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ORIGINAL INVESTIGATION

Acute cocaine induced deficits in cognitive performance in rhesus macaque monkeys treated with baclofen

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Abstract
Rationale Acute and/or chronic exposure to cocaine can affect cognitive performance, which may influence rate of recovery during treatment.
Objective Effects of the GABA-B receptor agonist baclofen were assessed for potency to reverse the negative influence of acute, pre-session, intravenous (IV) injection of cocaine on cognitive performance in *Macaca mulatta* nonhuman primates.
Methods Animals were trained to perform a modified delayed match to sample (DMS) task incorporating two types of trials with varying degrees of cognitive load that had different decision requirements in order to correctly utilize information retained over the delay interval. The effects of cocaine (0.2, 0.4, and 0.6 mg/kg, IV) alone and in combination with baclofen (0.29 and 0.40 mg/kg, IV) were examined with respect to sustained performance levels. Brain metabolic activity during performance of the task was assessed using PET imaged uptake of [^{18}F]-fluorodeoxyglucose.
Results Acute cocaine injections produced a dose-dependent decline in DMS performance selective for trials of high cognitive load. The GABA-receptor agonist baclofen, co-administered with cocaine, reversed task performance back to nondrug (saline IV) control levels. Simultaneous assessment of PET-imaged brain metabolic activity in prefrontal cortex (PFC) showed alterations by cocaine compared to PFC metabolic activation in nondrug (saline, IV) control DMS sessions, but like performance, PFC activation was returned to control levels by baclofen (0.40 mg/kg, IV) injected with cocaine.
Conclusions The results show that baclofen, administered at a relatively high dose, reversed the cognitive deficits produced by acute cocaine intoxication that may have implications for use in chronic drug exposure.

Keywords DMS cognitive task · Monkeys · Cocaine-impaired cognition · Baclofen reversal of cocaine effects · PET imaging correlates

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Introduction

Recent clinical studies have examined whether the GABA-B receptor agonist baclofen (CGP44532) can reduce drug use in confirmed human drug addicts (Leggio et al. 2010; Addolorato et al. 2011) and if this agent, when administered to human subjects, also influences activity in brain regions involved in motivation and cognition (Miller and Cohen 2001; Boettiger and D'Esposito 2005; Dalley et al. 2011; Franklin et al. 2011). Although some studies have shown no effect of baclofen on cocaine usage in human subjects (Kahn et al. 2009), because of its potential to affect inherent GABAergic systems, baclofen is one agent that may have the potential to reverse the actions of dopamine-disruptive drugs such as cocaine on cognition (Weerts et al. 2007; Tyacke et al. 2010; Halbout et al. 2011). This investigation therefore tested the ability of baclofen to reverse performance decrements produced by acute cocaine in macaque monkeys (nonhuman primates, NHPs) in order to determine effects on brain areas shown previously to be involved in cognitive processing which could potentially be used as "markers" for the degree of altered function after chronic drug exposure.

Prior work has demonstrated that frontal and prefrontal cortical (PFC) areas of the brain in NHPs respond to increasing cognitive load (task difficulty) with local cerebral

metabolic rate (LCMR) measured via imaging of [^{18}F]-fluorodeoxyglucose (FDG) uptake with positron emission tomography (PET) that is associated with performance accuracy on high cognitive load trials in a delayed-match-to-sample (DMS) memory task (Porrino et al. 2005; Deadwyler et al. 2007; Hampson et al. 2009). Similar investigations have shown that cognitive function in this and other tasks is disrupted by administration of cocaine during the DMS testing session (Opris et al. 2009) and that these cocaine-induced alterations in task performance are accompanied by changes in single neuron activity in the PFC correlated with alterations in metabolic activity via [^{18}F]-FDG PET imaging in the same animals (Hampson et al. 2011). The present study shows that baclofen administered at a higher dose than previously employed in NHPs (Weerts et al. 2007) reduced the detrimental effects of acute cocaine administration on DMS trials that required a higher level of cognitive processing of task-specific information (i.e., cognitive load). PET imaging during the same sessions showed activation in PFC by baclofen alone, not previously reported, which reversed cocaine-induced alterations in task activation in the same sessions where baclofen improved performance.

Methods

Animals All procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Wake Forest University, and performed in accordance with established practices as described in the National Institutes of Health and Public Health Service policy on humane care and use of laboratory animals. Six adult male rhesus (*Macaca mulatta*) NHPs (6–15 kg) were housed in stainless steel cages in temperature- and humidity-controlled colony rooms with lighting maintained on a 0600:1800 day/night cycle and visual contact with conspecifics at all times except during experimental sessions (Deadwyler et al. 2007; Hampson et al. 2011). Animals were fed a daily diet of NHP chow supplemented by fresh fruit and chewable multiple vitamin tablets. All six animals were tested using FDG PET imaging procedures (Porrino et al. 2005).

