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Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice

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Abstract

Drug addiction is characterized by dysregulated dopamine neurotransmission. Although dopamine functioning appears to partially recover with abstinence, the specific regions that recover and potential impact on drug seeking remain to be determined. Here we used functional magnetic resonance imaging (fMRI) to study an ecologically valid sample of 15 treatment-seeking cocaine addicted individuals at baseline and 6-month follow-up. At both study sessions, we collected fMRI scans during performance of a drug Stroop task, clinical self-report measures of addiction severity, and behavioral measures of cocaine seeking (simulated cocaine choice); actual drug use in between the two study sessions was also monitored. At 6-month follow-up (compared with baseline) we predicted functional enhancement of dopaminergically-innervated brain regions, relevant to the behavioral responsiveness toward salient stimuli. Consistent with predictions, whole-brain analyses revealed responses in the midbrain (encompassing the ventral tegmental area/substantia nigra complex) and thalamus (encompassing the mediodorsal nucleus) that were higher (and more positively correlated) at follow-up than baseline. Increased midbrain activity from baseline to follow-up correlated with reduced simulated cocaine choice, indicating that heightened midbrain activations in this context may be marking lower approach motivation for cocaine. Normalization of midbrain function at follow-up was also suggested by exploratory comparisons with active cocaine users and healthy controls (who were assessed only at baseline). Enhanced self-control at follow-up was suggested by a trend for the commonly hypoactive dorsal

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Author Contributions

SJM, DT, NDV, and RZG designed research; DT, PAW, TM, NAK, FT, GJW, and RW performed research; PAW, RS, DC, JAT, and JB coordinated research recruitment; SJM, DT, JH, and RW analyzed data; SJM, DT, NDV, and RZG wrote the paper. All authors critically reviewed content and approved final version for publication.

Disclosure/Conflict of Interest

None declared.

anterior cingulate cortex to increase response during a drug-related context. Together, these results suggest that fMRI could be useful in sensitively tracking follow-up outcomes in drug addiction.

Keywords

cocaine addiction; follow-up outcome; fMRI; midbrain; thalamus; dopamine; anterior cingulate cortex; drug Stroop

INTRODUCTION

A core feature of drug addiction is dysregulated dopaminergic neurotransmission, including decreased dopamine receptor availability and release (Volkow et al., 2004), and functional impairments in frontal brain regions innervated by dopamine (Goldstein and Volkow, 2002). Such dopaminergic dysregulation in addiction is associated with abnormalities in how brain reward circuits respond to drugs/drug-related stimuli (Robinson and Berridge, 2003) and natural reinforcers (Garavan et al., 2000; Martin-Sölch et al., 2001), such that the pursuit of drugs surpasses that of other reinforcers (Goldstein and Volkow, 2002). For example, the more blunted the striatal dopaminergic release to a stimulant challenge (Martinez et al., 2007) and the lower the striatal dopamine D1 receptor availability (Martinez et al., 2009) in cocaine abusers, the higher is the choice to self-administer cocaine over receiving money. However, as indicated by non-human primate studies (Beveridge et al., 2009; Melega et al., 1997) and human positron emission tomography (PET) studies (Volkow et al., 2001), such striatal dopaminergic dysregulation may partly recover with abstinence [but see (Iyo et al., 2004)]. Other studies using different imaging modalities and targeting different regions/systems have similarly revealed partial recovery with abstinence (Bell et al., 2011; Ernst and Chang, 2008; Kim et al., 2006; Nordahl et al., 2005). However, the extent to which such results translate to an ecologically valid sample of treatment-seeking drug addicted individuals remains to be determined.

The goal of the present functional magnetic resonance imaging (fMRI) study was to test whether the blood oxygen level dependent (BOLD) response in dopaminergically-innervated brain regions changes over a six-month follow-up period in initially treatment-seeking cocaine addicted individuals. We were especially interested in functional enhancements of these regions, which we expected to correlate with measures of reduced drug seeking. At baseline and again at 6-month follow-up, subjects performed an emotionally salient (drug Stroop) task while undergoing fMRI. In previous fMRI investigations of this drug Stroop task, active cocaine abusers showed midbrain response to the drug cues (Goldstein et al., 2009b), consistent with this region's role in mediating the behavioral reactivity to motivationally salient stimuli through phasic and tonic dopamine release (Montague et al., 2004; Schultz, 2010). Also on this task, active cocaine abusers showed hypoactivity in dorsal and rostro-ventral subregions of the anterior cingulate cortex (ACC) (Goldstein et al., 2009a). These ACC subregions were normalized after administration of an indirect dopamine agonist (methylphenidate) as associated with better control of behavior (Goldstein et al., 2010), consistent with these regions' respective roles in cognitive control (Ridderinkhof et al., 2004) and emotional conflict resolution (Etkin et al., 2006). Collectively, these findings speak to the ability of this drug Stroop task to interrogate dopaminergically-innervated brain regions, which mediate functions of high pertinence to a treatment-seeking population (e.g., cognitive functioning, motivational salience). These previous fMRI studies, in combination with previous PET studies showing recovered midbrain (Volkow et al., 2001), striatum (Volkow et al., 2001), and thalamic (Wang et al., 2004) function after abstinence in methamphetamine abusers, guided our current hypotheses. We predicted that at 6-month follow-up (compared with baseline), subjects

would show increased activity in the midbrain, ACC, thalamus, and striatum, as associated with reduced cocaine choice behavior (a measure previously shown to correlate with actual cocaine use [Moeller et al., 2009]).

