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# fMRI of Cocaine Self-Administration in Macaques Reveals Functional Inhibition of Basal Ganglia

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Disparities in cocaine-induced neurochemical and metabolic responses between human beings and rodents motivate the use of non-human primates (NHP) to model consequences of repeated cocaine exposure in human subjects. To characterize the functional response to cocaine infusion in NHP brain, we employed contrast-enhanced fMRI during both non-contingent injection of drug and self-administration of cocaine in the magnet. Cocaine robustly decreased cerebral blood volume (CBV) throughout basal ganglia and motor/pre-motor cortex and produced subtle functional inhibition of prefrontal cortex. No brain regions exhibited significant elevation of CBV in response to cocaine challenge. Theses effects in NHP brain are opposite in sign to the cocaine-induced fMRI response in rats, but consistent with previous measurements in NHP based on glucose metabolism. Because the striatal ratio of D2 to D1 receptors is larger in human beings and NHP than rats, we hypothesize that the inhibitory effects of D2 receptor binding dominate the functional response in primates, whereas excitatory D1 receptor stimulation predominates in the rat. If the NHP accurately models the human response to cocaine, downregulation of D2 receptors in human cocaine-abusing populations can be expected to blunt cocaine-induced functional responses, contributing to the weak and variable fMRI responses reported in human basal ganglia following cocaine infusion.
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## INTRODUCTION

Neuroimaging studies of cocaine dependence and addiction in human populations face a series of obstacles. Ethical imperatives preclude controlled longitudinal studies of drug exposure, and cross-sectional studies are confounded by poly-drug abuse and variable exposure histories (Gatley *et al*, 2005). These issues impede an understanding of how biochemical stimulation of the brain evolves into drug dependence and addiction.

Animal systems, and particularly rodents, have been employed to model how repeated exposure to drug produces behavioral reinforcement and neurochemical adaptations, but disparate results between primates and rodents have been reported in response to acute or chronic cocaine infusion. Neurochemically, chronic exposure to drug is associated with unchanged or even reduced levels of extracellular dopamine following drug infusion in human beings (Volkow *et al*, 1997; Martinez *et al*, 2007) and non-human primates (NHP) (Bradberry and Rubino, 2006; Kirkland Henry *et al*, 2009), whereas repeated exposure to cocaine in rats leads to dopaminergic sensitization in response to acute injection of drug (Kalivas and Stewart, 1991). Positron emission tomography (PET) studies of raclopride displacement suggest that D2/D3 receptor binding is reduced as a consequence of chronic cocaine exposure in both human beings (Volkow *et al*, 1993) and NHP (Nader *et al*, 2006), whereas the rodent literature on D2/D3 receptor regulation in response to repeated cocaine exposure is discordant (Narendran and Martinez, 2008). In terms of the systems' biological response, acute cocaine infusion has been reported to reduce cerebral metabolism in human subjects (London *et al*, 1990) and NHP (Lyons *et al*, 1996), but elevate metabolism in rats (Porrino, 1993).

fMRI facilitates cross-species comparisons (Vanduffel *et al*, 2002) and enables a wide variety of experimental strategies that exploit the temporal domain. However, the reported blood oxygen level-dependent (BOLD) response patterns to cocaine infusion in human cocaine-abusing populations have been inconsistent across studies, leaving an unsettled picture as to the nature of the cocaine-induced

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functional response in human beings. Comparisons of pre- and post-infusion periods, or correlations between MRI signal and subject ratings of euphoria, have found signal increases in basal ganglia (Breiter *et al*, 1997), bilateral signal reduction in accumbens without significant effects on caudate or putamen (Kufahl *et al*, 2005), or lateralized BOLD reductions in accumbens and putamen, but an increase in caudate (Risinger *et al*, 2005; Kufahl *et al*, 2008). In prefrontal cortex, the pattern again is variable across studies, with more regions responding positively than negatively.

Conversely to human studies, fMRI reports of the cocaine-induced response in rats have been broadly concordant. Using techniques that are sensitive to cerebral blood volume (CBV), cerebral blood flow (CBF), high-field BOLD signal, or cellular uptake of manganese through calcium channels (Marota *et al*, 2000; Mandeville *et al*, 2004; Schmidt *et al*, 2006; Lu *et al*, 2007), cocaine infusion increases cerebral activity in basal ganglia and cortical areas in agreement with previous autoradiographic measurements based on metabolism (Porrino, 1993) and CBF (Stein and Fuller, 1993). Positive cocaine-induced functional responses are largely blocked by a D1 receptor antagonist (Marota *et al*, 2000), suggesting a dominant role of D1 receptor stimulation by cocaine infusion in the rat. Because agonist/antagonist experiments have shown that stimulation of D1 and D2 receptor families produce opposite effects on fMRI signal (Marota *et al*, 2000; Chen *et al*, 2005; Choi *et al*, 2006), interspecies variations in the basal ratio of D1 to D2 receptors, or other synaptic targets, could alter functional responses in rats with respect to primates.

Although the NHP provides the closest neuroanatomical and neurochemical model for human drug abuse studies (Weerts *et al*, 2007), imaging the effects of drug stimuli in awake monkeys is technically challenging. Previous NHP neuroimaging studies using PET (Howell *et al*, 2002, 2010) have reported cocaine-induced elevation of cortical CBF, in apparent disagreement with previous reports of the metabolic effects of cocaine in NHP (Lyons *et al*, 1996) and with our preliminary fMRI reports in this model (Mandeville *et al*, 2005; Jarraya *et al*, 2007).

In this study, we report the cocaine-induced functional response in awake NHP using the sensitive "increased relaxation for optimized neuroimaging" (IRON) technique that has proven to be so effective for fMRI in rodents (Mandeville *et al*, 1998; Chen *et al*, 2001) and in NHP studies using sensory stimuli (Vanduffel *et al*, 2001; Leite *et al*, 2002). To maintain doses within a behaviorally relevant range and to evaluate a model of chronic cocaine exposure, we employed a contingent model of cocaine delivery in which we replaced the traditional bar-pressing procedure for drug self-administration with visual saccades to drug-reinforced targets. The self-administration task- and cue-associated functional responses has been presented in preliminary form (Choi *et al*, 2009).

