Pharmacology, Biochemistry and Behavior 92 (2009) 277–282

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Differential effects of acute cocaine and placebo administration on visual cortical activation in healthy subjects measured using BOLD fMRI

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ARTICLE INFO

Article history:
Received 12 August 2008
Received in revised form 12 December 2008
Accepted 15 December 2008
Available online 24 December 2008

Keywords:
BOLD fMRI
Cocaine
Drug expectancy
Non-specific effects
Placebo
Visual stimulation

ABSTRACT

Many blood oxygenation level dependent (BOLD) functional magnetic resonance imaging studies have shown a strong response due to cocaine in brain regions with high concentrations of dopamine receptors. However, cocaine also has non-specific effects, including cardiovascular changes that may cause changes in BOLD signals, raising the possibility that measured changes could be due to these non-specific effects. The following experiment was conducted to address this concern. Subjects were given either cocaine or saline infusions during a long BOLD functional magnetic resonance imaging study. A flashing uniform-field stimulus, periodically alternating between on and off, provided a strong activation of primary visual cortex. There was a significant main effect of drug between cocaine and placebo. Although we did not demonstrate a significant drug×time interaction, BOLD signal changes associated with visual stimulation appeared unchanged after cocaine administration, whereas the signal differences appeared to decrease during placebo. Explanation of the differential response between the two groups may reflect cocaine expectancy instead of a direct effect of cocaine on BOLD signal changes but will require further investigation to fully elucidate.

1. Introduction

Cocaine use remains a significant public health problem, as more than 1.5 million Americans met the criteria for cocaine abuse or dependence in 2003 (Office of Applied Studies, 2004). Cocaine is highly reinforcing, rapidly leading to increasing rates of self-administration in the face of strong negative consequences (Dackis and O'Brien, 2001). While the behavioral and physiological consequences of its use are well known, the effects of cocaine on a user's brain that actually lead to cocaine drug-taking behavior are varied and complex, and significant aspects remain unknown.

Functional magnetic resonance imaging (fMRI) techniques are well suited to the study of brain processes, yielding excellent spatial localization and good temporal resolution with minimal risk and discomfort. Several studies have used fMRI techniques to study brain activity related to drug abuse and dependency. A seminal study used blood oxygenation level dependent (BOLD) to image the whole brain before, during, and after cocaine infusion (Breiter et al., 1997). A number of brain regions showed changed activation. Subjective ratings and blood and plasma cocaine levels reach peak levels about 3–6 min following intravenous cocaine infusion (Muntaner et al., 1989; Breiter et al., 1997; Mendelson et al., 1998; Newton et al., 2005), while cardiovascular effects peak near 6–10 min post infusion (Muntaner et al., 1989; Foltin et al., 1995; Mendelson et al., 1998; Kaufman et al., 1998; Newton et al., 2005). Thus, one would expect peak BOLD effects to occur at similar times.

Cocaine directly alters brain activity, but also induces systemic cardiovascular changes that can result in altered global cerebral blood flow and neurovascular coupling. This makes it difficult to interpret blood flow changes due to neural activations. Luo et al. (2003) addressed this confound. In an attempt to dissociate altered cardiovascular tone from changes in neuron activity, Luo and colleagues gave rats either cocaine or cocaine methiodide. The latter compound is selective for systemic cardiovascular changes because the polar methiodide group prevents passage through the blood-brain barrier. With cocaine methiodide, Luo and colleagues found no activation in any of the nine regions of interest studied at any of four dosages, but found a strong effect, increasing with dose, for cocaine. Thus, BOLD changes due to cocaine appear to arise from neural effects, rather than just systemic cardiovascular changes.