METHODS & MATERIALS

Subjects

Our main sample included 15 treatment-seeking cocaine abusers (11 males, 41.4 ± 9.1 years old), all right-handed, native English speakers, and free of sustained/maintenance medications that could affect the BOLD signal for > 30 days prior and throughout the study (see Supplementary Information for subject exclusion criteria). All subjects twice completed our emotionally salient fMRI drug Stroop task (described below) without loss of data due to motion or technical difficulties: at baseline after detoxification (≈ 3 weeks after last drug use: 111.5 ± 151.4 days) and then again at 6-month follow-up. The average time between scanning sessions for these subjects was 198 days (6.4 months) ± 30.5 days (1 month). Subjects were referred from three drug treatment facilities located in the New York Tri-State area (for information on these facilities, see Supplementary Information): Phoenix House (N=8), Samaritan Village (N=2), and Yale Cocaine Research Clinic (N=5). Subjects met criteria for current cocaine dependence (N=11), or cocaine dependence in partial (N=3) or sustained remission (N=1), as determined by a comprehensive diagnostic interview conducted at baseline (see Supplementary Information for interview components and subject comorbidities). We tracked subjects' abstinence between the two scanning sessions (see Supplementary Information for our three-tiered tracking system), which revealed that eight subjects remained abstinent (they had been abstinent 190.9 ± 17.3 days at second study session) while seven subjects had at least one lapse where cocaine was used between the two sessions. The last drug use for these seven relapsing subjects occurred 71.3 ± 61.8 days prior to the second study session. There were no differences between relapsers and abstainers in baseline abstinence (i.e., the number of days of abstinence prior to the first scan) [$t(7.0)=2.1$, $p>0.07$]. There were also no differences in the amount of days elapsed between scans among those who relapsed versus those who remained abstinent [$t(13)=1.0$, $p>0.3$].

To establish norms, generalizability of results, and the prospect of normalization of function, we also compared these 15 treatment-seeking cocaine subjects with 13 actively using cocaine subjects (verified by positive cocaine urine screen on study day) and 13 healthy control subjects with no history of substance abuse. Although comparisons between these active users and controls were reported previously (Goldstein et al., 2009a; Goldstein et al., 2009b), these analyses are entirely novel because these previous subjects have never been compared with a treatment-seeking sample; and most importantly, here for the first time we report direct comparisons between baseline and follow-up in these treatment-seeking subjects. Because these matched active users and controls completed the drug Stroop task only once, all analyses that included active users and controls were considered exploratory, therefore primarily reported in Supplementary Information. All subjects provided written consent to participate in accordance with the Stony Brook University Institutional Review Board and the associated treatment facility's Institutional Review Board.

Task

After training (Supplementary Information), subjects viewed 40 drug words and 40 matched neutral (household) words (2000 ms per word), in a blocked on-off or off-on order (i.e., drug-neutral or neutral-drug), counterbalanced between subjects and sessions (Goldstein et al., 2009a; Goldstein et al., 2010) (Figure S1). We selected a blocked design because prior behavioral studies have demonstrated that salient stimuli (here, drug words) become more potent when grouped together into blocks, rather than when intermixed with neutral trials

(Holle et al., 1997); blocked designs, where the BOLD signal is measured between blocks of trials and not individual trials (D'Esposito et al., 1999), are also more robust than event-related designs against vascular pulsatility effects on the midbrain [one of our main regions of interest (ROIs)], which is an acknowledged concern (D'Ardenne et al., 2008). There were eight 3.4 min task repetitions (four drug, four neutral), each containing two blocks of 20 drug or neutral words, interleaved with a 20 s white fixation cross overlaid on a black background. Each word trial consisted of a 500 ms fixation cross, a 2000 ms word presentation (for word reading), a 500 ms response window, and a 500 ms feedback slide (correct/incorrect). During the 500 ms response window, subjects had to press one of four buttons (yellow, blue, red, green) on a commercially available MRI response pad (Cedrus brand Lumina model LP-400), matching the ink color of the word they had just read; word color order was pseudorandomized across all task runs. Note that low response variability on this task was expected [driven by the current blocked design and by the extended separation between word reading and button press that reduced working memory concerns but also reduced cognitive conflict (Goldstein et al., 2007)]. To further increase saliency of this task (beyond that already afforded by the salient drug words, see Supplementary Information), subjects performed each word sequence under one of four counterbalanced monetary reward amounts (50¢, 25¢, 1¢, or 0¢), gained for correct performance for up to \$75 of real money. The monetary value to be gained for correct performance was displayed at the beginning of each run and at the end of each trial. Because contrasting these task conditions would have been overly punitive in this relatively small sample size, and because money did not interact with session or word for either task accuracy or reaction time (see Supplementary Information, where there was only a main effect of money on task performance that further attests to this task's emotional salience and ability to tap into reward responsiveness), we collapsed results across the money conditions throughout the behavioral and fMRI analyses. Therefore, and although our MRI scanner provides sufficient coverage of this region (except for perhaps its most ventral aspects) (see Figure S2), we did not have specific hypotheses for the orbitofrontal cortex.