## MATERIALS AND METHODS

### Animal Model

Experiments procedures were approved by the Subcommittee on Research Animal Care at the Massachusetts General Hospital and conform to the Public Health Service standards of humane care and use of laboratory animals. The basic methods for performing fMRI in awake, behaving rhesus monkeys (*Macaca mulatta*) have been described in previous publications (Vanduffel *et al*, 2001; Leite *et al*, 2002). In addition, central venous catheters were implanted in the internal jugular vein of the two monkeys (M1 and M2) used in these studies and connected to an access port attached to the dental cement surrounding the head post; this venous line enabled iron oxide injection and drug delivery. During these studies, monkeys weighed 5–6 kg and were 5 and 8 years of age.

### Behavioral Task

A simple visual choice task was designed to infuse drug according to behavioral selection. For baseline visual fixation, two identical white circular cues with central fixation dots were presented in the horizontal plane at a separation of 7°. During periods of cocaine availability, as indicated by a yellow border surrounding the presentation screen, choices between a white and yellow cue indicated the opportunity for drug delivery after fixation on the drug-reinforced (yellow) cue for 6 s, a period that did not need to be contiguous in time. Upon satisfying the fixation criteria for the yellow cue, 0.015 mg/kg of cocaine in a 0.5 mg/ml solution was infused at a rate of 10 ml/min over a time of about 1.2 s. Presentation of the next cocaine-reinforced cue occurred after a lockout time that was inversely proportional to the fixation percentage on the previous cue, but never less than 15 s; using this method, the total dose of injected drug was proportional to selection for the yellow cue. Including the time required to saccade to the yellow cue, monkeys fixated on cocaine-reinforced cues about 70% of the time that the cues were present. This resulted in an average duration between drug infusions of about 30 s ($(6 + 15)/0.7 = 30$).

Initial training sessions in both monkeys used long periods of cocaine availability and restriction to reinforce selections for cocaine by ensuring that plasma levels of drug were higher during periods of cocaine availability relative to cocaine restriction. Initial fMRI experiments in monkey M1 (26 fMRI runs in nine sessions) employed this basic paradigm by using a single 15-min period of cocaine availability during each fMRI run (Figure 1a). For the purposes of temporally separating the direct effects of cocaine (slow pharmacodynamics) from responses to cues (fast sensorimotor and cognitive processing), a modified experimental design was used in monkey M2 (20 fMRI runs in seven sessions) and in a subsequent set of experiments in monkey M1 (24 fMRI runs in eight sessions). In this design, alternate 5-min periods of availability and restriction were used (Figure 1b). The minimum duration of drug availability (5 min) was selected to allow time for the drug-induced response to nearly reach a maximum value so that peak response values could be compared across infusion paradigms. Although the basic pattern of cocaine-induced functional response were similar between the two scanning periods in monkey M1, the second scanning period produced significantly smaller responses and was not included in assessments of cocaine's direct effects to reduce potential effects from neuroadaptation to drug.

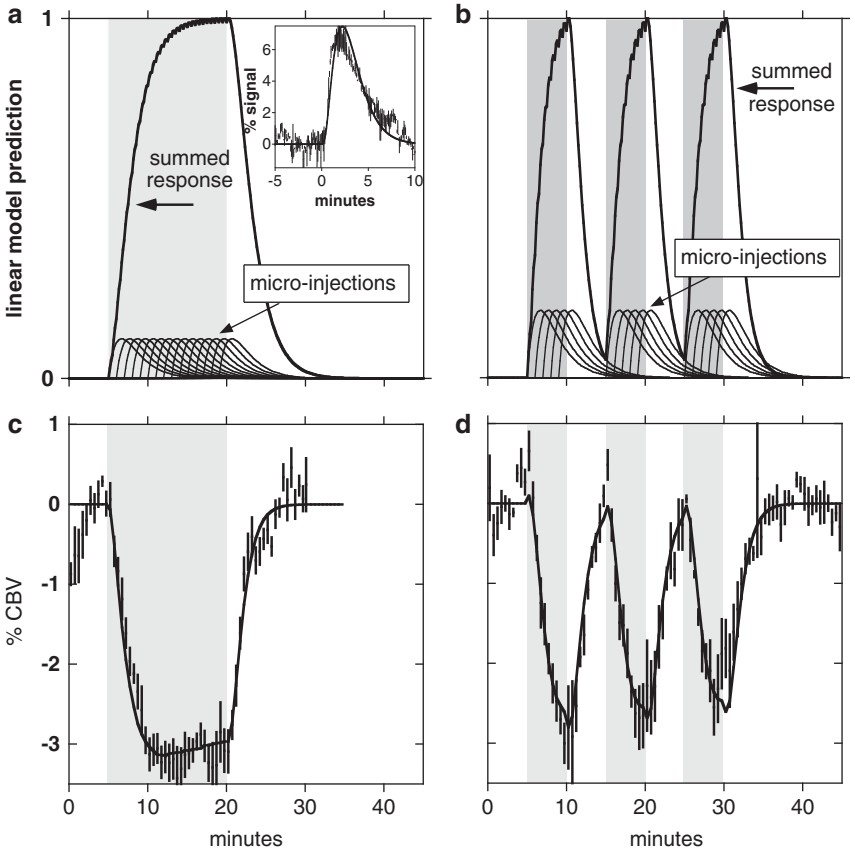


**Figure 1** (a) Based on the measured non-contingent response to bolus infusion of 0.25 mg/kg cocaine (inset), the response to multiple microinjections can be predicted from a linear model during an extended period of cocaine availability (a) or periodic periods of drug availability and restriction (b). For simplicity, only half of the microinjections used to predict the total response are shown. Contingent infusion data (standard errors) from whole putamen are compared with predictions, which are the analysis regressors, based on the actual timing of infusions of 0.015 mg/kg cocaine in monkeys M1 (c) and M2 (d).

