need to develop therapeutic strategies to improve the activity of brain circuits involved in sustained attention; future treatment efforts need to especially consider the generalized neurobiological impairment underlying attention in cocaine addiction. In this respect medications that enhance noradrenergic activity may be particularly beneficial in improving the attention deficits in cocaine abusers. Our results also highlight the importance of evaluating the cognitive effects of all psychoactive medications used in the treatment or management of drug addiction.

4.6. Withdrawal

The activation abnormalities were accentuated in cocaine abusers with positive urines suggesting that the imaging results might reflect acute effects of cocaine withdrawal. Cocaine withdrawal is associated with impaired performance in cognitive functions including attention, vigilance and executive function (Goldstein et al., 2004; Kelley et al., 2005; Pace-Schott et al., 2005) and imaging studies of cocaine abusers tested during withdrawal have reported reduced dopamine (DA) activity (Volkow et al., 1997). In this study, however, cocaine subjects with positive urines had similar performance accuracy and RT to those with negative urines and controls, probably reflecting the small sample size of the cocaine sub-groups. The confounding vasoactive effects of cocaine in the blood stream (Gollub et al., 1998) are unlikely to be of high impact in this study because cocaine's half life in the brain is very short (20 min) (Volkow et al., 1995); all subjects were supervised during several hours prior the current study.

4.7. Motivation

We recently suggested that the lateral PFC modulates motivation and control, and that a disrupted perception

of motivational drive might contribute to impaired self-control and poor insight into illness in cocaine abusers (Goldstein et al., 2007c). The similar behavioral responses (performance accuracy and RT) in all study groups in the current report suggest minimal motivational differences between the groups during this VA task.

4.8. Study limitations

1) This study did not control for potential differences in eye movement between control subjects and cocaine abusers. Since neurons in the mediodorsal nucleus of the thalamus might relay a corollary discharge of saccades from the midbrain superior colliculus to the cortical frontal eye field (Sommer and Wurtz, 2006), the differential thalamic activation between the control and cocaine groups might also reflect differential eye movements rather than differential attentional alertness. However, the lack of performance differences between the groups on this task minimizes such a possibility. 2) Furthermore, in fMRI studies the spatial uncertainty is not uniform in the imaging volume due to macrovascular (Tomasi and Caparelli, 2007) and susceptibility effects, varies across MR instruments and pulse sequences, and is enlarged during image post-processing (motion correction, spatial normalization and spatial smoothing). In this study, the EPI distortion near (~1 cm) the sinus cavity and the temporal bone was as large as 1–2 cm. In other regions (PFC, occipital and parietal cortices, thalamus and cerebellum), however, image distortion was smaller, and the spatial normalization and smoothing dominated the final spatial uncertainty of the imaging volumes in these regions. Thus, for regions not severely affected by susceptibility artifacts, the root–sum–square of all contributions (susceptibility, realignment, normalization, and smoothing) to the spatial uncertainty was 11 mm. Near the sinus cavity and the temporal bone, however, it can be up to 23 mm. The visual attention task did not activate/deactivate brain regions near the sinus cavity or the temporal bone.

In summary, we used a sustained VA task to demonstrate that cocaine abusers have lower thalamic activation, larger occipital and PFC activation, and larger rACG deactivation than controls. We suggest that larger recruitment of neural resources in the PFC and occipital cortical areas is required to compensate for the impaired attention functioning in the cocaine abusers due to impaired NE or DA regulation in the thalamus.

Acknowledgements

We are thankful to Drs. Linda Chang and T. Ernst for providing the VA task. The study was partly supported by the Laboratory Directed Research and Development Award from U.S. Department of Energy (Office of Biological and Environmental Research), the National Institutes of Health (GCRC 5-MO1-RR-10710), NARSAD Young Investigator Award, and the National Institute on Drug Abuse (R03 DA 017070-01 and 1K23 DA15517-01).