Behavioral Measures

Task Performance and Targeted Neuropsychological Drug-Choice Tasks—

Reaction time and accuracy data were collected across all trials. The total money earned throughout the task was also ascertained. Since all subjects were treatment-seeking (and more than half of the sample was abstinent throughout the study), targeted neuropsychological tasks of simulated implicit and explicit drug-seeking were adopted in lieu of actual drug use variables (the latter included a preponderance of zeros, complicating data analysis; nevertheless, we still explored baseline prediction of subsequent drug use, as described in Results and Supplementary Information). These tasks were previously associated with/modulated by actual drug use [cocaine urine status or frequency of recent cocaine use (Moeller et al., 2010; Moeller et al., 2009)], therefore of particular utility in the current treatment-seeking population. In the current study, although not reaching significance likely due to sample size, cocaine choice was also positively associated with actual cocaine use (Supplementary Information). In brief, both *drug-seeking tasks* measure the extent to which cocaine images are selected for viewing compared with pleasant, unpleasant, or neutral images. In the explicit task, choice is made between two fully visible side-by-side images; in the implicit task, selections are made between pictures hidden under flipped-over cards (and thus location of the drug stimuli needs to be acquired through experience) (Moeller et al., 2009). Dependent variables were the total number of cocaine images selected for viewing in each task (Table 1).

MRI Data Acquisition

MRI scanning was performed on a 4T whole-body Varian/Siemens MRI scanner, equipped with a self-shielded whole-body Siemens Sonata EPI hardware [maximum gradient strength per channel 44mT/m, slew rate 176 mT/(m-ms)]. A standard quadrature head resonator is used for all studies. The BOLD responses were measured as a function of time using a T2*-weighted single-shot gradient-echo echoplanar imaging sequence (echo time/repetition time=20/1600 ms, 3.125×3.125 mm² in-plane voxel size, 4 mm slice thickness, 1 mm gap, typically 33 coronal slices, 20×20×16.5 cm³ field of view, 64×64 matrix size, 90° flip angle, 200 kHz bandwidth with ramp sampling, 128 time points, and 4 dummy scans to be discarded to avoid nonequilibrium effects in the fMRI signal). Padding minimized motion, which was also monitored immediately after each fMRI run (Caparelli et al., 2003). Earplugs and headphones minimized the interference effect of scanner noise (Tomasí et al., 2005). Anatomical MRI started with the acquisition of a sagittal T1-weighted gradient-echo localizer (TE/TR 10/100 ms, 5 mm slice thickness, 20 cm FOV, matrix size=256×192, 128 phase encoding steps, 13 sec scan time). This was followed by an axial T1-weighted 3D-MDEFT (three-dimensional modified driven equilibrium Fourier transform) sequence (TE/TR=7/15ms, 0.94×0.94×1 mm spatial resolution, 256 readout and 192×96 phase-encoding steps, partial k-space acquisition, 16 minutes scan time) (Lee et al., 1995), and a modified T2-weighted hyperecho sequence (Hennig and Scheffler, 2001). Images were reconstructed in IDL (Interactive Data Language, Research Systems, Boulder, CO) using a Hamming filter, a phase correction method that produces minimal ghost artifacts, and an iterative phase correction to partially recover the signal loss due to susceptibility effects (conducted by an MRI physicist). Anatomical images were reviewed by a neurologist to rule out gross morphological abnormalities.

MRI Data Processing

Analyses were performed with Statistical Parametric Mapping (SPM2) (Wellcome Trust Centre for Neuroimaging, London, UK). A six-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment and for correction of head motion; criteria for acceptable motion were 2 mm displacement and 2° rotation in any of the axes in any of the task repetitions. The realigned datasets were spatially normalized to the standard stereotactic space of the Montreal Neurological Institute (MNI) using a 12-parameter affine transformation (Ashburner et al., 1997) and a voxel size of 3×3×3 mm. An 8 mm full-width-half-maximum Gaussian kernel was used to spatially smooth the data.

BOLD fMRI Analyses

A general linear model (Friston et al., 1995) and a box-car design convolved with a canonical hemodynamic response function and high-pass filter (cut-off frequency: 1/520 s) was used to calculate the individual BOLD-fMRI maps. Four contrast maps per subject were calculated, reflecting percent signal change from fixation for each of two task conditions during two scan sessions (drug and neutral epochs at baseline and follow-up). These individual contrast maps were included in a second-order (random-effects) 2 (session: baseline, follow-up) × 2 (word: drug, neutral) repeated measures ANOVA SPM2 model. We also inspected whole-brain correlations (simple regressions), where the task performance and clinical variables listed in Table 1 were entered as covariates regressed against the drug Stroop contrasts. To specifically test the hypothesis of change, these whole-brain correlations were conducted using follow-up>baseline difference scores. Considering the main effects reported below, correlations with the drug choice tasks and clinical variables were conducted using the averaged drug Stroop contrasts (averaged across the drug and neutral contexts); correlations with the *task specific* accuracy and reaction time (RT) variables were conducted separately for the drug and neutral contexts. Thus, we performed nine targeted whole-brain correlations, which employed similar whole-brain correction

procedures as the ANOVA analyses (described below). In addition, to explore abstinence as a potential mechanism of change, we (A) repeated our main analyses while also including relapse (yes, no) as a between-subjects factor; and (B) conducted preliminary analyses where we used fMRI data (at baseline and change at follow-up) to predict actual drug use that occurred between study sessions (these prediction analyses are primarily reported in Supplementary Information).