## MRI Acquisition and Motion Correction

All experiments employed a 3 T Trio scanner (Siemens Medical System, Erlangen, Germany). Data were acquired at an isotropic resolution of 1.2 mm across whole brain using two-dimensional echo-planar imaging, a repetition rate of 2 s, and an echo time of 19 ms. A four-channel coil array enabled twofold accelerated imaging by the GRAPPA method (Griswold *et al*, 2002) in a high-powered gradient insert ('AC88', Siemens Medical System, Erlangen, Germany); these methods reduced the sensitivity of images to motion in units of millimeters per hertz by a factor of 3.5 relative to non-accelerated imaging in a standard Trio system. Following image localization and before fMRI, monocrystalline iron oxide nanocompound was injected at an iron dose of 10–12 mg/kg to sensitize signal to changes in CBV (Leite *et al*, 2002).

For monkey fMRI using head fixation, standard rigid-body techniques that address real motion are inappropriate solutions to apparent brain motion that results from field perturbations induced by body motion. Apparent brain motion in our model consisted of a shift in the phase-encoding direction (left–right) that increased nonlinearly in the posterior and ventral directions near the monkey body. Consequently, we employed a custom motion-correction algorithm consisting of a shift parameter to account for global changes in the magnetic field, as previously described by others (Pfeuffer *et al*, 2007), plus a deformation term described as a position-dependent shift in the phase-encoding direction.

## Spatial Coordinates and Regions of Interest

Session-averaged functional volumes were registered to a stereotaxic space for rhesus monkey brain (Saleem and Logothetis, 2006) using the population-averaged T1-weighted rhesus monkey brain (McLaren *et al*, 2009) as the registration target. Automated alignment employed a 12-parameter affine registration, followed by adjustment of three-dimensional nonlinear distortion fields using publicly available software by the first author (www.nitrc.org/projects/jip).

Regions of interest employed were defined from the Saleem–Logothetis atlas in conjunction with the anatomical contrast provided by the macaque MRI templates, and the definitions of cortical regions were informed by the probabilistic surface atlases of Lewis and Van Essen (2000) and Ferry *et al* (2000) as visualized by CARET software (Van Essen *et al*, 2001). The anterior–posterior division of putamen was marked at 19 mm anterior to ear bars; this division was selected (1) to reflect rostro-caudal gradients of D1 and D2 receptors (Piggott *et al*, 1999), and (2) because apparent longitudinal changes in the cocaine-induced

response in monkey M1 (Figure 6) were most pronounced in the anterior portion of putamen. The region defined as OFC primarily included Brodmann areas (BA) 11 and 12; this region was restricted to slices 38–44 mm anterior to ear bars on the volumetric data set. DLPFC included areas 45 and 46, but excluded area 9; based on the resolution of this study, it also included small contributions from areas 44 and 8A. Anterior cingulate cortex (ACC) was restricted to slices 34–40 mm anterior of ear bars. The region defined as posterior cingulate cortex (PCC) was centered at 12 mm anterior to ear bars and extended 8 mm in both anterior and posterior directions, so that it included the posterior aspect of ACC. The area defined as 'motor' included contributions from BAs 1–4 on slices 14 and 15 mm anterior to ear bars. Amygdala was restricted to slices 0–3 mm dorsal to ear bars.

### Statistical Analysis

Statistical analyses for each fMRI run employed the standard general linear model (GLM) after spatial smoothing using an isotropic 2 mm Gaussian kernel. Regressors unrelated to the effects of cocaine included a third-order polynomial to account for signal drift, motion-correction parameters as described previously, mean values and standard deviations of eye traces, total fixation percentage, and the cues presented for the contingent task. All regressors except motion parameters were convolved with our previously reported hemodynamic response function for IRON fMRI (Leite *et al*, 2002). Time-course data shown in Figure 1 have been corrected to remove baseline variations and the effects of non-cocaine regressors, as fit within the GLM.

Regressors for the direct effects of cocaine were based on the measured response to non-contingent cocaine injection together with the timing of cocaine infusions defined by the selection of reinforced cues. Figure 1a (inset) shows the response of whole putamen to a non-contingent infusion of 0.25 mg/kg cocaine that was administered over 30 s; note that a positive signal response corresponds to a reduction in CBV. The response reaches a peak value within 2.5 min. To model the measured cocaine response for this extended duration of cocaine infusion and derive an appropriate estimation for a very short bolus, we used a gamma-variate function that peaked at 100 s as an impulse response model, and the curve in the figure (inset) resulted from convolution of this impulse response function with the 30-s infusion duration. In this study of contingent cocaine administration, microinjections of cocaine were delivered in less than 2 s, so we used the gamma-variate function without temporal convolution to describe the impulse response to each infusion based on the actual timing recorded by the behavioral computer. The total response to cocaine was predicted by summating the individual responses, as depicted in Figure 1a and b.

To account for cross-session and cross-subject variance for the production of the statistical maps, we used a second-level GLM (Worsley *et al*, 2002) across repeated measurements using 46 fMRI runs in 16 sessions (seven sessions for monkey M1, and nine sessions for monkey M2), as shown in Figure 2c. Functional maps show the percentage change in CBV for all voxels that passed a statistical threshold of $p<0.05$ after correction for multiple comparisons across 30 000 resolution elements in the brain (Worsley *et al*, 1996).

## RESULTS

At the beginning of fMRI experiments, lifetime cumulative cocaine doses were 27 and 75 mg/kg in monkeys M1 and M2, respectively. By the end of these experiments, cumulative doses were 75 and 102 mg/kg. During fMRI and training sessions, the timing and cumulative doses of cocaine were dependent on behavior, but animals typically received about two infusions per minute. This infusion rate approximately equals the rate of cocaine infusions by self-administration using single bar presses with this unit dose of drug (Flory and Woods, 2003). During the 15 min of cocaine availability allowed within each fMRI run, cumulative cocaine doses per fMRI run were $0.51 \pm 0.10$ mg/kg (mean $\pm$ SD) in monkey M1 and $0.42 \pm 0.07$ mg/kg in monkey M2.

Figure 1 shows the temporal responses of whole putamen to cocaine infusion in the two monkeys using a single 15-min block of cocaine availability in monkey M1 (Figure 1c) and repeated on–off blocks of drug availability in monkey M2 (Figure 1d). Data are presented in 30-s time bins to simplify presentation. Analysis regressors (solid lines) were derived from shifted summations of a parametric response curve that was determined from the measured response induced by a larger non-contingent dose of cocaine (Figure 1a and b). Clearly, the assumption of temporal linearity proved to be accurate for this dose regimen, as the shape of the analysis regressor provided an excellent fit to data in basal ganglia.