Behavioral apparatus and training NHPs were trained to sit quietly in a custom-designed primate chair (Crist Instruments, Hagerstown, MD) configured for free arm movement across a horizontal platform surface in front of the chair positioned 1.5 m from a 1.0×1.0 m LCD-front-projection screen. The chairs were housed in a sound attenuated cubicle in a larger animal testing room with low light CCD cameras to allow constant observation (Hampson et al. 2011). The primate chair contained a juice reward delivery system which motivated the animals to perform the task with an electrically operated juice valve to gravity feed juice from a reservoir to a sipper tube mounted in front of the animal's lips. Limb position was tracked via a fluorescent adhesive reflector affixed to the back of the hand by a small LCD camera positioned 30 cm above the hand. Horizontal position of the illuminated target was computed using a Plexon Video Tracker (Plexon, Inc., Dallas, TX) that displayed hand position as a bright yellow cursor on the projection screen. Animals were trained to move the cursor on the projection screen by positioning the hand within a two-dimensional coordinate system mapped onto the surface of the platform of the chair which positioned the cursor into 25-cm clip-art images on the screen. Different sets of images were downloaded daily from a website and stored for usage in six to eight testing sessions per day across all animals in the task.

Multi-item visual delayed-match-to-sample task A previously utilized version of the delayed-match-to-sample short-term memory task custom designed for trials with variable task difficulty or "cognitive load" for NHPs (Porrino et al. 2005; Deadwyler et al. 2007; Hampson et al. 2009; Hampson et al. 2010; Lindner et al. 2008) was implemented in order to test the effects of baclofen on cocaine-induced deficits in performance of the same task. Figure 1a shows the features of the DMS task in terms of the sequence of trial events, start signal, sample, delay, and match phases during a single trial. Each trial was varied as to (1) the number of individual clip-art distracter images (one to six) randomly presented with the sample image in the match phase and (2) the duration of the intervening randomly varied delay interval (duration, 1–60 s) in which the screen was blanked between the occurrence of the sample response and onset of presentation of images in the match phase. The response in the match phase (match response) to information presented in the sample phase was committed on each trial, after which the screen was blanked for the intertrial interval of 10 s. All combinations of delay and number of images were presented randomly in normal daily testing sessions consisting of 100–150 trials and all clip art images (sample or distracter) were unique for all trials within the session. Each session consisted of two types of trials, 'object' or 'spatial', indicated by the trial start signal image (circle or square, Fig. 1a) and varied randomly within the session. If the start signal was a circle, it indicated that the subsequent sample image (i.e., the object itself) was to be recalled and selected in the match phase of that trial irrespective of where it appeared on the screen (Fig. 1a, match phase, red arrow, object trial). Alternatively, if the start signal was a square, it meant that the spatial position of where the sample image was presented on the screen during the sample phase was to be recalled and selected in the subsequent match phase (Fig. 1a, match phase blue arrow, spatial trial) irrespective of what other image occupied that location on the screen in the match phase. In each case correct choices were rewarded by delivery of 0.5 ml of fruit juice following the match response