Brain activation clusters were corrected for multiple comparisons using the continuous random field calculation (Adler, 1981), here based on the expected Euler characteristics of the regions above a $p < 0.001$ voxel uncorrected threshold, where clusters with at least 15 contiguous voxels that were $p < 0.05$ cluster-level corrected were considered significant for all analyses. This conservative threshold was chosen to minimize Type I error in this sample size. An even more stringent statistical threshold (whole-brain $p < 0.05$ family-wise error correction at the voxel level, and $p < 0.05$ error correction at the cluster level) was employed for the between-group analyses because the groups were compared pairwise and post-hoc (see also Supplementary Information). Anatomical specificity was corroborated with the MRICron software. Brain activation and deactivation clusters were further evaluated with complementary ROI analyses to identify outliers and to report (and graphically represent) average values in a volume comparable to the image smoothness [e.g., the volume of the resolution elements or “resels” (Worsley et al., 1992)], rather than single-voxel peak values. Thus, 9-mm isotropic cubic masks were created and centered at the exact coordinates in Table 2 and were kept invariant across subjects; the average BOLD fMRI signal amplitudes in these regions were computed using a custom program written in IDL. These ROIs, which give precise spatial localization of the functional responses (Tomasi et al., 2007a, b), were analyzed with the appropriate (e.g., ANOVA, correlation) analyses in SPSS, and were used to rule out potentially confounding covariates (Supplementary Information).

RESULTS

Below, we report within-subjects (follow-up versus baseline) comparisons and brain-behavior correlations in the primary sample of 15 treatment-seeking cocaine subjects (Table S3 provides all task activations and deactivations in this sample across both study sessions). We also report between-group comparisons among the treatment-seeking subjects, actively using subjects, and healthy controls – but only those comparisons that directly bear on our a priori ROIs; all other effects from these between-group analyses are reported in Supplementary Information (see also Tables S4–S5; Figures S4–S5).

Behavior (Table 1)

Task accuracy and RT (for the correct trials) were separately analyzed with 2 (session: baseline, follow-up) \times 2 (word: drug, neutral) repeated measures ANOVAs. The clinical self-report measures and neuropsychological drug-related tasks were separately analyzed with paired t -tests. These behavioral measures generally did not differ between baseline and follow-up (Table 1). Of all possible effects, only the word \times session interaction for RT reached significance [$F(1,14)=8.3$, $p < 0.05$], driven by faster performance at follow-up than baseline, but only during the neutral trials (Table 1).

SPM fMRI (Table 2)

Whole-Brain Within-Subjects Analyses—The follow-up>baseline contrast revealed main effects in the bilateral midbrain (ventral tegmental area/substantia nigra complex) (Figure 1A–1C) and right thalamus (mediodorsal nucleus) (Figure 1A, 1D). Table 2 lists the other regions that showed either follow-up>baseline or follow-up<baseline main effects; the latter contrast revealed activations in regions of the control network (e.g., pre-supplementary

motor area, inferior parietal cortex). At the voxel level, there was a word \times session interaction in the left dorsal ACC/midcingulate, explained by higher drug than neutral responses at follow-up but a reverse pattern at baseline. However, this interaction did not reach cluster level significance (Table 2). There were no drug>neutral or drug<neutral main effects (i.e., effects of word that were independent of session), and no effects for the rostro-ventral ACC or striatum.

Brain-Behavior Correlations—There was a negative correlation between changed response (follow-up>baseline) in the right midbrain and changed (follow-up>baseline) explicit cocaine choice behavior (Figure 2A), indicating that higher midbrain response was associated with *reduced* cocaine-seeking behavior. In contrast, changed cerebellum response (despite lack of main effects in this region) correlated with *increased* explicit cocaine choice (Table 2). Brain-behavior correlations with the other clinical severity measures were not significant.

In addition to these primary correlation analyses, preliminary correlation analyses revealed that one midbrain ROI at baseline ($x=12$, $y=-21$, $z=-15$ mm) negatively predicted the number of days of any drug use (cocaine, alcohol, or marijuana) during the three months preceding the second study session ($r=-0.59$, $p<0.05$); this effect was driven by midbrain BOLD response to neutral words ($r=-0.69$, $p<0.01$). However, this effect was not confirmed with whole-brain analysis. For all other results of these BOLD-fMRI correlations with actual drug use, see Supplementary Information.

Midbrain-Thalamus Correlations—Given similar signal increases in midbrain and thalamus, and following our a priori hypotheses regarding enhanced BOLD signal in these regions at follow-up, we undertook exploratory correlation analyses that tested for their increased correlation at follow-up. Masks around the two midbrain and one thalamus peak coordinates from Table 2 (the follow-up>baseline contrast) were entered as seeds into three whole brain correlation analyses, separately at baseline and follow-up (thus totaling six analyses). Contrasts for these analyses were response to averaged drug and neutral trials compared with fixation. There were no correlations at baseline, but, as expected, one of the two midbrain seeds was significantly correlated with the bilateral thalamus at follow-up (Figure 2B–2C) (Table 2). Note that this midbrain-thalamus correlation remained significant even after excluding the potential outlier in the upper right quadrants ($p<0.05$).

Effects of Relapse—We re-analyzed task accuracy and RT using 2 (session: baseline, follow-up) \times 2 (word: drug, neutral) \times 2 (relapse: yes, no) mixed ANOVAs; money gained and the clinical variables were analyzed with 2 (session: baseline, follow-up) \times 2 (relapse: yes, no) mixed ANOVAs. Including relapse into these analyses did not alter results; group also did not interact with any of these variables ($p>0.1$), indicating that change in task performance and clinical severity from baseline to follow-up did not differ as a function of abstinence.

Similarly, adding the same between-subjects variable (relapse: yes, no) into ROI analyses (the extracted BOLD signals of the two midbrain ROIs and the one thalamic ROI as implemented in SPSS) indicated that the enhanced activations in these regions from baseline to follow-up were not differentially driven by either the relapsers or non-relapsers (all $p>0.05$). Taken together, these analyses justify the inclusion of all treatment-seekers into a single group.