The response to repetitive cocaine stimulation using this small unit dose showed little indication of acute tolerance across fMRI runs within each session, as illustrated by Figure 2c. Because subtle effects of acute tolerance within runs can be lost in corrections for signal drift, we additionally analyzed data by employing three separate regressors to fit cocaine-induce responses during each of the three periods of drug availability for monkey M2. In this analysis, responses to the second and third infusion trains were reduced progressively relative to those from the first period by $11 \pm 10$ and $20 \pm 12$%, respectively, but these effects did not reach significance across sessions.

Contingent and non-contingent cocaine infusion produced similar spatial patterns of CBV reduction throughout basal ganglia and motor cortex (Figure 2b and d). Both maps show all positive and negative cocaine-induced CBV changes that reached statistical significance using a blue-green color range for negative changes in CBV and a red-yellow color range for positive changes. Note that the non-contingent map in Figure 2b uses a fourfold larger range of CBV changes than used for the contingent data in this or other figures. Figure 2c shows the response of CBV in putamen during all self-administration sessions; points and error bars were derived from the first-level GLM analysis and represent peak response magnitudes of the regressors that were fit to the data (see Figure 1c and d). Responses were consistent between the two monkeys and across imaging sessions.

Figure 3 shows the cocaine-induced functional response using a mosaic format of 15 transverse slices across basal ganglia from +9 to +20 mm in a standard stereotaxic coordinate system (Saleem and Logothetis, 2006). Data were registered to the multi-subject macaque brain template

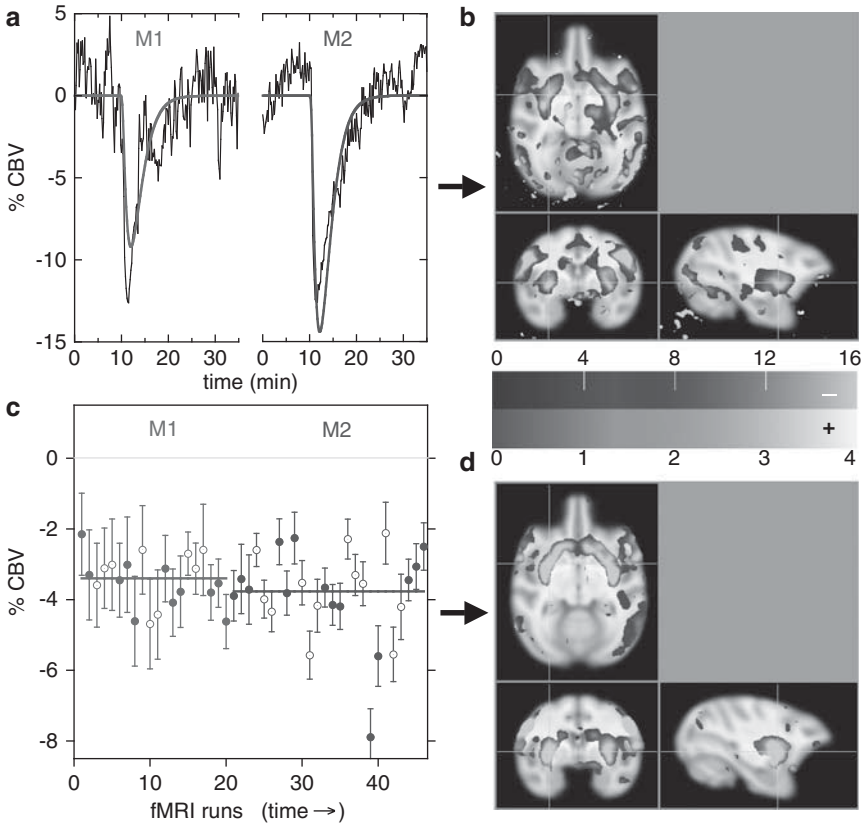


**Figure 2** Non-contingent (a, b) and contingent (c, d) data. (a) The temporal response of whole putamen to bolus injection of 0.5 mg/kg cocaine in monkeys M1 and M2. (b) Percentage changes in CBV generated from the non-contingent infusion data. (c) Repeated measurements from whole putamen using cocaine self-administration. Each point indicates a result from one fMRI run, and groups of adjacent filled or open circles correspond to multiple runs within a single fMRI session. Lines represent the average response magnitude for each monkey after accounting for error bars. (d) The spatial pattern during self-administration produced from a random-effects analysis across all fMRI runs; note the fourfold smaller scale relative to the non-contingent map. Colored voxels in both maps passed a statistical threshold of $p<0.05$ after a correction for multiple comparisons. See online version for color information.

(McLaren *et al*, 2009) that underlies the functional map in the figure, and outlines of putamen, caudate, and accumbens were defined using T1- and T2-based image contrast from the averaged MRI brain template in conjunction with coordinates from the stereotaxic atlas. Assuming a coupling between fMRI and metabolic responses, all regions of basal ganglia exhibit pronounced functional inhibition. In addition, decreases in CBV were clearly evident in motor and premotor cortex.

Responses to cocaine in prefrontal cortex were smaller and more variable across monkeys. Figure 4 depicts the subject-averaged cocaine-induced response in frontal cortex on a partially inflated cortical surface. Brodmann boundaries rely on the probabilistic atlases of Lewis and Van Essen (2000) together with Ferry *et al* (2000). Although bilateral cocaine-induced reductions of CBV were pronounced throughout premotor cortex (BA 6 in the figure) and motor cortex posterior to BA 6, orbital frontal cortex (BA 11, BA 12) and dorsolateral prefrontal cortex (BA 46, BA 45 inside sulcus) showed smaller and more lateralized reductions of CBV.

Figure 5 quantifies regional changes in both monkeys. Using a conservative across-session analysis, cocaine infusion decreased CBV significantly throughout basal ganglia in each monkey, including the anterior and posterior putamen, caudate, and nucleus accumbens ($p<0.01$ after correction for multiple comparisons using Dunnett's method). When averaged across animals, all regions listed in the figure exhibited significant decreases in CBV, except for primary visual cortex, ACC and PCC, and amygdala. No regions responded differently between monkeys ($p>0.05$). No cocaine-induced increases in CBV were observed in any regions that reached significance by conservative random-effects statistical analysis within or across monkeys.