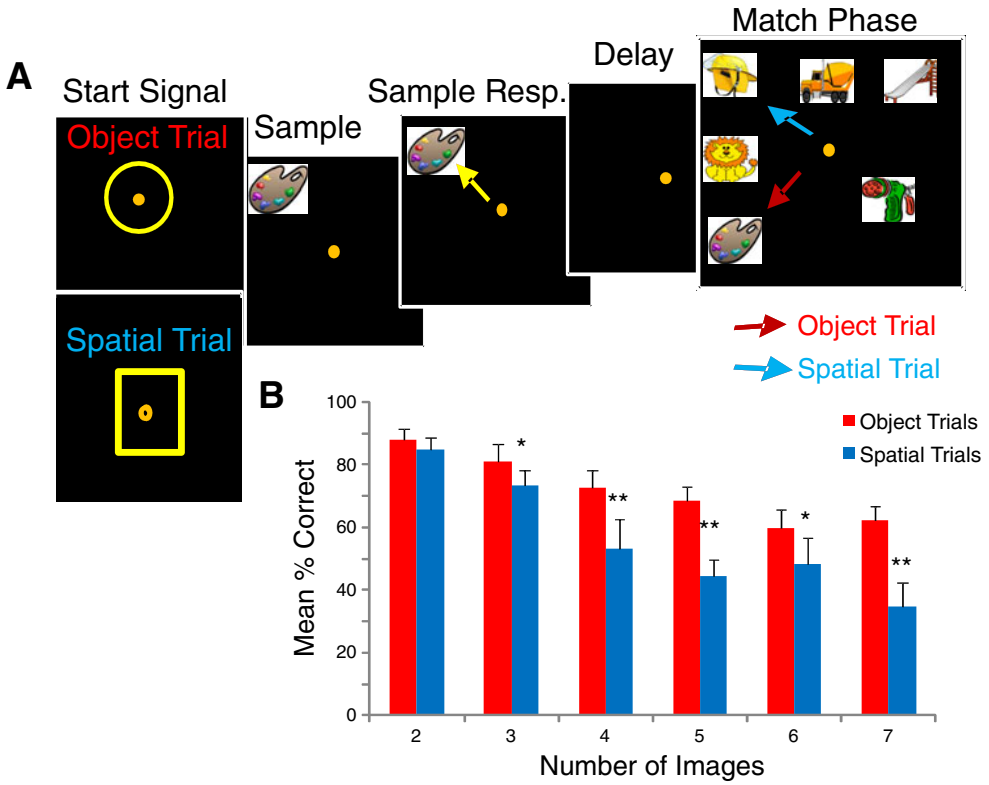

Fig. 1 DMS task and cognitive performance. **a** Behavioral paradigm of DMS task. Object trial and spatial trial reward contingencies signaled by *circle* and *square*, respectively. Object trial: correct match phase response was to select the same *image* presented in sample phase irrespective of where it occurred on the screen which was also occupied by other 'distracter' images. Spatial trial: correct match response required selection of the image that occupied the same *spatial position* on the screen where the sample image was presented. Trials within a single session ($n=100$) consisted of delay intervals of 1–60 s combined randomly with two to seven images in the match phase. **b** DMS task performance as a function of increased cognitive demand (number of images in match phase of DMS task) for object and spatial type trials shown in (**a**). Performance on spatial trials was significantly worse than object trials for all trials with >3 images to choose from in the match phase. *Asterisks*: object vs. spatial trials $*F_{(1,486)}=7.96$, $p<0.01$, $**F_{(1,486)}=11.04$, $p<0.001$

(Fig. 1a) via the sipper tube in front of the animal's mouth. For drug sessions, injections were administered 30 and 10 min prior to onset of the session depending on the drug. Each animal had a history of at least 1.5 years experience performing this version of the DMS task at an overall mean level of 75 % or higher on trials with two images at all delay intervals under both trial type conditions. Overall proficiency (average % correct) across animals is shown in Fig. 1b in terms of the number of images in the match phase for each trial type.

Drug administration Each animal was previously prepared with a vascular access port implanted into a major vein (internal or external jugular, femoral, or brachial) for intravenous injections of each drug prior to the session (Hampson et al. 2011). Control sessions consisted of saline injections at the same pre-session time intervals as drug administration sessions. Cocaine was injected 10 min prior to the onset of the testing session and was examined at three different dose levels (0.20, 0.40, and 0.60 mg/kg, IV) in order to select the final dose of 0.6 mg/kg that consistently reduced performance across all animals as shown previously (Hampson et al. 2011) to assess in the effects of baclofen. The GABA-B receptor agonist baclofen (CGP44532) was injected at two different dose levels (0.29 and 0.40 mg/kg, IV) one dose per session, 30 min prior to session onset due to the uptake time and dissipation of muscle relaxant effects (Addolorato et al. 2011). In sessions in which baclofen was injected with cocaine (baclofen + cocaine) injections of baclofen preceded cocaine administration by 15–20 min across all animals because of temporal constraints in arranging testing sessions across animals. Baclofen alone at the high dose (0.40 mg/kg, IV) was also delivered to the same animals 20–30 min prior to the DMS test session. Each drug delivery was preceded or followed by the appropriate saline control injection to control for the effects of the two drug delivery method. Following each session, the IV injection port was filled with heparinized saline (25 U/ml) and the animal returned to its home cage. All animals received 18 acute injections of cocaine and each session in which cocaine or cocaine + baclofen was administered was preceded and followed by saline control injections to make sure normal levels of DMS performance were maintained over days throughout the study.

Positron emission tomography Procedures employed for the measurement of rates of local cerebral metabolic activity (CMRglu) in NHPs were similar to those described previously (Porrino et al. 2005; Beveridge et al. 2006; Deadwyler et al. 2007; Hampson et al. 2011). Awake, conscious animals were placed in the primate chair to perform the DMS task and at 10 min into the session injected IV with 5–6 mCi [^{18}F]-FDG, after which performance of the DMS task continued for 40 min to allow the tracer to be incorporated into brain (Porrino et al. 2005). Blood samples were obtained from a vein different from the injection site prior to, 8 and 45 min after [^{18}F]-FDG injection. All animals were thoroughly habituated to these procedures. After 40 min of task performance following [^{18}F]-FDG injection, animals were anesthetized with ketamine (15 mg/kg, IM) and transported to a "GE Advance NXi PET scanner with in-plane (transaxial) resolution of approximately 6.0–6.5 mm in stationary mode and 5.2 mm in wobbled mode. PET assessment consisted of a 5-min transmission scan to set parameters, followed by a 15-min emission scan to detect FDG concentrations in brain. Glucose concentrations were computed from baseline, 8 and 45 min blood samples, calibrated from a standard arterial/venous blood glucose, time × concentration, curve. PET image data was normalized for glucose metabolic constants, then subjected to 3D region-of-interest and voxel-based multivariate statistical analyses using standard SPM8 programs for human brain image analyses adapted to rhesus macaque brain coordinates (Beveridge et al. 2006; Hampson et al. 2009; Hampson et al. 2011). Each animal was subjected to four imaging sessions, control (saline), cocaine alone (0.60 mg/kg, IV), baclofen + cocaine, and baclofen alone (0.40 mg/kg, IV), in which PET scans were obtained 40 min after [^{18}F]-FDG injection at the start of the session. All animals received an MRI scan for PET reconstruction of brain areas.