Pharmacological MRI (phMRI) experiments of drugs of abuse typically produce effects that vary quite slowly, on the order of several minutes. A number of low-frequency noise sources, including physiological fluctuations (Biswal et al., 1995), and scanner drift, plague BOLD phMRI experiments. Signal changes associated with drug effects are confounded by these low-frequency fluctuations, making

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doi:10.1016/j.pbb.2008.12.014

Table 1
Mean ± standard error of subject demographic information

Variable	Subjects receiving		Two-tailed significance
	Placebo	Cocaine	
Age (years)	26.6±0.8	25.0±1.1	0.32
Body mass index (kg/m^2)	23.2±0.8	24.3±0.7	0.32
Lifetime cocaine use (# times)	12.2±3.3	21.3±4.4	0.14
Monthly alcohol use (# times)	11.7±3.4	15.6±2.5	0.36
Monthly marihuana use (# times)	4.2±2.7	6.9±2.4	0.46
Daily cigarette use (# times)	1.4±1.1	3.0±1.8	0.52

the analysis of the effect of interest difficult. In contrast, sensory stimulation and motor tasks typically have much faster timescales, lending themselves to shorter blocks of task vs. non-task, and yielding readily detectable activations. However, studies that are designed to probe drug effects in reward-related regions are more germane to drug abuse problems than studying the effect of, for example, cocaine on visual stimulation, given that the primary actions of cocaine are through the mesolimbic dopamine system. Investigators have instead used visual stimulation paradigms to provide information about the non-specific effects that drugs may have on brain activity, such as global BOLD signal changes associated with altered cardiovascular tone (caffeine: Mulderink et al., 2002; Liu et al., 2004; nicotine: Jacobsen et al., 2002; alcohol: Levin et al., 1998; cocaine: Gollub et al., 1998). If a drug does cause non-specific alterations in cerebrovascular tone, activation associated with drug actions of interest can be obscured or rendered difficult to interpret (see Salmeron and Stein, 2002 for a detailed discussion). Gollub et al. (1998), showed that although there was a small but significant decrease in cortical cerebral blood flow, regional BOLD activation was not affected. Due to study constraints, they were only able to measure BOLD activation associated with visual stimulation prior to drug administration and approximately 25 min post-infusion. This study and the companion study by Breiter et al. (1997) provided valuable insight into the mechanisms of action of cocaine on brain activity. We further investigate the effects of cocaine on BOLD visual activation, with measurements made before and during the peak drug effects, especially during the peak cardiovascular effects that have the potential to cause non-specific changes in global BOLD signal that can influence measurements of focal activation.

Preliminary results of BOLD response to visual stimulation in subjects receiving either cocaine or placebo suggested a trend toward increased BOLD response in subjects who received cocaine as compared with those who received placebo (Levin et al., 1999). Scanner artifacts rendered data from some of the subjects unusable in the original study, and recently developed filtering techniques have enabled the inclusion of their data (see Data Pre-processing, below). The increased number of usable subjects prompted a reanalysis of the data, using a more quantitative approach, which we present here. Fully understanding possible non-specific effects is crucial to the interpretability of BOLD fMRI studies of cocaine effects. Although preliminary evidence suggests such an absence, this is the first study of cocaine effects on visual stimulation in humans with measurements made continuously before, during, and after cocaine administration.

2. Methods

2.1. Subjects

Male subjects were recruited through newspaper advertisements. Respondents underwent a telephone screening, and those indicating a history of occasional cocaine use and no major medical problems were invited to undergo a complete medical examination. This screening included hematological, liver function, and urinalysis laboratory tests, an electrocardiogram, and assessments of current and past drug use. All subjects were interviewed by a board-certified psychiatrist or neurologist to rule out the presence of a significant neurological, psychiatric, or medical disorder, which would have been grounds for exclusion from the study. No respondent with a diagnosis of abuse of or dependence on any drugs except nicotine was accepted into the study. Twenty-two respondents were accepted for study participation, and all were judged to be in good health. Subjects provided written informed consent, which along with the study protocol was approved by the McLean Hospital Institutional Review Board. Subjects' age was 25.6±3.5 years (mean±SD; range 21–34), and body mass index averaged 23.8±2.5 kg/m^2 (range 19.9–30.7; all were either normal or overweight). Self-reported lifetime cocaine use was almost exclusively via the intranasal route, and was categorized into ranges, with four subjects reporting 1–4 exposures, seven reporting 5–10 exposures, nine reporting 11–39, and two reporting 40 or more. Subjects were asked to report drug use in these ranges to enhance accuracy in reported values (Kaufman et al., 1998). Potential ethical concerns regarding administration of cocaine to light users have been addressed by a study that has shown that exposure to a single dose of cocaine in a laboratory setting does not change subsequent cocaine use (Kaufman et al., 2000; see Discussion).