Comparisons with Active Users or Healthy Controls: Treatment-Seekers at Baseline:

At baseline, the treatment-seekers showed lower left midbrain activation than controls, but did not differ from active users. This result indicates that the treatment-seekers may have

had initially impaired functioning of this region, therefore suggesting that these treatment-seekers were representative of cocaine abusers at baseline (e.g., not initially different due to enhanced motivation to abstain) (Figure 3).

Comparisons with Active Users or Healthy Controls: Treatment-Seekers at Follow-Up:

At follow-up, the treatment-seekers activated the midbrain more than active users (who were assessed at baseline). In contrast, treatment-seekers at follow-up did not differ from healthy controls (who were assessed at baseline) (Figure 3) (note, however, that when relaxing the threshold to $p < 0.001$ voxel uncorrected, controls continued to show higher midbrain activity than the treatment-seekers: peak voxel: $x = -12$, $y = -15$, $z = -9$ mm, $x = -9$, 49 voxels, $Z = 4.4$, $p = 0.021$ cluster-level uncorrected). These results in the treatment-seekers at follow-up, in combination with results in the treatment-seekers at baseline (above) and the means presented in Figure 1, could collectively indicate that initial midbrain hypoactivations were partially normalized after six months.

DISCUSSION

The present longitudinal fMRI study revealed enhanced BOLD-fMRI activations in the dopaminergic midbrain and thalamus at 6-month follow-up compared with baseline in initially treatment-seeking cocaine addicted individuals. Because this midbrain response to drug and neutral words was (A) enhanced at 6-month follow-up compared with baseline, and (B) at baseline, lower than healthy controls but not different from active users, whereas at follow-up, higher than active users but still somewhat lower than controls, we interpret this increased BOLD response to indicate a partial restoration of response in this region, which was initially deactivated. Also consistent with this interpretation were the behaviorally meaningful correlations between increased midbrain activity and reduced cocaine-seeking behavior, and between midbrain response at baseline and actual drug use over the next six months. Although the latter correlation was not confirmed with whole-brain analysis, it nonetheless supports the idea that baseline midbrain activity during this salient task predicts positive abstinence-related outcomes; more generally, it also contributes to a growing body of literature in which baseline neuroimaging assessments are used to predict future drug-related outcomes (Brewer et al., 2008; Janes et al., 2010; Jia et al., 2011; Martinez et al., 2011; Paulus et al., 2005). Because midbrain dopamine heavily innervates the mediodorsal nucleus of the thalamus (Sanchez-Gonzalez et al., 2005), and because both regions participate in conditioned reinforcement and reward expectation (Corbit et al., 2003; Mitchell et al., 2007; Volkow et al., 2003) and general reward processing (Liu et al., 2011), one could indeed expect these regions to show parallel functional enhancement. In further support, we observed higher (more positive) correlations between the midbrain and thalamus at follow-up than baseline, which may suggest that over this 6-month study period there was partial restoration of connectivity between these regions – a connection that is disrupted in active users (Tomasi et al., 2010). Taken together, these midbrain and thalamus results echo previous studies in substance abusers showing that increased responsiveness to positive reinforcers predicted better clinical outcome (Heinz et al., 2007; Lubman et al., 2009). Our results are also relevant to the concept of allostasis in addiction, such that the neuroadaptations from chronic exposure to addictive drugs, which change the threshold for rewards (Koob and Le Moal, 2008), may have partially recovered during this 6-month follow-up period. Behaviorally, such recovery might manifest as enhanced responsiveness during a non-drug related context, possibly indicated in the current study by faster RT during the neutral trials at follow-up. Overall, although BOLD-fMRI activity is an indirect marker of dopaminergic neurotransmission (Tomasi et al., 2009) and although other (non-dopamine) systems may also be involved, we interpret these collective midbrain and thalamus effects, and correlations with reduced drug-seeking behavior and drug use, as possibly marking improved dopaminergic functioning at follow-up.

This study also revealed several unexpected/null findings. First, although we initially expected higher cognitive control at follow-up compared with baseline, the only support for this hypothesis was a word \times session interaction in the dorsal ACC, which was significant at the uncorrected voxel level but not the corrected cluster level. This trend, showing higher activity to the drug words at follow-up, may reflect increased effort/control specifically during a drug-related context among individuals putatively motivated to remain abstinent (here, treatment-seekers at 6-month follow-up) (Nestor et al., 2011), befitting the posited role of this region in response selection (Bush et al., 2002; Vogt, 2005) and in general conflict resolution (Egner et al., 2008). Other regions relevant to cognitive control [e.g., pre-supplementary motor area and inferior parietal cortex (Seeley et al., 2007)] showed follow-up < baseline main effects, possibly reflective of higher cognitive demands when the task was novel (i.e., more activity was needed to achieve comparable performance). Another unexpected result was the lack of effects in the rostro-ventral ACC. Nevertheless, given the more pronounced group differences in this region at follow-up than baseline (i.e., when treatment-seekers were compared with active users or controls) (Supplementary Information, Figure S5), within-subjects differences may indeed emerge with larger sample sizes. Finally, given that the striatum showed partial recovery following abstinence in both animal (Beveridge et al., 2009; Melega et al., 1997) and human (Volkow et al., 2001) studies, and given that the dorsal striatum was proposed as a mechanism of cocaine craving (Volkow et al., 2006), one could have anticipated the striatum to reduce activity to drug words at follow-up. However, because this drug Stroop task did not reveal striatum effects in our previous reports (Goldstein et al., 2009a; Goldstein et al., 2009b), null results for this region become less surprising.