Data analysis DMS task performance data was evaluated over at least three sessions per condition (cocaine alone, cocaine + baclofen) and compared with long standing control responding in the same animals over a range of 9–14 months on the same DMS task parameters. A multifactor ANOVA, general linear model with incomplete block design (Neter and Wasserman 1974), was employed as the overall model incorporating type of trial (object vs. spatial), number of images per trial, control (saline) sessions, doses of cocaine and baclofen as well as cocaine + baclofen to assess differences in performance as the percentage of correct trials. Behavioral data was analyzed for main effects of type of trial (object vs. spatial), dose of cocaine (saline, 0.20, 0.40, and 0.60 mg/kg, IV) dose of baclofen (saline, 0.29 and 0.40 mg/kg, IV), and repeated measures across number of images. Main effects and interactions are reported where indicated and other tests utilized linear contrasts for simple effects and pairwise comparisons between specific conditions all within the same general model. Analysis of PET scans consisted of determination of brain regions activated or modified specifically during performance of DMS task via subtraction of images in the same animal obtained under separate conditions and sessions and the resulting alterations displayed as difference images superimposed on MRIs of relevant cortical regions. The resulting "difference maps" show the regions activated in the task via statistically (SPM8) assessed plots of voxel-by-voxel differences in scans taken under separate task conditions (Porrino et al. 2005; Deadwyler et al. 2007). The effects of the different drug conditions described above were assessed in terms of modifications of task-related brain activity in PET ([^{18}F]-FDG) imaged regions during sessions with saline vehicle injections vs. images from sessions in which drugs were delivered.

Results

Performance of the DMS task showed differential performance levels within sessions across all variables including duration of delay, number of images, as well in relation to the type of match phase selection rule (object or spatial position) present on each trial. Therefore the task included a combination of short-term memory (retention of the sample phase information) and cognitive decision making (selection of the appropriate target in the match phase) present on each trial which provoked a wide range of performance related directly to the above three factors that influenced cognitive demand and involvement of appropriately related brain structures (Hampson et al. 2004, 2009). Results across all animals (n=6) were consistent in showing differential performance levels on object vs. spatial trials in terms of different levels of cognitive demand defined by the number of images (# images) in the match phase of the DMS task. The overall ANOVA was significant ($F_{(131,486)}$= 30.83, p<0.001), as were the main effects of trial type ($F_{(1,486)}$=83.31, p<0.001), cocaine dose ($F_{(3,486)}$=118.01, p< 0.001), baclofen dose ($F_{(2,486)}$=20.75, p<0.001), and number of images ($F_{(5,\ 486)}$=45.01, p<0.001). All interactions were significant to at least the p<0.05 level except for four-way "trial type × baclofen dose × # images" (p=0.09), therefore comparisons reported below were justified on the basis of the interaction terms in the ANOVA model. Pairwise comparison utilized linear contrasts constructed within the overall ANOVA to compare specific effects.

The type of trial signified by the start signal (Fig. 1a) effectively controlled overall performance levels and it is clear from Fig. 1b that spatial trials were more difficult than object trials. Performance on object trials was significantly higher than on spatial trials for all trials with more than three images in the match phase, as revealed by a significant interaction between trial type vs. number of images ($F_{(5,486)}$=46.52, p<0.001). This same distinction was apparent when the task was performed

following acute administration of cocaine (Fig. 2) in which there was a dose-dependent (0.20, 0.40, and 0.60 mg/kg) decrease in performance on both object and spatial trials but with a greater decrement in performance of spatial trials. These dose-dependent influences were significant as indicated by the fact that and the effects of cocaine for 0.4 and 0.6 mg/kg increased as a function of task demand (Fig. 2) revealed by a significant interaction between cocaine dose level and number of images ($F_{(15,486)}$=9.45, p<0.001). Finally, the same dose of cocaine was more influential on spatial vs. object trials as evidenced by the significant interaction between trial type and cocaine dose ($F_{(3,486)}$=15.35, p<0.001), specifically indicated in Fig. 2 by the differences in performance on spatial vs. object trials with five to seven images (linear contrast: $F_{(1,486)}$= 16.39, p<0.001). These dose-dependent alterations in cognitive performance produced by cocaine administration formed the basis for testing baclofen to see if it could reverse the effects