The randomization yielded 13 subjects who received cocaine, and 9 who received placebo. Table 1 presents demographics for these two groups.

The two groups did not differ significantly with respect to age, body mass index, or use of cocaine, alcohol, marihuana, or cigarettes ($p<0.05$, *T*-test). For cigarettes, classifying the subjects as either smokers (daily cigarette use >0), or nonsmokers (use=0) yielded 5 of the 13 cocaine subjects and 2 of the 9 placebo subjects; this was not significant either ($p=0.4212$, chi-square test).

2.2. Drug administration and visual stimulus

Urine toxicology and breath alcohol testing was performed prior to each experimental session and all subjects tested negative. Each subject had an 18-gauge angiocath inserted in an antecubital vein with a normal saline drip to facilitate drug infusion. Vital signs, including heart rate and blood pressure, were continuously monitored with an MRI-compatible four-lead electrocardiogram, blood pressure cuff, and pulse oximeter (In Vivo Research, Orlando). Heart rate was recorded at four time points: before the scan (serving as a baseline), and at approximately 5, 10, and 20 min following infusion.

In a randomized, double-blinded manner, subjects received either cocaine (0.4 mg/kg cocaine HCl) or saline vehicle placebo administered by slow intravenous infusion over 60 s followed by a 1 min saline flush, starting 8 min into the scan. The infusate was warmed and administration occurred out of the subjects' view, so that subjects did not know when the infusion started. Fig. 1 provides a schematic representation of the protocol.

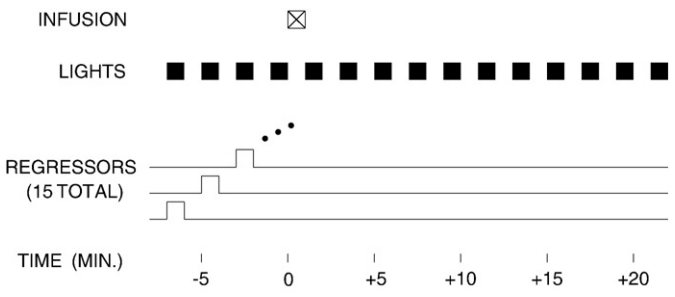

Fig. 1. Schematic representation of the experimental design. The infusion (top; cocaine or placebo, depending on the subject) started at time zero (8 min into the study) and lasted 1 min. Flashing lights (middle row) alternated between off and on every minute, starting with off. Each on period was modeled by a regressor that was positive for that period and zero otherwise (bottom row). Time, relative to infusion start, ranged from −8 min at the beginning of the experiment to +22 min at the end.

Subjects were asked to rate their feelings of high on a scale of 0 to 10 before scanning (baseline), at the end of the scan (approximately 22 min after infusion), and retrospectively at the midpoint of the scan (approximately 5 min after infusion). Subjects were informed before the scan that this retrospective rating would occur.

Subjects were exposed to a flashing light stimulus at an 8 Hz rate (5% duty cycle, 3.5 candela peak brightness) delivered by lightproof red diffuse LED goggles (Grass Instruments, Warwick, RI). The scans started with the stimulus off, and then alternated between off and on every minute thereafter. (See Fig. 1).

2.3. Image acquisition

Imaging was conducted on a 1.5-T General Electric Signa Scanner (Milwaukee), retrofitted with an Instascan whole-body echo planar imaging coil (Advance NMR, Wilmington, MA); signals were acquired using a five-inch receive-only surface coil (General Electric) placed on the occipital cortex. A single-shot gradient echo imaging sequence was used to acquire functional data (TE=40 ms, TR=3 s, flip angle=75°). Echo planar images were collected from three slices parallel to the calcarine fissure using an interleaved acquisition (slice order 0, 2, 1). Slices were acquired with 7 mm thickness and 1 mm skip, matrix size 128×64, FOV=40 cm×20 cm (in-plane resolution=3.125 mm×3.125 mm). Images were later truncated to a 64×64 matrix, preserving the center 20 cm×20 cm of the field of view. The number of repetitions was 600, for a total imaging time of 30 min (not counting the first four repetitions, discarded to ensure spin equilibrium). Structural scans were acquired using the same scanner and coil set, using a spin-echo T1 contrast matched anatomic sequence (TE=12 ms, TR=0.5 s, flip angle=90°). Slices were identical to those of the functional scan, with the exception of the matrix size (256×256) and FOV (40 cm×40 cm; in-plane resolution=1.5625 mm×1.5625 mm).