The primary limitation of this study is the potential for practice effects. We attempted to reduce this concern by (A) controlling for sleepiness, which did not attenuate the current findings (Supplementary Information); and (B) performing exploratory between-group SPM analyses, which supported the idea that our midbrain main effect could reflect normalization of an initially impaired function (Results) (although we acknowledge that these analyses, though buttressing the within-subject analyses, are subject to the same practice effects). In addition to these analyses, this concern of practice effects is lessened when considering that midbrain activity negatively correlated with sleepiness (Supplementary Information), there was a substantial (6-month) interval between scanning sessions to minimize habituation, and enhanced midbrain response (that would indicate increased dopamine firing) more likely reflects task engagement/motivation than disengagement (Boehler et al., 2011; Satoh et al., 2003; Volkow et al., 2010). Nevertheless, future longitudinal investigations should include control subjects who also complete the task twice, and alternate versions of the task at the two time points. A second limitation is that our primary effects emerged averaged across the drug and neutral words, complicating interpretations vis-à-vis cognitive control or reactivity to drug-related stimuli. Future studies with more subjects (power) and/or more lenient statistical thresholds might be needed to detect differential effects as a function of word, as was the case in our previous report (Goldstein et al., 2009b). A third limitation is that the midbrain correlation with drug choice, although cluster-level significant at $p < 0.05$, was one of nine whole-brain analyses. Given that this correlation would not have reached significance with an additional Bonferroni correction (i.e., $p < 0.005$ cluster-level corrected), it needs to be replicated in future studies. A final limitation is that the precise mechanism of the midbrain and thalamic effects remains to be studied further; in particular, the respective contributions of therapy, abstinence, and subject self-selection into the study need to be disentangled in larger samples. Yet this latter limitation is balanced by ecological validity (studying treatment-seekers exposed to various treatment modalities), which increases generalizability.

In summary, to our knowledge the current results show for the first time elevated midbrain and thalamic fMRI response, and correlation between these regions, in initially treatment-seeking cocaine addicted individuals at a 6-month follow-up, and with associated decreases in drug seeking. By scanning study subjects twice, the current study extends previous work that has used baseline neural response to predict clinical outcome (Brewer et al., 2008; Janes et al., 2010; Jia et al., 2011; Martinez et al., 2011; Paulus et al., 2005). Consistent with previous studies (Nestor et al., 2011; Volkow et al., 2001; Wang et al., 2004), the present study found improvement effects in the more subcortical regions; in the more prefrontal cortical regions, impairments may be more intractable, as supported by studies revealing functional or structural abnormalities in addicted individuals even after 1 year abstinence especially in prefrontal cortical regions (Durazzo et al., 2011; Ersche et al., 2005; Nestor et al., 2011). The robust effects in the current study are striking in light of the marked heterogeneity of this treatment-seeking sample (e.g., length of abstinence, comorbidity, inpatient status, remission status, etc.), and the associated potential for increased variability and reduced power. Overall, our results suggest that functional imaging, and brain-behavior correlations, could provide sensitive biomarkers of abstinence-related outcomes in drug addiction – biomarkers that are detectable even in the general absence of behavioral differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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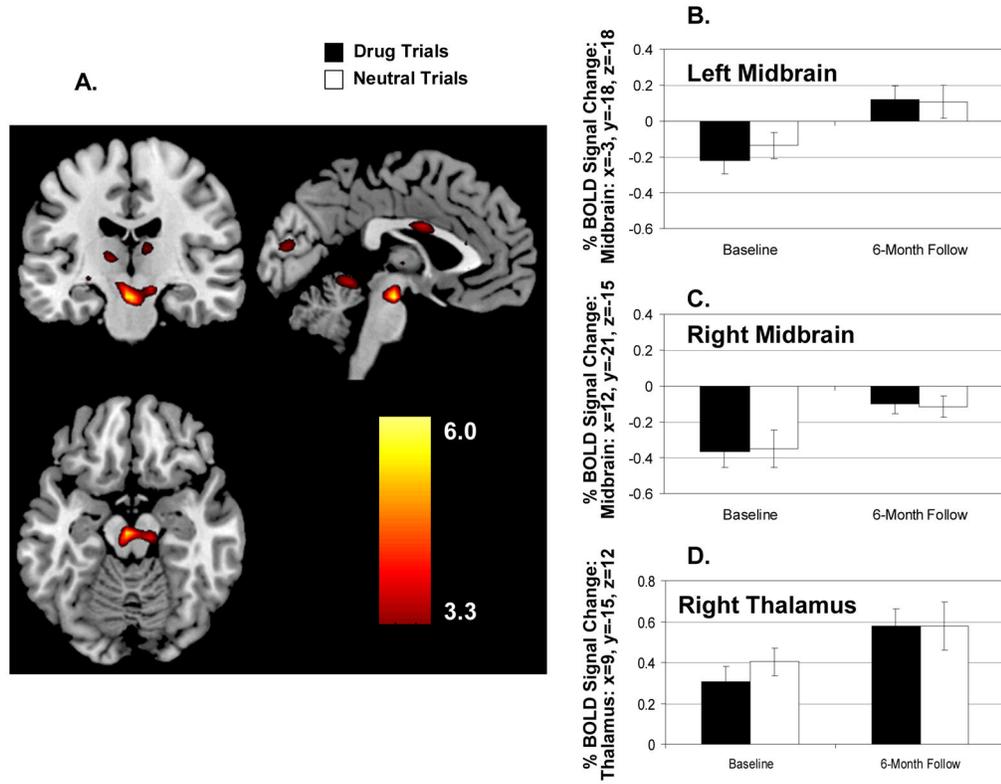


Figure 1. Bilateral midbrain and thalamic response at 6-month follow-up. (A) mean % BOLD signal change in the midbrain and thalamus at 6-month follow-up compared with initial baseline (3 weeks detoxified). (B, C, D) Means and standard errors of these peak BOLD responses, separately for drug and neutral trials, showing the follow>baseline main effects (N=15). Images are in neurological convention (left=left).