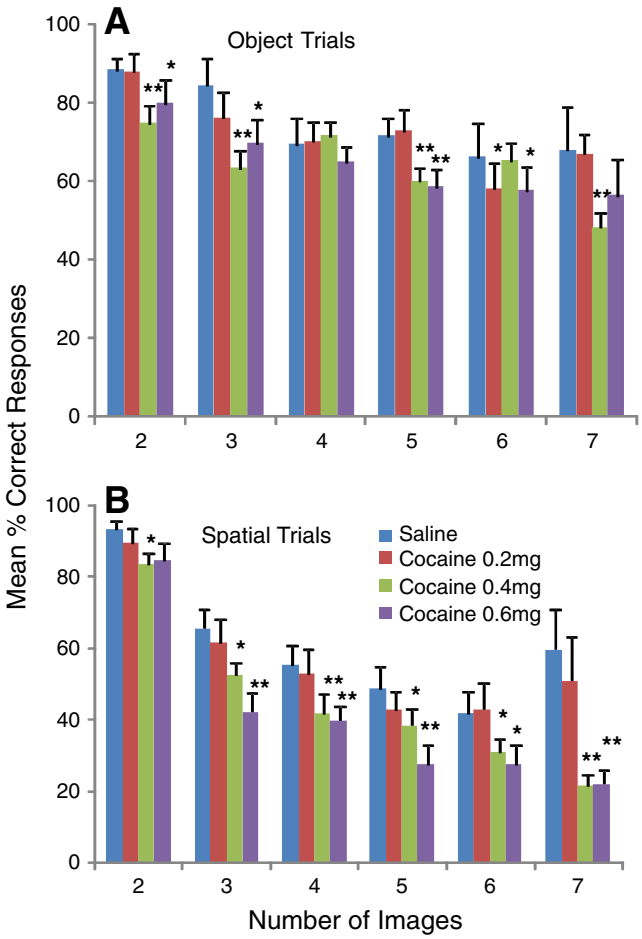

Fig. 2 Effects of cocaine administration on object vs. spatial trials. Differential performance on object and spatial trials as a function of number of images in the match phase of the task was dose-dependently decreased by increased doses (0.2, 0.4, and 0.6 mg/kg, IV) of cocaine administered 10 min prior to start of session. Effects were more pronounced on object (*upper*) vs. spatial (*lower*) trials. *$F_{(1,486)}$=7.15, p<0.01; **$F_{(1,486)}$=12.44, p<0.001, cocaine vs. saline sessions

if administered 20 min prior to the time in which cocaine was delivered prior to the start of the session.

Figure 3 shows results for cocaine only (0.6 mg/kg), cocaine + baclofen (0.29 mg/kg and 0.40 mg/kg), and baclofen + vehicle (saline) for both object (Fig. 3a) and spatial trials (Fig. 3b). As previously demonstrated (Fig. 2), cocaine alone (0.60 mg/kg) at this dose influenced performance in a task-dependent manner with more of a difference in performance between spatial vs. object trials in cocaine alone vs. saline sessions (linear contrast: difference of cocaine 0.60 mg/kg vs. saline on object vs. spatial trials, $F_{(1,486)}$=21.85, p<0.001). Doses of pre-administered baclofen (0.29 and 0.40 mg/kg) were assessed for their ability to reverse the effects of this dose (0.60 mg/kg) of cocaine. In sessions with baclofen (0.40 mg/kg) + cocaine (0.60 mg/kg), baclofen reversed deficits in performance produced by cocaine (0.60 mg/kg) alone as revealed by a significant difference in cocaine vs. baclofen + cocaine ($F_{(1,486)}$=19.48, p<0.001, overall linear contrast) performance summed over both trial types (object vs. spatial). Improvement of cocaine impaired performance by pre-injection of baclofen (0.4 mg/kg) on object trials (Fig. 3a) was significantly greater if the trials were more difficult in terms of number (five to seven) of images (linear contrast; cocaine + baclofen (0.40 mg/kg) vs. cocaine alone $F_{(1,486)}$= 7.28, p<0.01). Performance on the same (five to seven images) trials in the more difficult spatial version of the DMS task (Fig. 3b) was even more improved by the higher dose (0.40 mg/kg) of baclofen (linear contrast; cocaine alone 0.60 mg/kg vs. cocaine + baclofen (0.40 mg/kg) $F_{(1,486)}$= 13.22, p<0.001). The dose dependence of baclofen reversal of cocaine effects was demonstrated by the fact that cocaine reduced performance on trials with higher cognitive load (four to seven images) were not significantly improved by the low dose (0.29 mg/kg) of baclofen (linear contrast, average over four to seven images; cocaine alone vs. baclofen 0.29 + cocaine, $F_{(1,486)}$=3.62, NS), but the higher dose of baclofen (0.40 mg/kg) significantly reduced cocaine effects on performance on all trials with more than three images (linear contrast average over four to seven images—cocaine alone vs. baclofen 0.40 + cocaine 0.60, $F_{(1,486)}$=15.83, p<0.001) as shown in Fig. 3b. The high dose of baclofen (0.40 mg/kg) was also more effective in reducing the effects of cocaine on spatial vs. object trials when assessed across all trial types (interaction: trial type × cocaine vs. saline × cocaine + baclofen 0.29 and 0.4 mg/kg; $F_{(5,486)}$=8.24, p<0.001) in Fig. 3a and b. Interestingly, on the most difficult spatial DMS trials in which seven images appeared in the match phase of the task (Fig. 1a), baclofen administered alone with saline significantly improved performance above all other conditions including saline controls (Fig. 3b; baclofen, 0.40 mg/kg + saline, $^{\#\#}F_{(1,486)}$=12.31, p<0.001).