2.4. Data pre-processing

Three of the functional data sets had excessive radiofrequency impulse noise ("spikes"), clearly visible on a plot of intensity vs. time averaged over all voxels. We therefore applied a despiking filter to all functional data sets to remove this artifact (see Appendix A). All subsequent processing and pre-processing were performed using FSL Release 4.0 (FMRIB Analysis Group, Oxford University, UK, http://www.fmrib.ox.ac.uk/fsl/), specifically FEAT version number 5.92. As only three image slices were collected, full 6-degrees-of-freedom motion correction for the functional scans was not practical. We therefore corrected for in-plane motion only, using mcflirt (Jenkinson et al., 2002), with normalized correlation as the cost function, four search stages, and a sinc-based final rendering. The reference was the center image. For each motion parameter (x- and y-axis displacements, and rotation angle theta) we calculated the root-mean-square fluctuation over the entire 600-TR scan. We then combined the displacement values by squaring the x- and y-axis values, adding, and taking the square root. After motion correction, slice timing correction was performed; because only in-plane motion was corrected, the order of the corrections is not important. Next followed spatial filtering with a FWHM of 5 mm, and high-pass temporal filtering with a cutoff of 120 s. This cutoff value was chosen to match the period of the stimulus, and was found to yield a near-optimal signal-to-noise ratio.

2.5. Statistical modeling

A regularized autocorrelation function was independently estimated for each on period and voxel (Woolrich et al., 2001). The fifteen regressors were the 60-sec on periods (see Fig. 1), convolved with a gamma function having a width of 3 s and a delay of 6 s. The off periods were not modeled. A high-pass temporal filter with a cutoff of 120 s was applied to the regressors, matching the filtering applied to the data. The data were also temporally prewhitened. Motion parameters were not included as confound regressors, due to the long period of the stimulus (Johnstone et al., 2006). For each subject and each regressor, the general linear model approach yields the percent change in the BOLD signal correlated with the corresponding on period of the stimulus.

To increase statistical power, and because registration to standard space (MNI or Talairach) is problematic with only three slices available, we used a region-of-interest (ROI)-based analysis. As a first step, rectangular regions were drawn on each slice that encompassed V1 and V2 (Brodman areas 17 and 18). Within these regions we employed a functional ROI approach (Levin et al., 1998; Slotnick et al., 2003; Kraft et al., 2005; Saxe et al., 2006), using a contrast generated from the first two regressors (corresponding to 6–7 and 4–5 min before infusion, respectively; see Fig. 1). Voxels within the rectangular regions that were significantly activated ($p<q=0.001$, uncorrected) formed the mask, or ROI, for all subsequent regressors for that subject. Contrasts were formed by subtracting the mean of the first two regressors from subsequent regressors. Thus the first of these contrasts has regressor weights of [−0.5, −0.5, 1, 0, 0, …]. Contrasts were not formed by subtracting this mean from either of the first two regressors (weighting of [0.5, −0.5, 0, 0, …], for example) (Mitsis et al., 2008). Averages over the mask ROI corresponding to each of the thirteen subsequent contrasts form the main dependent variable. After checking for sphericity, a 2×(13×22 subjects) ANOVA was performed, and post-hoc tests followed as indicated. This analysis was also performed using regressors based on the 14 60-sec off periods following stimuli, because male heavy cocaine users may have decreased response in the off condition compared with normal controls (Lee et al., 2003).