References

Adler, C., Sax, K., Holland, S., Schmithorst, V., Rosenberg, L., Strakowski, S., 2001. Changes in neuronal activation with increasing attention demand in healthy volunteers: an fMRI study. Synapse 42, 266–272.

Aharonovich, E., Nunes, E., Hasin, D., 2003. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive–behavioral treatment. Drug and Alcohol Dependence 71, 207–211.

Aharonovich, E., Hasin, D., Brooks, A., Liu, X., Bisaga, A., Nunes, E., 2006. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug and Alcohol Dependence 81, 313–322.

Arrington, C., Carr, T., Mayer, A., Rao, S., 2000. Neural mechanisms of visual attention: object-based selection of a region in space. Journal of Cognitive Neuroscience 12 (Suppl 2), 106–117.

Ashburner, J., Neelin, P., Collins, D.L., Evans, A.C., Friston, K.J., 1997. Incorporating prior knowledge into image registration. NeuroImage 6, 344–352.

Beveridge, T., Smith, H., Nader, M., Porrino, L., 2005. Effects of chronic cocaine self-administration on norepinephrine transporters in the nonhuman primate brain. Psychopharmacology (Berl) 180, 781–788.

Born, R., Bradley, D., 2005. Structure and function of visual area MT. Annual Review of Neuroscience 28, 157–189.

Botvinick, M., Nystrom, L., Fissell, K., Carter, C., Cohen, J., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179–181.

Buchel, C., Josephs, O., Rees, G., Turner, R., Frith, C.D., Friston, K.J., 1998. The functional anatomy of attention to visual motion: a functional MRI study. Brain 121, 1281–1294.

Chang, L., Tomasi, D., Yakupov, R., Lozar, C., Arnold, S., Caparelli, E., Ernst, T., 2004. Adaptation of the attention network in human immunodeficiency virus brain injury. Annals of Neurology 56, 259–272.

Chang, L., Yakupov, R., Cloak, C., Ernst, T., 2006. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 129, 1096–1112.

Christian, B., Lehrer, D., Shi, B., Narayanan, T., Strohmeyer, P., Buchsbaum, M., Mantil, J., 2006. Measuring dopamine neuromodulation in the thalamus: using [F-18] fallypride PET to study dopamine release during a spatial attention task. NeuroImage 31, 139–152.

Cools, R., Stefanova, E., Barker, R., Robbins, T., Owen, A., 2002. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain 125, 584–594.

Corbetta, M., Kincade, J., Ollinger, J., McAvoy, M., Shulman, G., 2000. Voluntary orienting is dissociated from target detection