[^{18}F]-FDG PET imaging was utilized to investigate differences in local cerebral metabolic rate in brain areas

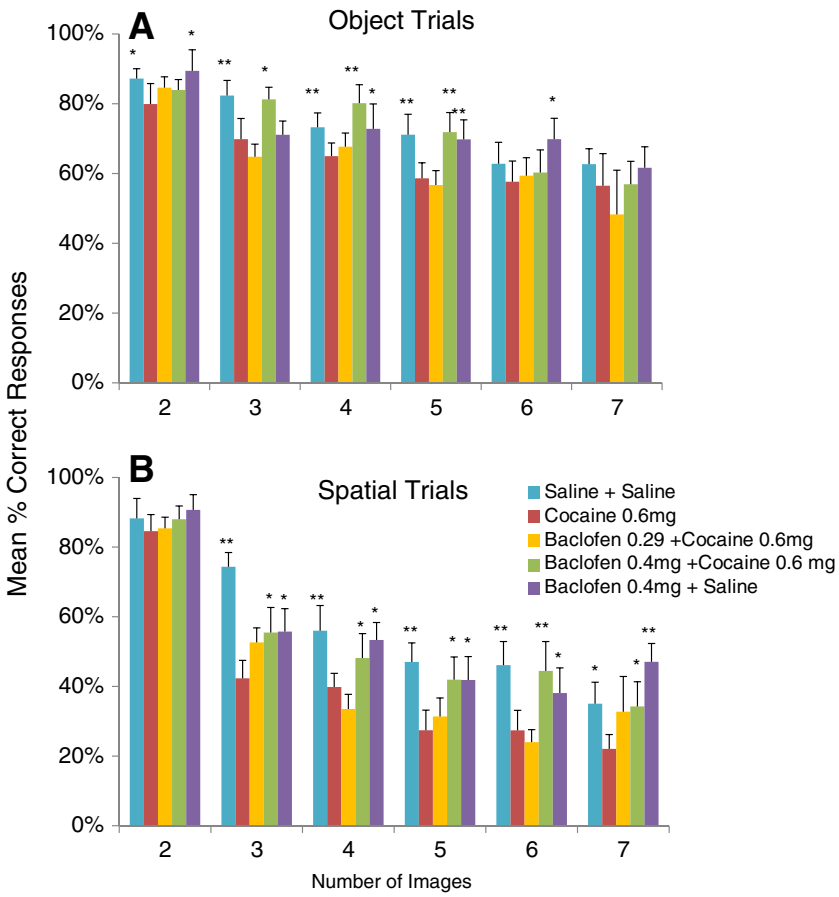

Fig. 3 Reversal by baclofen, of effects of cocaine on DMS performance. **a** Object trials: comparison of performance on cocaine only (0.6 mg/kg, IV), baclofen only (0.40 mg/kg, IV), and cocaine + baclofen in the same doses, with vehicle (saline) administration on object trials. Baclofen (0.29 mg/kg, 0.40 mg/kg, IV) injected 20 min prior to cocaine (0.6 mg/kg, IV) administration at 10 min before start of session. $*F_{(1,486)}=7.09$, $p<0.01$; $**F_{(1,486)}=13.75$, $**p<0.001$, vs. cocaine 0.6 mg/kg. **b** Spatial trials: effects of the same doses of cocaine and baclofen alone and baclofen + cocaine on performance on spatial trials. The higher dose of baclofen (0.40 mg/kg, IV) was significantly different from the lower dose (0.29 mg/kg, IV) in reversing the effects of cocaine, especially when more images were presented on spatial trials. $*F_{(1,486)}=7.26$, $p<0.01$, $**F_{(1,486)}=11.79$, $p<0.001$, compared to cocaine 0.6 mg/kg. $^{\#\#}F_{(1,486)}=12.31$, $p<0.001$ compared to saline

known to be engaged during the DMS task (Porrino et al. 2005; Deadwyler et al. 2007). The difference maps in Fig. 4a ($n=6$ animals) show regions in red that indicate increases in LCMR following whole brain analyses with probability thresholds set to $p<0.01$ at the voxel-level and corrected at the cluster level ($p<.001$, corrected). In agreement with other reports the effect of the acute cocaine injection (0.6 mg/kg) was to increase activation during DMS performance in the dorsolateral prefrontal (Fig. 4b left image) and medial parietal cortical (Fig. 4b right image) areas relative to activity during sessions with saline injection (Porrino et al. 2001; Hoshi and Tanji 2004; Fogassi et al. 2005; Volkow et al. 2005; Bradberry 2007; Hampson et al. 2011; Parvaz et al. 2011). Figure 4b shows difference maps of brain areas activated in the same animals during cocaine (0.6 mg/kg) DMS sessions preceded by treatment with baclofen (0.4 mg/kg). Unlike sessions with cocaine alone, neither were differentially activated during the task but there was increased activation of dorsal striatum (left) and posterior temporal lobe (right), when the same animals were pretreated with baclofen (Fig. 4b). The lack of differential activation in prefrontal and parietal cortices indicates that the effect of pretreatment with baclofen prior to cocaine sessions was similar to the effect of cocaine alone. However, the basis for this lack of differential activation by cocaine + baclofen was revealed in sessions in which scans were taken from the same animals treated with baclofen (0.4 mg/kg) alone (shown in Fig. 3) and compared to saline sessions. The difference brain map in Fig. 4c shows that baclofen alone was capable of increasing activity in prefrontal cortex during the task in the same regions affected by pre-injection of cocaine alone (Fig. 4a). Therefore, this similar activation pattern from both drugs alone (baclofen or cocaine) in prefrontal cortex (Fig. 4a, c) was the basis for the lack of registration of differential activation in Fig. 4b when both drugs were administered together in the same session.