The spatiotemporal response to cocaine was specific to injection of drug. In two sessions in monkey M2, the pump was turned off during alternating periods of cocaine availability to compare responses with and without infusion of drug. In two sessions in monkey M1 and three sessions in monkey M2 that occurred after all cocaine-reinforcement studies, saline was substituted for cocaine. Pooling these data to create a control group for an analysis of regional effects across monkeys owing to infusion of drug, the same regions shown in Figure 5 reached significance, except for DLPFC.

## DISCUSSION

As a monoamine transporter blocker, cocaine acts as an indirect agonist for dopamine, serotonin, and norepinephrine neurotransmitters (Ritz *et al*, 1990). As such, regional

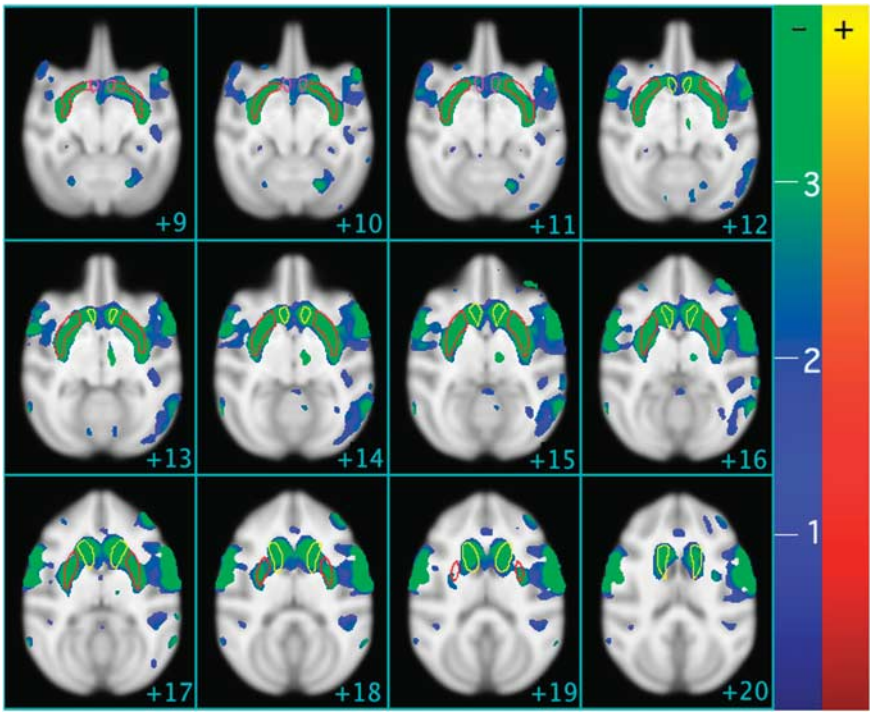


**Figure 3** A spatial map of the peak magnitude of the cocaine-induced response averaged across animals, transposed onto a population-averaged rhesus brain (McLaren *et al*, 2009), and reported as a percentage change in CBV, with negative changes using the blue-green color scale and positive changes using the red-yellow scale. Slices cover basal ganglia from 9 to 20 mm anterior to ear bars in a stereotaxic coordinate space (Saleem and Logothetis, 2006). Highlighted regions include putamen (red lines), caudate (yellow), and nucleus accumbens (purple).

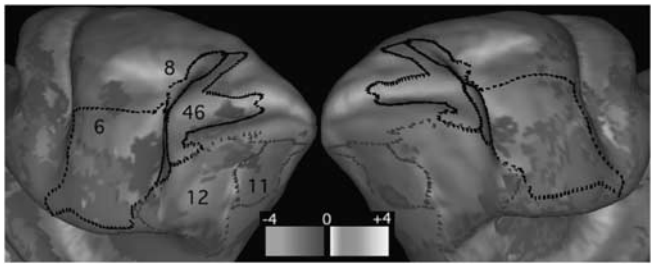


**Figure 4** Functional activation in the frontal cortex measured as the percentage change in CBV (color scale) for regions that responded significantly by a random-effects analysis across fMRI sessions and monkeys. Activity is shown on right and left partially inflated hemispheres of the F99 cortical surface template (Van Essen *et al*, 2001). Numerals indicate Brodmann areas based on macaque probabilistic atlases: black borders from Lewis and Van Essen (2000); green borders from Ferry *et al* (2000). See online version for color information.

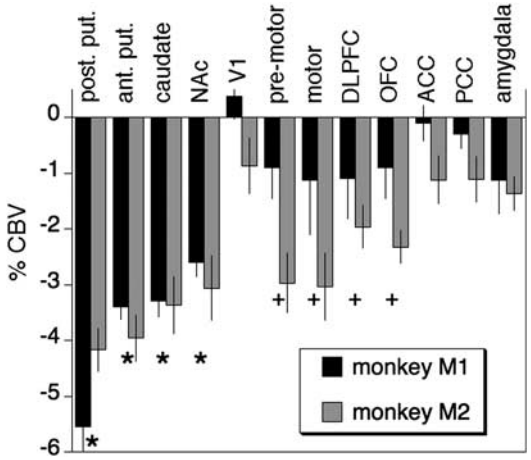


**Figure 5** Functional changes in CBV (mean ± standard error) associated with cocaine infusion. Asterisks indicate significance ($p<0.01$) in each monkey across sessions after correction for multiple comparisons. Plus signs indicate significance averaged across animals.

cocaine-induced changes in fMRI signal represent the summated effects of elevated extracellular levels of multiple neurotransmitters that can be excitatory or inhibitory at neural or vascular receptors to produce responses that are either local or distributed through neural circuitry. Despite this obvious complexity, as well as incomplete understandings of neurovascular coupling mechanisms, empirical data support the notion that cocaine-induced fMRI signal changes can be viewed as a metabolic surrogate. Autoradiographic measurements in the rat show that the regional coupling ratio between blood flow and glucose utilization is preserved during cocaine stimulation (Sharkey *et al*, 1991). Consistent with cocaine-induced effects on glucose metabolism in rats and NHP (Lyons *et al*, 1996), the fMRI response to cocaine in the NHP is opposite in sign to the response observed in the rat.