in human posterior parietal cortex. Nature Neuroscience 3, 292–297.
Coull, J., Frith, C., Frackowiak, R., Grasby, P., 1996. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34, 1085–1095.
Coull, J., Buchel, C., Friston, K., Frith, C., 1999. Noradrenergically mediated plasticity in a human attentional neuronal network. NeuroImage 10, 705–715.
Culham, J.C., Brandt, S.A., Cavanagh, P., Kanwisher, N.G., Dale, A.M., Tootell, R.B.H., 1998. Cortical fMRI activation produced by attentive tracking of moving targets. Journal of Neurophysiology 80, 2657–2670.
de Fockert, J., Rees, G., Frith, C., Lavie, N., 2001. The role of working memory in visual selective attention. Science 291, 1803–1806.
Devilbiss, D., Waterhouse, B., 2004. The effects of tonic locus ceruleus output on sensory-evoked responses of ventral posterior medial thalamic and barrel field cortical neurons in the awake rat. Journal of Neuroscience 24, 10773–10785.
Fan, J., McCandliss, B., Fossella, J., Flombaum, J., Posner, M., 2005. The activation of attentional networks. NeuroImage 26, 471–479.
Fassbender, C., Murphy, K., Foxe, J., Wylie, G., Javitt, D., Robertson, I., Garavan, H., 2004. A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. Cognitive Brain Research 20, 132–143.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J., 1996. Structured Clinical Interview for DSM-IV Axis I disorders — Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute, New York.
Fone, K., Nutt, D., 2005. Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. Current Opinion in Pharmacology 5, 87–93.
Fozard, J., Mobarok Ali, A., Newgrosh, G., 1979. Blockade of serotonin receptors on autonomic neurones by (−)-cocaine and some related compounds. European Journal of Pharmacology 59, 195–210.
Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Franckowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general approach. Human Brain Mapping 2, 189–210.
Garcia-Cabezas, M., Rico, B., Sanchez-Gonzalez, M., Cavada, C., 2007. Distribution of the dopamine innervation in the macaque and human thalamus. NeuroImage 34, 965–984.
Gaspar, P., 1992. Topography and collateralization of the dopaminergic projections to motor and lateral prefrontal cortex in owl monkeys. Journal of Comparative Neurology 325, 1–21.
Goldman-Rakic, P., Mully, E., Williams, G., 2000. D1 receptors in prefrontal cells and circuits. Brain Research 31, 295–301.
Goldstein, R., Volkow, N., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. American Journal of Psychiatry 159, 1642–1652.
Goldstein, R., Leskovjan, A., Hoff, A., Hitzemann, R., Bashan, F., Khalsa, S., Wang, G., Fowler, J., Volkow, N., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447–1458.
Goldstein, R., Tomasi, D., Alia-Klein, N., Cottone, L., Zhang, L., Telang, F., Volkow, N., 2007a. Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. Drug and Alcohol Dependence 87, 233–240.
Goldstein, R., Tomasi, D., Rajaram, S., Cottone, L., Zhang, L., Maloney, T., Telang, F., Alia-Klein, N., Volkow, N., 2007b. Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. Neuroscience 144, 1153–1159.
Goldstein, R., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L., Maloney, T., Telang, F., Caparelli, E., Chang, L., Ernst, T., Samaras, D., Squires, N., Volkow, N., 2007c. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? American Journal of Psychiatry 164, 1–9.
Gollub, R.L., Breiter, H.C., Kantor, H., Kennedy, D., Gastfriend, D., Mathew, R.T., Makris, N., Guimaraes, A., Riorden, J., Campbell, T., Foley, M., Hyman, S.E., Rosen, B., Weisskoff, R., 1998. Cocaine decreases cortical cerebral blood flow but does not obscure regional activation in functional magnetic resonance imaging in human subjects. Journal of Cerebral Blood Flow and Metabolism 18, 724–734.
Gottschalk, P., Kosten, T., 2002. Cerebral perfusion defects in combined cocaine and alcohol dependence. Drug and Alcohol Dependence 68, 95–104.
Govindaiah, G., Cox, C., 2005. Excitatory actions of dopamine via D1-like receptors in the rat lateral geniculate nucleus. Journal of Neurophysiology 94, 3708–3718.
Hennig, J., Scheffler, K., 2001. Hyperechoes. Magnetic Resonance in Medicine 46, 6–12.
Hester, R., Garavan, H., 2004. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. Journal of Neuroscience 24, 11017–11022.
Hester, R., Murphy, K., Foxe, J., Foxe, D., Javitt, D., Garavan, H., 2004. Predicting success: patterns of cortical activation and deactivation prior to response inhibition. Journal of Cognitive Neuroscience 16, 776–785.
Horvath, T., 1998. An alternate pathway for visual signal integration into the hypothalamo-pituitary axis: retinorecipient intergeniculate neurons project to various regions of the hypothalamus and innervate neuroendocrine cells including those producing dopamine. Journal of Neuroscience 18, 1546–1558.
Jovanovski, D., Erb, S., Zakzanis, K., 2005. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. Journal of Clinical Neuropsychology 27, 189–204.
Jovicich, J., Peters, R.J., Koch, C., Braun, J., Chang, L., Ernst, T., 2001. Brain areas specific for attentional load in a motion tracking task. Journal of Cognitive Neuroscience 13, 1048–1058.
Kahkonen, S., Ahveninen, J., Pekkonen, E., Kaakkola, S., Huttunen, J., Ilmoniemi, R., Jaaskelainen, I., 2002. Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study. Clinical Neurophysiology 113, 1894–1902.
Kastner, S., Pinsk, M., De Weerd, P., Desimone, R., Ungerleider, L., 1999. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 22, 751–761.
Kaufman, J., Ross, T., Stein, E., Garavan, H., 2003. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. Journal of Neuroscience 23, 7839–7843.
Kelley, B., Yeager, K., Pepper, T., Beversdorf, D., 2005. Cognitive impairment in acute cocaine withdrawal. Cognitive and Behavioral Neurology 18, 108–112.
Kromer, L., Moore, R., 1980. A study of the organization of the locus coeruleus projections to the lateral geniculate nuclei in the albino rat. Neuroscience 5, 255–271.
Kubler, A., Murphy, K., Garavan, H., 2005. Cocaine dependence and attention switching within and between verbal and visuospatial working memory. European Journal of Neuroscience 21, 1984–1992.