Discussion

The above results provide potential insights into tactics for reversing disruptions in cognitive performance produced by drugs of abuse such as cocaine (Jentsch et al. 2002; Kalivas and Volkow 2005; Browndyke et al. 2004; Hester et al. 2004; Bechara and Martin 2004; Kalivas 2004, Bradberry 2007; Porter et al. 2011; Volkow et al. 2006). One factor elucidated was that the effects of high acute doses of cocaine (0.4 and 0.6 mg/kg) on cognitive performance were not simply related to deficits in short-term memory but also to task difficulty in terms of (1) number of images and (2) type of trial (object or

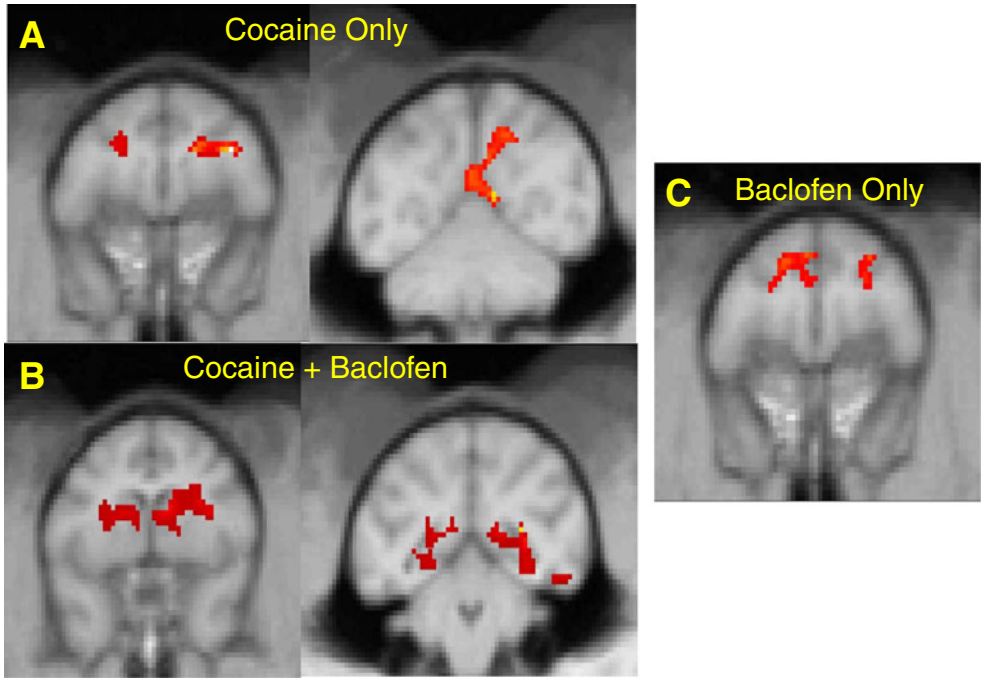

Fig. 4 Average [^{18}F]-FDG PET difference images from NHPs (n=6 animals) performing DMS task show changes in brain activation (LCMR) following treatment with drugs vs. vehicle (saline) sessions. **a** Difference maps show cocaine injection (0.6 mg/kg, IV) increased activation of prefrontal (*left*) and medial parietal cortex (*right*) during DMS performance. *Regions in red* show increased metabolic activity. Effects are plotted on representative MRIs of the same brain areas. **b** Difference maps for sessions in which baclofen (0.40 mg/kg, IV) was administered prior to cocaine (0.6 mg/kg, IV) injection (Fig. 3) relative to images from sessions with cocaine alone in (**a**). Areas shown activated by cocaine alone in (**a**) were not differentially increased in baclofen + cocaine sessions. Areas of increased activation relative to cocaine alone sessions are shown in *red* and include the dorsal striatum (*left*) and posterior hippocampus (*right*). **c** Difference map shows effect of baclofen (0.4 mg/kg, IV) administered alone prior to saline delivery at the time of cocaine administration in other sessions (**a**, **b**). Increased activation of prefrontal cortex, similar to cocaine alone (**a**), is shown relative to normal saline vehicle alone sessions. Probability thresholds set to $p<0.05$ at the voxel level and corrected at the cluster level ($p<0.001$, corrected)

spatial) described in Fig. 2a and b. Second, co-administered baclofen at the high dose (0.4 mg/kg) reversed the effects of cocaine, and also showed greater reversal in performance in the more difficult spatial (vs. object) task in which cocaine was more detrimental on trials with higher cognitive load as indicated by more images (asterisks in Fig. 3a and b). However, if administered in the same manner with cocaine but at a lower dose (0.29 mg/kg), performance deficits induced by cocaine were not significantly reversed, so the effect of baclofen was dose dependent. Third, an important feature of the reversal of the acute effects of cocaine on more difficult trials by baclofen at the high dose (0.40 mg/kg) was the specificity of action indicated by the fact that baclofen at the same dose administered alone did not alter performance from normal (saline) levels irrespective of cognitive load (number of images) or type of trial (object or spatial) as shown in Fig. 3a and b.