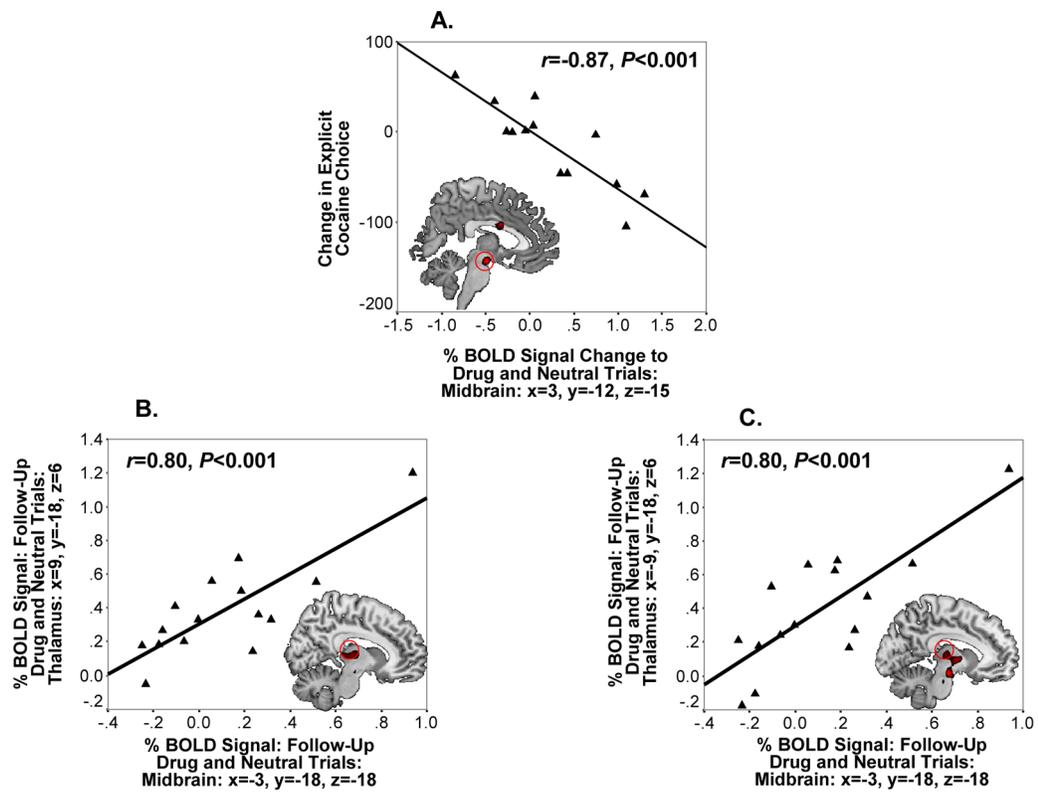


Figure 2. Midbrain correlations with behavior and thalamus. (A) Negative correlation between change in midbrain activity during drug and neutral trials and change in cocaine choice behavior. (B, C) Positive correlation between one of the midbrain seeds ($x=-3, y=-18, z=-18$) and bilateral thalamus activity at follow-up (B: right thalamus; C: left thalamus). The parallel correlations between midbrain and thalamus at baseline were not significant (data not shown).