Lawrence, N., Ross, T., Hoffmann, R., Garavan, H., Stein, E., 2003. Multiple neuronal networks mediate sustained attention. Journal of Cognitive Neuroscience 15, 1028–1038.

Le, T., Pardo, J., Hu, X., 1998. 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. Journal of Neurophysiology 79, 1535–1548.

Lee, J.H., Garwood, M., Menon, R., Adriany, G., Andersen, P., Truwit, C.L., Ugurbil, K., 1995. High contrast and fast three-dimensional magnetic resonance imaging at high fields. Magnetic Resonance in Medicine 34, 308–312.

Lee, J.H., Telang, F.W., Springer, C.S.J., Volkow, N.D., 2003. Abnormal brain activation to visual stimulation in cocaine abusers. Life Sciences 73, 1953–1961.

Leonards, U., Sunaert, S., Van Hecke, P., Orban, G., 2000. Attention mechanisms in visual search-an fMRI study. Journal of Cognitive Neuroscience 12 (Suppl 2), 61–75.

MacDonald, A.R., Cohen, J., Stenger, V., Carter, C., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.

Mair, R., Zhang, Y., Bailey, K., Toupin, M., Mair, R., 2005. Effects of clonidine in the locus coeruleus on prefrontal- and hippocampal-dependent measures of attention and memory in the rat. Psychopharmacology (Berl) 181, 280–288.

Mattay, V., Tessitore, A., Callicott, J., Bertolino, A., Goldberg, T., Chase, T., Hyde, T., Weinberger, D., 2002. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Annals of Neurology 51, 156–164.

Melchitzky, D., Lewis, D., 2001. Dopamine transporter-immunoreactive axons in the mediodorsal thalamic nucleus of the macaque monkey. Neuroscience 103, 1033–1042.

Mulders, W., Robertson, D., 2001. Origin of the noradrenergic innervation of the superior olivary complex in the rat. Journal of Chemical Neuroanatomy 21, 313–322.

Munsch, T., Yanagawa, Y., Obata, K., Pape, H., 2005. Dopaminergic control of local interneuron activity in the thalamus. European Journal of Neuroscience 21, 290–294.

Nieoullon, A., 2002. Dopamine and the regulation of cognition and attention. Progress in Neurobiology 67, 53–83.

Pace-Schott, E., Stickgold, R., Muzur, A., Wigren, P., Ward, A., Hart, C., Walker, M., Edgar, C., Hobson, J., 2005. Cognitive performance by humans during a smoked cocaine binge–abstinence cycle. American Journal of Drug and Alcohol Abuse 31, 571–591.

Pylyshyn, Z.W., Storm, R.W., 1988. Tracking multiple independent targets: evidence for a parallel tracking mechanism. Spatial Vision 3, 179–197.

Raiteri, M., Del Carmine, R., Bertollini, A., Levi, G., 1977. Effect of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine and 5-hydroxytryptamine. European Journal of Pharmacology 41, 133–143.

Remy, P., Doder, M., Lees, A., Turjanski, N., Brooks, D., 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128, 1314–1322.