The above results definitely indicate effects related to cognitive involvement in the DMS task along several dimensions. While efficacy of short-term memory was a definite contributing element in controlling performance, two other major variables, namely execution of a particular type of sample selection indicated by the type of trial as well as the unpredictable complexity of the screen on which the sample information was displayed (i.e., cognitive load, Hampson et al. 2009), also controlled performance on a given trial. Several different cognitive variables were therefore exercised and tested including memory. While sample retention was critical for selection of the appropriate match phase "target" after a variable delay interval, the context (trial type, object or spatial) in which retention of such information was applied was also shown to be a deciding factor in controlling performance (Figs. 1–3). Therefore, the dose-dependent differential effects of cocaine and baclofen were likely due to interactions with the above "cognitive factors" operative within this version of the DMS task as shown in prior reports (Porrino et al. 2005; Deadwyler et al. 2007; Hampson et al. 2009; Hampson et al. 2011).

While assessment of such actions is not always possible, it has been shown that some drugs known to enhance cognitive performance are in fact effective at reversing performance deficits produced by chronic cocaine administration (Browndyke et al. 2004; Kenna et al. 2007; Karila et al. 2008; Oleson et al. 2011). The fact that baclofen was capable of facilitating cocaine-impaired DMS performance is similar to other reports of the effectiveness of this drug in animal models for reversing the effects of other drugs and

enhancing rewarded behavior (Weerts et al. 2007; Arai et al. 2009; Terrier et al. 2011), but additional evidence is presented here for the fact that baclofen at a relatively high level (0.40 mg/kg) systematically reversed (Fig. 3) the tendency for cocaine administration to "increase" cognitive demand (Fig. 2) in this task (Hampson et al. 2011).

A possible basis for baclofen reversal of the cognitive effects of cocaine was revealed by [^{18}F]-FDG PET imaging in the same animals performing the same task under the same drug exposure conditions (Fig. 4). Other reports provide support for the brain areas (prefrontal cortex, striatum, and medial temporal cortex) shown to be altered by cocaine in this study (Nader et al. 2002; Robbins and Everitt 2002; Bolla et al. 2003; Hester et al. 2004; Goldstein et al. 2004; Elston et al. 2006; Genovesio et al. 2006; Torregrossa et al. 2008; Koya et al. 2009; Opris et al. 2009; La Lumiere et al. 2010; Gould et al. 2012). However, some studies of the actions of baclofen and other GABA receptor agonists in animal models and in the brains of substance abusers (Spano et al. 2007; Karila et al. 2008; Arai et al. 2009; Moore and Boehm 2009; Garbutt et al. 2010; Franklin et al. 2011; Oleson et al. 2011; Terrier et al. 2011) have shown different types of involvement than reported here even with higher dose levels.

What is unique about the results reported here is the fact that baclofen administered alone activated the same brain areas (Fig. 4b) recently reported to be altered by cocaine administration alone (Hampson et al. 2011) when performance was disrupted in the same manner as shown here (Fig. 4a). The lack of "differential" activation of prefrontal cortex in [^{18}F]-FDG PET images from combined drug sessions, where baclofen counteracted the cognitive effects of cocaine (Fig. 4), suggests a direct interaction between processes affected in prefrontal cortex when both drugs were present. This is supported by the fact that an increase in activation would have been observed due to the added effects of baclofen in prefrontal cortex if the previously demonstrated activation by cocaine alone in that same area was not suppressed by the presence of baclofen (Fig. 4c). Therefore, the effect of the baclofen could have been to increase operation of other primary cortical synaptic processes (i.e., GABAergic inhibition) which counteracted cocaine's disruption of that same microcircuitry (Arai et al. 2009; Moore and Boehm 2009; Oleson et al. 2011).

In addition, in combined drug sessions, baclofen increased task-related activation of the dorsal striatum and temporal lobe (Fig. 4b), areas previously shown to be activated during performance of the same DMS task (Porrino et al. 2005; Deadwyler et al. 2007; Hampson et al. 2009). These two actions, (1) removal of cocaine-induced suppression of GABAergic operations (Oleson et al. 2011) and (2) recruitment of other task-relevant brain regions, could have been the basis for recovery of cognitive performance by baclofen in this task. The above results, although specifically related to the acute effects of cocaine on cognitive performance, provide an indication that drugs such as baclofen that enhance GABAergic function (Franklin et al. 2011) if systematically administered *during* chronic drug exposure could possibly retard or prevent the well-documented depression in mental activity that results from addictive drug use (Addolorato et al. 2011).

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