Interpreting the systems-level functional response to a complex drug like cocaine requires consideration of the spatiotemporal profile of signal changes and the underlying metabolic contributions. We argue that the fMRI response to cocaine in the NHP strongly implicates dopaminergic mechanisms, and that known species-dependent differences

in dopaminergic receptor concentrations probably underlie observed differences in functional responses to cocaine. The NHP provides a model for interpreting cocaine-induced fMRI signal changes in human beings and associating these changes with cocaine-induced neuroplasticity.

## Cocaine-Induced fMRI Response in NHP

Although cocaine binds to multiple neurotransporters, the fMRI spatial response to cocaine in the NHP (Figure 3) most closely mimics the pattern of dopamine transporter density (McCann *et al*, 1998; Tsukada *et al*, 2001), dopamine D2 receptor density (Volkow *et al*, 1993; Nader *et al*, 2006), and cocaine binding (Fowler *et al*, 1989), all of which localize to basal ganglia in human beings and NHP as shown by PET. Conversely, the fMRI response does not match the reported spatial distribution of norepinephrine transporters, which are not found at detectable levels in cat or NHP caudate (Charnay *et al*, 1995; Seneca *et al*, 2006), or the spatial distribution of serotonin transporters, which are most dense in mid-brain, and more uniformly distributed throughout brain than the other monoamine transporters (Huang *et al*, 2002). These considerations suggest that the fMRI response in basal ganglia primarily arises from dense dopaminergic processes, which may be modulated by serotonin and norepinephrine.

In addition to functional inhibition of basal ganglia, cocaine-induced decreases in cortical CBV were most pronounced in motor regions, but also included some effects in prefrontal cortex. Because fMRI assesses brain function through flow-metabolism coupling, the signal reflects the biochemical effects of cocaine both at binding sites and in associated circuitry. Functional responses in both motor and prefrontal cortex are consistent with cortico-basal ganglia pathways, in which outputs from basal ganglia project back to motor and prefrontal cortex through segregated but parallel pathways through globus pallidum, mid-brain, and thalamic nuclei to cortex (Haber and Calzavara, 2009). Although rodent and primate basal ganglia differ anatomically and functionally, rodent data support the notion that much of the cortical response arises from striatal projections; unilateral 6-OHDA dopaminergic lesions along the nigrostriatal pathway in anesthetized rats ablate the fMRI response to dopaminergic stimuli in both ipsilesional striatum and cortex (Chen *et al*, 1999; Nguyen *et al*, 2000). Relative to cocaine-induced response patterns in rats, which exhibit widespread cortical activation using metabolic, cellular, or vascular markers of function (Sharkey *et al*, 1991; Marota *et al*, 2000; Lu *et al*, 2007), the functional response in NHP was more circumscribed within the mesolimbic system. Given the pronounced species differences in cortical anatomy and dopamine-mediated connectivity between cortex and striatum/mid-brain (Goldman-Rakic *et al*, 1999), it is difficult to isolate a single explanation for less expansive cocaine-induced cortical activity in the NHP. However, it has been suggested that the low density of D1 receptors in the middle input layers of NHP cortex may reflect less dopaminergic innervation of cortex via thalamic pathways (Richfield *et al*, 1989).

In the temporal domain, a bolus infusion of cocaine induced an fMRI response that reached a peak value in basal ganglia in less than 3 min. This result is consistent with microdialysis of cocaine-induced extracellular dopamine, which reaches a peak response between 2 and 4 min in NHP basal ganglia (Bradberry, 2000). The response of fMRI signal also is consistent with the rapid removal of cocaine from arterial blood plasma by redistribution before the slower elimination phase; in both human beings (Evans *et al*, 1996) and rats (Booze *et al*, 1997), the redistribution half-life is faster than 1 min, and arterial concentrations of cocaine drop fivefold during the first 5 min. Because residual levels of cocaine in the plasma are eliminated slowly over tens of minutes, repeated boluses during a self-administration task presumably produce progressive effects from accumulation, but small low-frequency responses are difficult to distinguish from other sources of signal drift.

A striking feature of these data are that the cocaine-induced fMRI response in rhesus monkeys is opposite in sign to the result seen in rats using BOLD or IRON fMRI (Marota *et al*, 2000; Mandeville *et al*, 2001) or blood flow (Stein and Fuller, 1993). This result agrees with a previous study based on invasive autoradiography (Lyons *et al*, 1996), which reported cocaine-induced reductions of glucose metabolism in a different NHP species (*Macaca fascicularis*), in contrast to results obtained in rats by the same group (Porrino, 1993) or others (Sharkey *et al*, 1991). The change in response from excitatory in the rat to inhibitory in the NHP, according to fMRI and metabolic indices, occurs despite the rough equivalence in the percentage elevation of extracellular dopamine in each species following injection of 0.5 mg/kg (Bradberry, 2000; Schwarz *et al*, 2004), the dose employed in Figure 2a. The opposite cocaine-induced responses in motor cortex between the two species have behavioral correlates: cocaine infusion increases gross locomotor activity in rodents (Kalivas and Stewart, 1991), but not in NHP (Bradberry, 2007). Because rats are such a mainstay of biomedical research, it is critical to understand the mechanisms underlying the profoundly different response to cocaine in research rat strains relative to primates, particularly in basal ganglia regions associated with behavioral reinforcement for the intake of drugs that elevate dopamine.