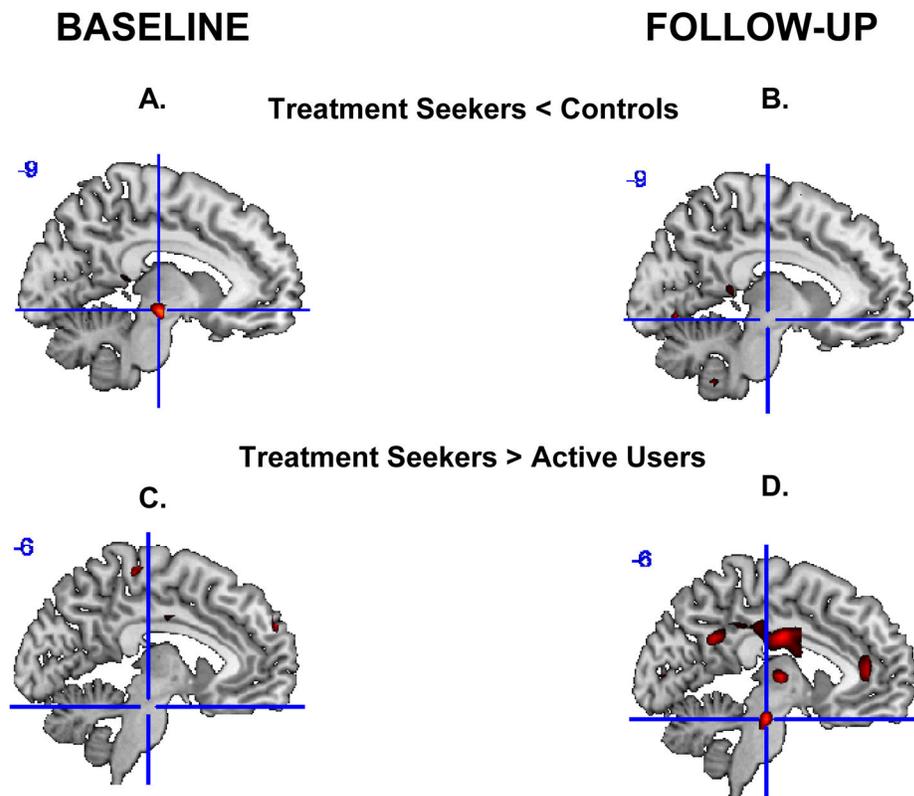


Figure 3. Midbrain activation comparisons between treatment-seekers, active users, and healthy controls. Midbrain activation is lower in treatment seekers than in controls (A) at baseline, but (B) not at 6-month follow-up. Further, midbrain activation in treatment-seekers is (C) not higher than in active users at baseline, but (D) higher than in active users at 6-month follow-up.

Table 1

Task Performance and Clinical Outcome Variables at Initial Baseline and 6-Month Follow-up in 15 treatment-seeking subjects with cocaine use disorder.

| | Paired <i>t</i> | Baseline | Follow-up |
|---|-----------------|--------------|--------------|
| TASK PERFORMANCE | | | |
| Total Correct (max: 20): Drug Words | 1.0 | 17.3 ± 1.6 | 17.0 ± 1.6 |
| Total Correct (max: 20): Neutral Words | 0.3 | 17.1 ± 1.9 | 17.0 ± 1.5 |
| Reaction Time (Correct Trials) (ms): Drug Words ^A | 0.6 | 253.9 ± 15.9 | 252.2 ± 17.1 |
| Reaction Time (Correct Trials) (ms): Neutral Words | 2.2 * | 258.7 ± 12.9 | 250.8 ± 16.9 |
| NEUROPSYCHOLOGICAL DRUG TASKS | | | |
| Implicit Choice: Drug Images | -0.5 | 13.5 ± 8.4 | 14.5 ± 10.0 |
| Explicit Choice: Drug Images | 1.1 | 76.5 ± 83.4 | 62.3 ± 68.9 |
| CLINICAL VARIABLES | | | |
| Cocaine Selective Severity Assessment Scale (withdrawal/craving symptoms; range: 0–126) | 1.7 | 13.9 ± 12.2 | 10.6 ± 10.3 |
| Severity of Dependence Scale (range: 0–15) | 2.1 | 10.0 ± 3.8 | 7.5 ± 3.8 |
| Cocaine Craving Questionnaire (range: 0–45) | 0.5 | 8.1 ± 5.8 | 7.4 ± 8.7 |

Note: Numbers are $M \pm SD$; consistent with the text, task performance variables are averaged across four money conditions;

^A significantly differs from the neutral words at baseline;

* $p < 0.05$.

Task activations, deactivations, and correlations with behavior at baseline versus at 6-month follow-up in 15 treatment-seeking subjects with cocaine use disorder.

Table 2

| | BA | Side | Voxels | Z | p | cluster level corrected | x | y | z |
|--|----|------|--------|------|---|-------------------------|-----|-----|-----|
| Follow-up>Baseline | | | | | | | | | |
| Midbrain (VTA/substantia nigra complex) | L | | 75 | 4.9 | | .024 | -3 | -18 | -18 |
| | R | | | 4.2 | | | 12 | -21 | -15 |
| Thalamus | R | | 125 | 3.7 | | .002 | 9 | -15 | 12 |
| Precuneus | 7 | L | | 3.9 | | | -6 | -60 | 39 |
| Cuneus | 18 | M | | 3.7 | | .022 | 0 | -84 | 15 |
| Follow-up<Baseline | | | | | | | | | |
| Medial Frontal Gyrus/Pre-SMA | 6 | M | | 4.8 | | | 0 | -3 | 57 |
| Postcentral Gyrus | 4 | R | | 4.2 | | .000 | 39 | -21 | 54 |
| Precentral Gyrus | 6 | L | | 3.4 | | | -42 | 0 | 54 |
| Inferior Parietal Lobule | 40 | R | | 4.3 | | .036 | 45 | -36 | 42 |
| Inferior Occipital Gyrus | 19 | R | | 4.7 | | | 39 | -66 | -15 |
| Fusiform Gyrus | 37 | | | 3.8 | | .000 | 33 | -42 | -15 |
| Lingual Gyrus | 19 | | | 4.7 | | | -30 | -81 | -12 |
| Lingual Gyrus | 18 | L | | 3.7 | | .001 | -6 | -87 | -9 |
| Fusiform Gyrus | 19 | | | 3.5 | | | -27 | -66 | -9 |
| Correlations with Behavior: Follow-up>Baseline | | | | | | | | | |
| <i>Drug and Neutral Words</i> | | | | | | | | | |
| Explicit Cocaine Choice | | | | | | | | | |
| Cerebellum | | L | 178 | +4.3 | | .000 | -18 | -57 | -12 |
| Midbrain | | R | 30 | -4.4 | | .050 | 3 | -12 | -15 |
| Midbrain-Thalamus Correlations: Follow-up | | | | | | | | | |
| <i>Drug and Neutral Words</i> | | | | | | | | | |