Ritz, M., Lamb, R., Goldberg, S., Kuhar, M., 1987. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237, 1219–1223.

Rogawski, M., Aghajanian, G., 1980a. Activation of lateral geniculate neurons by norepinephrine: mediation by an alpha-adrenergic receptor. Brain Research 182, 345–359.

Rogawski, M., Aghajanian, G., 1980b. Modulation of lateral geniculate neurone excitability by noradrenaline microiontophoresis or locus coeruleus stimulation. Nature 287, 731–734.

Sanchez-Gonzalez, M., Garcia-Cabezas, M., Rico, B., Cavada, C., 2005. The primate thalamus is a key target for brain dopamine. Journal of Neuroscience 25, 6076–6083.

Simpson, J.R., Drevets, W.C., Snyder, A.Z., Gusnard, D.A., Raichle, M.E., 2001. Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. Proceedings of the National Academy of Sciences of the United States of America 98, 688–693.

Sommer, M., Wurtz, R., 2006. Influence of the thalamus on spatial visual processing in frontal cortex. Nature 444, 374–377.

Tanda, G., Pontieri, F., Frau, R., Di Chiara, G., 1997. Contribution of blockade of the noradrenaline carrier to the increase of extracellular dopamine in the rat prefrontal cortex by amphetamine and cocaine. European Journal of Neuroscience 9, 2077–2085.

Tomasi, D., Caparelli, E., 2007. Macrovascular contribution in activation patterns of working memory. Journal of Cerebral Blood Flow and Metabolism 27, 33–42.

Tomasi, D., Ernst, T., Caparelli, E.C., Chang, L., 2004. Practice-induced changes of brain function during visual attention: a parametric fMRI study at 4 T. NeuroImage 23, 1414–1421.

Tomasi, D., Caparelli, E.C., Chang, L., Ernst, T., 2005. fMRI-acoustic noise alters brain activation during working memory tasks. NeuroImage 27, 377–386.

Tomasi, D., Chang, L., Caparelli, E., Ernst, T., 2006a. Different activation patterns for working memory load and visual attention load. Brain Research 1132, 158–165.

Tomasi, D., Ernst, T., Caparelli, E.C., Chang, L., 2006b. Common deactivation patterns during working memory and visual attention tasks: an intra-subject fMRI study at 4 T. Human Brain Mapping 27, 694–705.

Ventura, J., Liberman, R.P., Green, M.F., Shaner, A., Mintz, J., 1998. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). Psychiatry Research 79, 163–173.

Vocci, F., Acri, J., Elkashef, A., 2005. Medication development for addictive disorders: the state of the science. American Journal of Psychiatry 162, 1432–1440.

Volkow, N., Ding, Y., Fowler, J., Wang, G., Logan, J., Gatley, J., Dewey, S., Ashby, C., Liebermann, J., Hitzemann, R., Wolf, A., 1995. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Archives of General Psychiatry 52, 456–463.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Hitzemann, R., Chen, A.D., Dewey, S.L., Pappas, N., 1997. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 386, 830–833.

Volkow, N., Wang, G., Fischman, M., Foltin, R., Fowler, J., Franceschi, D., Franceschi, M., Logan, J., Gatley, S., Wong, C., Ding, Y., Hitzemann, R., Pappas, N., 2000. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. Life Sciences 67, 1507–1515.

Volkow, N., Fowler, J., Wang, G., 2003. The addicted human brain: insights from imaging studies. Journal of Clinical Investigation 111, 1444–1451.

Wang, G., Volkow, N., Fowler, J., Ding, Y., Logan, J., Gatley, S., MacGregor, R., Wolf, A., 1995. Comparison of two pet radioligands for imaging extrastriatal dopamine transporters in human brain. Life Sciences 57, PL187–PL191.

Zhao, Y., Kerscher, N., Eysel, U., Funke, K., 2001. Changes of contrast gain in cat dorsal lateral geniculate nucleus by dopamine receptor agonists. NeuroReport 12, 2939–2945.