Table 2
Mean ± standard error of subject behavioral responses and heart rate

Variable	Time	Subjects receiving		Two-tailed significance
		Placebo	Cocaine	
High	Baseline	0.2±0.2	0.1±0.1	0.61
High	+5 min	1.6±0.8	8.3±0.5	5.5×10^{-7}
High	+20 min	1.5±0.8	2.4±0.9	0.48
HR (BPM)	Baseline	62.4±2.8	64.1±2.4	0.66
HR (BPM)	+5 min	1.3±3.0	45.2±6.3	2.5×10^{-5}
HR (BPM)	+10 min	−0.9±1.9	56.6±7.6	5.3×10^{-6}
HR (BPM)	+20 min	−1.3±1.4	32.6±5.6	7.6×10^{-5}

Heart rate values post-infusion are percent change from baseline.

3. Results

3.1. Behavioral and physiological measurements

Behavioral and cardiovascular results appear in Table 2. Subjects in the cocaine group had significantly higher subjective responses to the drug than those receiving placebo ($p<10^{-6}$ at 5 min post infusion; T-test), as well as much larger percent increases in heart rate ($p<10^{-4}$ for all three time points following infusion; T-test). Maximal heart rate increases occurred for the cocaine group at 10 min post infusion.

3.2. BOLD fMRI

As expected for a study involving stimulants, motion was noticeable, although not excessive. Over all subjects, we found root-mean-square motion values of 0.382 mm and 0.176° absolute average, and 0.944 mm and 0.424° worst case. Subjects in the cocaine group showed a trend towards larger rotation values, but this did not achieve significance ($p=0.14$, T-test).

The initial rectangular regions encompassed 756±13 voxels (51.7±0.9 cm^3, mean±S.D.); the threshold of $p<q=0.001$ for the

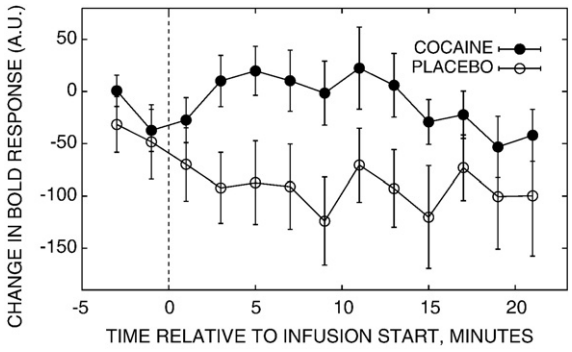

Fig. 2. Activation from a general linear model analysis of the 15 on periods, normalized to the average of the responses to the first two periods. Infusion occurred between the two thin vertical dashed lines, with a duration of 60 s. The onset defines time zero. Error bars display mean ± standard error. Values for subjects in the cocaine group appear as filled circles, while those for the placebo group are empty. An ANOVA yielded a significant group effect.

functional ROIs yielded ROI volumes of 302 ± 116 voxels (20.6 ± 7.9 cm^3, mean ± S.D.). These sizes did not differ significantly between the two groups (p = 0.06 and 0.5, respectively, T-test). The activations obtained for the contrast comprised of the first two regressors did not differ significantly between the two groups either (p = 0.4, T-test). The threshold q and ROI volumes employed thus yield an expected 0.3 false-positive voxels in each ROI. The time course of cocaine effects determined from the averaged voxel values for each subject and each segment are shown in Fig. 2. We also examined the effect of the size of the functional ROI on these results, using a variety of percent change thresholds. Results were qualitatively similar for all eight different thresholds examined, ranging from q = 0.0001 to 0.05.

A 2 × (13 × 22 subjects) two-factor repeated measures ANOVA yielded a significant drug effect [$F(1,20) = 5.252$, $p = 0.033$], but no significant time [$F(12,240) = 1.203$, $p = 0.282$] or interaction effects [$F(12,240) = 1.018$, $p = 0.433$]. Repeating this analysis for the off periods yielded quite similar results: $F(1,20) = 6.121$, $p = 0.022$; $F(11,220) = 0.813$, $p = 0.627$; and $F(11,220) = 0.996$, $p = 0.451$ for the drug, time, and interaction results, respectively.