D1 antagonism and D2 agonism both decrease CBV by fMRI, whereas D1 agonism and D2 antagonism increase CBV (Marota *et al*, 2000; Chen *et al*, 2005; Choi *et al*, 2006), illustrating the opposite effects of stimulation of these receptor subtypes on fMRI signal in rats using an indirect dopaminergic agonist like cocaine. Data relating selective stimulation of dopaminergic receptor subtypes to flow-metabolic effects in NHP are sparse, but D2 and D3 agonists both decrease fMRI signal in basal ganglia in NHP (Black *et al*, 1997; Sanchez-Pernaute *et al*, 2007), consistent with rats. Therefore, species differences in the relative densities of D1 *vs* D2 receptor families could account for observed species differences in response to cocaine. Radioligand binding assays support this hypothesis; in rat striata, the reported ratio of D1 to D2 receptor densities is nearly 3 (Hyttel and Arnt, 1987; Weed *et al*, 1998), whereas the same ratio in rhesus or cynomolgus striata is slightly larger than unity (Madras *et al*, 1988; Weed *et al*, 1998). Post-mortem studies in human subjects also show similar D1 and D2 striatal receptor densities (Hall *et al*, 1994; Piggott *et al*, 1999). Thus, the sign of cocaine-induced changes in flow

and metabolism in basal ganglia may reflect the dominant effects of D2 stimulation in human beings and NHP and D1 stimulation in rats.

Although species differences in the basal D1/D2 receptor ratio might well explain the opposite cocaine-induced functional responses observed in the NHP relative to the rat, several points warrant further discussion. First, this difference apparently cannot be generalized as a primate–rodent disparity, as autoradiography consistently has found cocaine-induced decreases in glucose utilization in mice (Rogers and Nahorski, 1973; Thanos *et al*, 2008), including one explicit comparison showing opposing results in mice and rats (Zocchi *et al*, 2001); no fMRI studies to date have evaluated the acute response to cocaine in mice. Wild-type mice appear to have similar levels of D1 and D2 receptor densities (Thompson *et al*, 2010), like primates and unlike the rat. Because pharmacological stimulation of D2 receptors has been shown to increase aggressive behavior in mice and cats (Puglisi-Allegra and Cabib, 1988; Sweidan *et al*, 1990; Nikulina and Kapralova, 1992), high D1/D2 ratios in rat research strains might be a consequence of selective breeding to decrease aggression, rather than a general trait of the rat species. To further complicate this issue, juvenile rats exhibit negative CBV changes in response to cocaine and little response to a D1 receptor agonist, whereas adult rats exhibit strong positive changes in CBV owing to infusion of cocaine or D1 agonist (Chen *et al*, 2010), further supporting the predominance of D1 stimulation in the cocaine response in adult rats.

The D1/D2 hypothesis does not simply explain why stimulation by amphetamine, but not cocaine, produces a positive fMRI response in NHP basal ganglia (Jenkins *et al*, 2004). This difference between cocaine and amphetamine emphasizes that a functional response to a pharmacological stimulus depends on the summation of all factors contributing to neural/vascular activity. In particular, amphetamine pre-synaptically stimulates dopamine release, which can be linked to elevated levels of intracellular calcium (Gnegy *et al*, 2004) and thereby to mechanisms that increase blood flow and metabolism (Jakovcevic and Harder, 2007). In addition, cocaine impacts non-dopaminergic neurotransmitter systems like serotonin. Selective receptor antagonism of cocaine-induced effects ultimately will be required to more fully elucidate the neurochemistry underlying fMRI signal changes to psychostimulants like cocaine and amphetamine.

## Comparisons with Neuroimaging of Cocaine in Human Beings and NHP

Inconsistencies in the cocaine response patterns reported by BOLD fMRI in human beings probably reflect biological adaptations to chronic drug use, competing influences of biochemical stimulation and cognitive processing, and technical limitations of BOLD fMRI. If the NHP accurately models the human response to cocaine, then downregulation of D2 receptors in human cocaine abusers likely produces a blunted (less negative) fMRI response in basal ganglia relative to the drug-naïve condition. Cognition and cocaine stimulation can produce opposite influences on fMRI signal, which are not easily disentangled. A recent study showed that an expectation of drug delivery modulates the BOLD response pattern, primarily in frontal cortical regions (Kufahl *et al*, 2008). Finally, all human BOLD studies of cocaine infusion have employed the most common clinical field strength, 1.5 Tesla. At this magnet field, BOLD fMRI is about fivefold less sensitive than the IRON method (Mandeville *et al*, 1998; Vanduffel *et al*, 2001). Future human BOLD studies at high field should offer better insight into the cocaine-induced functional response in human subjects.

Only a very few studies have reported flow responses to cocaine in awake NHP. Two PET studies assessed the functional response to non-contingent cocaine delivery using radiolabeled water to measure CBF at a time point 5 min after infusion of cocaine (Howell *et al*, 2002, 2010). Those studies reported activation of dorsomedial cortical regions in coronal slices at the level of the caudate, regions where we did not detect significant signal changes. Because the PET acquisitions were normalized to global CBF, decreases in blood flow in one area (eg, basal ganglia) might be indistinguishable from increases in other areas. In addition, the most recent paper by that group explicitly ignored regional decreases in CBF (Howell *et al*, 2010).

## Does the Sign of the Cocaine-Induced fMRI Response Matter?

If our hypothesis about the origin of the opposite cocaine-induced fMRI responses in the rat and NHP is correct, then measurements of flow and metabolism reflect a somewhat different balance of the same underlying processes in both species, and the fMRI signatures associated with the modulation of dopaminergic receptors will be different in the two species. For instance, downregulation of D2 receptors in the absence of other neuroadaptations should produce a smaller negative cocaine-induced fMRI response in the NHP, but a larger positive cocaine-induced response in the rat. Conversely, a reduced BOLD response in cocaine-treated rats (Febo *et al*, 2005) cannot be explained by the downregulation of D2 receptors and/or upregulations of D1 receptors, but potentially could indicate higher D2 and/or lower D1 expression following chronic cocaine treatment.

Inconsistencies between the rodent and primate literature pose the question as to whether the relative balance of basal receptors influences neuronal plasticity owing to repeated cocaine exposure. Homeostasis is a concept that often is invoked to rationalize receptor regulation in response to chronic drug exposure (Volkow *et al*, 1990) or in model preparations following acute exposure to a receptor agonist (Dumartin *et al*, 1998). In terms of mitigating the metabolic consequences of repeated cocaine infusion, downregulation of D2 receptors and/or upregulation of D1 receptors would represent homeostatic reactions to repeated dopaminergic stimulation in the NHP. Longitudinal studies in NHP have shown a decrease in D2 receptor binding potential during chronic cocaine exposure (Moore *et al*, 1998a; Nader *et al*, 2006; Beveridge *et al*, 2009), and human studies find reduced D2 binding in cocaine abusers relative to control subjects (Volkow *et al*, 1993). The literature on D1 regulation in response to drug exposure in the NHP is somewhat more variable, with two studies finding increased D1 receptor densities following cocaine self-administration

(Nader *et al*, 2002; Beveridge *et al*, 2009) and one study finding reduced D1 receptor levels (Moore *et al*, 1998b).