4. Discussion

Our results revealed a statistically significant difference in the mean visual cortical activation measured during cocaine and saline challenges. Although we did not detect a significant drug × time interaction, some insight into the apparent differences in the mean of the BOLD signal changes over all time points (the significant drug effect) between the saline and cocaine challenges can be gained by inspection of Fig. 2. Both challenges begin with similar baseline activations as expected, but saline and cocaine appear to have different effects on the visual activation. Given only two baseline time points and the level of noise in the data, it is not surprising that an interaction was not detectable. Furthermore, the signal changes associated with each visual stimulation block during the cocaine challenge show no change from the baseline. A strict interpretation of this curve suggests that cocaine does not affect the visual cortical response. In contrast, the saline curve exhibits a systematic reduction to an average of 70% of the baseline values. This suggests that saline does have an effect on the magnitude of the BOLD signal change associated with visual stimulation. With only nine subjects in the placebo group and a between-subjects design, our inability to find significant time or interaction effects may well be due to a lack of power.

The inclusion of a saline placebo condition in this study provides additional information for the interpretation of the impact of cocaine on BOLD signal changes. Although the comparison between post-infusion time points with pre-infusion time points is a valid and necessary method for discerning drug effects, the placebo control affords the opportunity to attempt to disentangle the differences due to drug effects versus a contribution, for example, to the administration procedure itself. In our study, baseline BOLD signal changes during placebo did not remain constant throughout the study; the activation decreased within the first few minutes of the start of the study and did not return to the baseline values. We consider two possible explanations for this effect: habituation to the visual stimulus that occurs during placebo administration that is eradicated by cocaine administration, or an effect of cocaine expectancy.

Many BOLD fMRI studies have addressed the possibility of habituation of the visual cortex to long visual stimuli. These studies have shown that this habituation depends on the nature of the stimulus used (Krüger et al., 1999; Hathout et al., 1994; Frahm et al., 1996; Bandettini et al., 1997; Howseman et al., 1998; Chen et al., 1998; Heekeren et al., 1997). Krüger et al. (1998) conducted a comprehensive study of various visual system stimulation protocols, including flashing diffuse light that periodically alternated between two luminance levels, although the low level was not off. This study, which examined stimulation patterns closest to our study, found a rapid decrease over the first minute, with no change thereafter. This suggests that it may be less likely that the placebo response in our results is due to habituation to the stimulus. Nevertheless, none of these studies matched ours, and as we did not measure activation in subjects who did not receive any infusions, it is possible that some form of habituation occurred.

The alternative hypothesis is that the decrease in the placebo response group following saline administration is attributable to cocaine expectancy. Breiter et al. (1997) observed activations during saline that represented both common effects of expectation between cocaine and saline (e.g., appeared in both cocaine activation maps and saline activation maps), as well as possible differential effects of expectancy that resulted in activations in the saline maps that were not observed in the cocaine maps. Notably, they observed signal changes in occipital regions during saline that did not occur during cocaine. Although our paradigm is very different than that used in the Breiter study, cocaine expectancy may explain our results. Anticipating the infusion represents an altered mental state that might induce changes in the response to the visual stimulus. All subjects were experienced cocaine users, and so knew what changes in mood and cardiovascular state to expect. Based on subjective ratings and heart rate data, the subjects who received cocaine almost certainly knew this fact, and likely knew when the infusion occurred. Although great care was taken to hide the ancillary stimuli associated with the infusion from the subject (warmed infusate given slowly, out of the subject's view) it is likely that subjects in the placebo group suspected that they received placebo during the course of the BOLD scan. All subjects reported experiencing cocaine previously, and therefore likely could differentiate between active and placebo infusates. Accordingly, subjects receiving cocaine had expectations that were met soon after the infusion, while the placebo group gradually realized that their expectations of cocaine infusion would not come to pass. Indeed, the subjective ratings of high bear this out. Therefore it is possible that cocaine itself did not alter the BOLD response so much as the expectancy attendant with the infusion itself either being met or not. Evidence exists for the abolition of placebo effects when subjects were informed of the nature of the administration (cocaine or placebo) immediately before the scan (Kufahl et al., 2005), although this experiment did not involve visual system response to visual stimulation. Ultimately, however, our experiment does not allow us to draw a definitive conclusion between the alternative hypotheses. Further work is required to more completely understand the interplay of these phenomena.

While neuovascular effects may not play a major role in our study, other brain regions have shown a direct blood flow change to acute

cocaine administration as measured by emission tomographic techniques (Johnson et al., 1998; Levin, 2001). Dopamine has been shown to increase blood flow through D1/D5 receptors on the microvasculature, as well as decreasing blood flow through D2/D3 receptors (Choi et al., 2006). Thus regions endowed with dopamine receptors may well respond to acute cocaine administration differently than does occipital cortex.

Another limitation arises from our not using a structured diagnostic interview to rule out neurological or psychiatric disorders, such as the SCID. However, both interviewers had extensive experience with conducting psychiatric and neurological examinations.

A study of low frequency fluctuations in visual cortex during rest found decreased spatial coherence during acute cocaine administration compared with placebo or no administration (Li et al., 2000). This paper examines spatial correlation during a resting state scan, while our work considers temporal correlation with a stimulus during an activation scan, making it difficult to link the two. However, the example data shown in Li et al. (2000) suggest that cocaine might increase oscillations at 0.0083 Hz (1/120 s) significantly, as established by multitaper frequency estimation.

Administration of cocaine to subjects with limited prior exposure to the drug might raise concerns regarding increased risk of future use of the drug. However, exposure to a single dose of cocaine in a laboratory setting does not change subsequent cocaine use for light (Kaufman et al., 2000) or heavy users (Elman et al., 2001). The context during which a drug is experienced plays an important role in subsequent drug-seeking behavior. As an example, fully 20% of Vietnam veterans reported narcotic addiction during military service, but only 12% of those reported any narcotics addiction during the first three years following return to the USA (Robins, 1993). Slow infusion of a warmed cocaine solution by medical personnel is a qualitatively different experience than the drug self-administration experience normally encountered, and therefore cross-reinforcement between these two environments is unlikely. This suggests that participation in our study would not alter subjects' subsequent cocaine use patterns (Kaufman et al., 2000).

Our results demonstrate that differential BOLD fMRI signal changes can be measured in the visual cortex due to visual stimulation in response to cocaine vs. placebo administration. These results are consistent with the findings of previous studies (Breiter et al., 1997; Gollub et al., 1998; Luo et al., 2003). However, we show for the first time BOLD fMRI signal changes during visual stimulation that are measured continuously before, during, and after drug administration, particularly during times of peak physiological effects. Distinguishing between alternative hypotheses — habituation and thus direct cocaine effects vs. expectancy and no direct cocaine effects — remains elusive but suggests avenues for further investigation. In sum, our results demonstrate that BOLD signal changes can be measured reliably in studies of the acute effects of cocaine in brain regions that are not rich in dopamine. However, further work is necessary to interpret the decrease in signal change during placebo administration.

Acknowledgements

The authors thank Anne Smith, RTR-MR, Eileen Connolly, RTR-MR, Megan Wardrop, and Erin Habecker for their technical assistance; and Drs. Scott Lukas, Perry Renshaw, and Rinah Yamamoto for their helpful comments and discussions.

Appendix A. Despiking filter

To ameliorate the impact of the scanner spikes, we applied a nonlinear filter to all the functional scans. Let $I(x,y,z,t)$ denote the value of the functional scan for a voxel at position (x,y,z) and time (image) t. We estimated a local mean m and standard deviation s for this voxel from the five images before and the five images after: $I(x,y,z,t-5)$, … $I(x,y,z,t-1)$, $I(x,y,z,t+1)$, … $I(x,y,z,t+5)$, excluding $I(x,y,z,t)$ itself. If $I(x,y,z,t)$ was smaller or larger than the local mean m by more than six times the local standard deviation (6 s), then $I(x,y,z,t)$ was replaced by the median value over the entire 11-value window. For t near zero or 600, we decreased the size of the window so that the first (or last) value used coincided with the first (or last) image available. For Gaussian distributed data, using this large margin (six standard deviations), the expected number of spurious replacements over all voxels, images, and subjects is less than 0.4, so this filter should not affect valid data.

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