Although homeostasis is a useful general notion to argue that neuronal processes evolve to counter repeated stimulation, the actual mediators of plasticity are unknown. Do neurotransmitter systems evolve to attenuate the metabolic consequences of repeated stimulation, so that receptor adaptations to repeated drug exposure are different in rats and NHP? Under this hypothesis, rats subjected to repeated cocaine exposure should exhibit upregulation of D2 receptors and/or downregulation of D1 receptors. Unfortunately, the literature on cocaine-induced changes in dopaminergic receptor levels in rats is much more inconsistent than in NHP and human studies (Narendran and Martinez, 2008). Contributions to the variable results in rats could include many factors, including different infusion protocols and durations of drug abstinence following exposure, but fundamentally different responses to repeated cocaine infusion between species and animal strains cannot be excluded given the available data.

Alternatively, receptor neuroadaptations might be dissociated from metabolic consequences. Some evidence indicates that D2 receptors are targeted for degradation by the GASP-1 sorting protein following agonist-induced endocytosis, whereas D1 receptors are more rapidly recycled back to the cell surface (Bartlett *et al*, 2005); thus, D2 receptors may be more susceptible than D1 receptors to degradation owing to repeated dopaminergic stimulation. Initial studies on D2 regulation in cocaine-exposed GASP-1 knockout mice have produced conflicting results (Thompson *et al*, 2010; Boeuf *et al*, 2009), and one knockout strain exhibited an altered basal D1/D2 receptor ratio (Thompson *et al*, 2010).

Our study was not designed to assess longitudinal effects of chronic cocaine exposure. In each monkey, periods of repeated scanning were relatively short (3 months), and changes in the cumulative cocaine dose were relatively small (25–50 mg/kg). No obvious time-dependent changes in the cocaine-induced fMRI response were observed within these time periods. In one monkey, however, we performed one series of scans using a continuous 15-min period of cocaine availability (Figure 1c), and then we performed a second series of scans 6 months later using alternating 5-min periods of cocaine availability, as in Figure 1d. The 6-month interval between successive sets of experiments included 3 months of cocaine abstinence followed by 3 months of self-administration reinstatement, with a cumulative cocaine dose of 17 mg/kg. Figure 6 shows repeated measurements of the cocaine-induced response in anterior basal ganglia during these two scanning periods. The response during the second scanning period was significantly smaller ($p < 0.005$ across sessions) than during the first scanning period in all basal ganglia regions of interest, even though average doses ($0.51 \pm 0.10$ *vs* $0.45 \pm 0.18$ mg/kg) were not different. Differences between scanning periods were most pronounced in anterior putamen and nucleus accumbens. Although further experiments in more monkeys will be required to confirm a diminished fMRI response owing to chronic cocaine exposure, this effect is consistent with downregulation of D2 receptors and/or upregulation of D1 receptors, and suggests one possible reason as to why a robust negative fMRI response in basal ganglia has not been reported in human subjects.

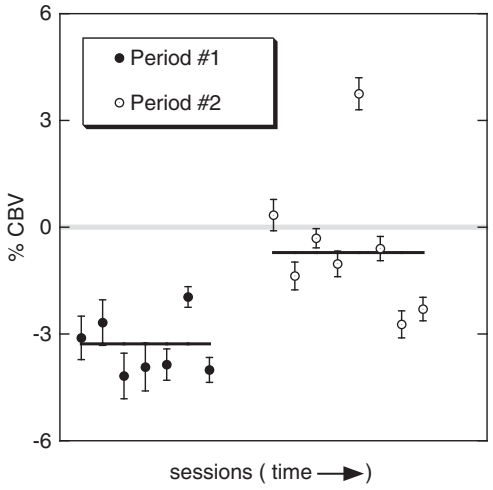


**Figure 6** During two scanning periods separated by 3 months of cocaine abstinence and 3 months of reinstatement in one monkey, the negative response magnitude in one monkey (M1) became statistically smaller, as assessed by repeated measurements across magnet sessions.

Given the opposite influences of D1 and D2 receptor stimulation on fMRI signal, cocaine-induced changes in receptor levels could not only diminish the fMRI response, but also make the cocaine-induced response invisible to fMRI. This possibility emphasizes the necessity to employ selective ligands using the fMRI modality to dissect cocaine pharmacology and neuroplasticity resulting from chronic exposure to cocaine or other drugs of abuse.

## Contingent Drug Administration Paradigms for fMRI in the NHP

A somewhat surprising methodological result from these studies was the degree to which fMRI responses using complicated contingent infusion paradigms were accurately predicted from the shape of the non-contingent response to drug (Figure 1c and d). This method of modeling the temporal response from a series of repeated injections assumes that each injection produces the same cerebral effect, so that responses sum linearly. Acute tolerance, a phenomenon in which repeated doses of cocaine produce progressively smaller effects, would be expected to reduce the accuracy of linear modeling. In human subjects, self-reports of cocaine craving are reduced during repeated cocaine infusions (Ward *et al*, 1997). In NHP, a bolus of 0.5 mg/kg cocaine elevates striatal extracellular dopamine by about 10–20% more than a subsequent bolus more than 1 h later (Bradberry, 2000).

In these experiments, data exhibited a consistent but nonsignificant trend for acute tolerance within runs, with the response during each period of drug availability reduced by about 10% relative to the previous period. When using a single regressor to describe the response to all three periods within each run, subtle effects from acute tolerance apparently were subsumed into regressors for baseline drift, such that it fits accurately the described data. However, the linear model may not work as well when using higher unit

doses together with short inter-infusion intervals. For small unit doses as used in this study, however, the ability to accurately model repeated infusions facilitates experimental designs that simulate binge patterns of drug use or that produce desirable kinetics for the purpose of temporally separating drug stimulation from sensorimotor and cognitive processing.

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