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Altered cerebellar and prefrontal cortex function in rhesus monkeys that previously self-administered cocaine

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Abstract

Rationale—Differences in brain function in cocaine users can occur even when frank deficits are not apparent, indicating neuroadaptive consequences of use. Using monkeys to investigate altered metabolic activity following chronic cocaine self-administration allows an assessment of altered function due to cocaine use, without the confound of pre-existing differences or polysubstance use often present in clinical studies.

Objectives—To evaluate alterations in metabolic function during a working memory task in prefrontal cortex and the cerebellum following one year of chronic cocaine self-administration followed by a 20 month drug-free period.

Methods—¹⁸F Fluorodeoxyglucose PET imaging was used to evaluate changes in relative regional metabolic activity associated with a delayed match to sample working memory task. Chronic cocaine animals were compared to a control group, and region of interest analyses focused on the dorsolateral prefrontal cortex (DLPFC) and cerebellum.

Results—Despite no differences in task performance, in the cocaine group, the cerebellum showed greater metabolic activity during the working memory task (relative to the control task) compared to the control group. There was also a trend towards a significant difference between the groups in DLPFC activity ($p=0.054$), with the cocaine group exhibiting lower DLPFC metabolic activity during the delay task (relative to the control task) than the control group.

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conflict of interest: none

Experiments conducted herein comply with current US law.

Conclusion—The results support clinical indications of increased cerebellar activity associated with chronic cocaine exposure. Consistent with evidence of functional interactions between cerebellum and prefrontal cortex, these changes may serve to compensate for potential impairments in functionality of DLPFC.

Cocaine addiction is a disorder associated with chronic risk of relapse even after long-term abstinence, and abstinent cocaine users suffer from multiple cognitive deficits (Beatty et al. 1995; Bolla et al. 2004; Bolla et al. 2003; Hanlon et al. 2011; Kelley et al. 2005) that are related to retention and success in treatment (Aharonovich et al. 2006; Brewer et al. 2008; Moeller et al. 2010b; Turner et al. 2009). It has been hypothesized that frontal abnormalities, whether functional (Moeller et al. 2010b; Tomasi et al. 2007) or structural (Franklin et al. 2002; Hanlon et al. 2011; Matochik et al. 2003), may underlie the cognitive disruption observed in cocaine abusers during abstinence. While cortical areas have gained the most attention, there is some evidence suggesting that cerebellar activity is also altered in cocaine abusers. Hester and Garavan, using functional magnetic resonance imaging (fMRI) during a Go/No-Go task with increased working memory demand, were the first to show increased cerebellar activity in active users and decreased cortical activity compared to healthy controls (Hester and Garavan 2004). The authors suggested that the cerebellum might be compensating for hypoactivity in cortical areas. In a similar study, (Tomasi et al. 2007) early abstinent cocaine users performing a verbal working memory task showed widespread disruption in cortical areas, but also showed increased cerebellar activity, which correlated with better working memory performance in cocaine users only. It is unclear whether the cerebellum continues to have increased activity in long-term cocaine abstainers.

A weakness of cross-sectional clinical studies is the inability to control for pre-existing differences or polysubstance abuse that limits interpretations of drug-specific effects. These concerns do not apply to animal studies given the randomized assignment of subjects to experimental and control groups. The purpose of the present study was to look at cerebral metabolic function in rhesus macaque monkeys that were drug free for 20 months after self-administering cocaine chronically for 12 months. Using [^{18}F]-2deoxy-2-fluoro-D-glucose (FDG) with positron emission tomography (PET) during a visual working memory task allowed us to examine whether there were any between groups differences in cerebral metabolic function during a task which is dependent upon intact PFC (Mishkin and Manning 1978), and which engages task specific single unit activity (Wilson et al. 1993) and produces metabolic increases in monkey prefrontal cortex as measured by FDG/PET (Porrino et al. 2005). In light of previous work, we hypothesized that the cerebellum would show greater metabolic activity in the cocaine group relative to the control group (Hester and Garavan 2004; Tomasi et al. 2007). We also hypothesized that the dorsolateral prefrontal cortex (DLPFC), a region shown to be active with FDG-PET during the delay period of a working memory task (Porrino et al. 2005), would show decreased metabolic activity in the cocaine group.

Materials and methods

Subjects

The principles of laboratory animal care outlined in the eighth edition of the “Guide for the Care and Use of Laboratory Animals” (2011) were followed, as were United States laws governing the use of animals in research. An environmental enrichment plan addressing social grouping, foraging opportunities, and manipulanda was in place. Young adult (age 8–9) male rhesus macaques that previously self-administered cocaine (n=6) were compared to a control group (n=5) that self-administered water over a 12 month period. Cumulative cocaine exposure ranged from 503 to 540 mg/kg total exposure over the 12 months of self-administration. Self-administration sessions were generally conducted 4 days per week (Tues-Fri), with cognitive assessments (reported in (Porter et al. 2011) taking place on Mondays). During the self-administration sessions, the unit dose of cocaine available was 0.5 mg/kg. i.v., with a forced ten min time out between infusions. All infusions were typically taken, as indicated by the limited variability between individuals. The cocaine group was drug-free for 20 months prior to the start this study. During that time, they participated in behavioral studies that have been reported (Porter et al. 2013), but did not undergo any drug exposure other than ketamine for TB testing or other routine clinical procedures. The animals are a subset of those used for a previous study of cognitive deficits associated with chronic cocaine self-administration (Porter et al. 2011). Only 5 out of 6 of the original control monkeys and 6 out of 8 of the original cocaine monkeys from (Porter et al. 2011) were available due to unexpected illness or loss of motivation. Animals were water-regulated 7 days a week and were supplemented to meet physiological needs at the end of each day following training and testing. Animals were fasted for 12 hours prior to all FDG-PET scans.

Working memory task

A delayed match to sample (DMTS) task was used to assess working memory. Animals were seated in a Primate Products behavioral chair inside a sound-attenuating audiometric booth during task performance, which was conducted between the hours of 8 am and 1 pm, typically 3–5 days per week. Each trial started with a sample image centered on the touch-screen. Holding the image for 1-second led to an intra-trial delay period of 0, 5, 10 or 20 seconds. After the delay, four figures were presented on the match screen, one of which was the sample image, and the other three were non-match distractor images. Match images were never placed in the same position for two consecutive trials. Touching the match image resulted in a water reward of 0.07ml/kg. Animals had to respond within a 10-second window. An incorrect response, or a failure to respond (animals rarely omitted a response) ended the trial. There was an inter-trial interval of 2 seconds. Approximately 500–600 unique images with distant features were used per session, with none of images repeated within a session. Images could by random selection very occasionally be repeated in different sessions.

A similar version of the DMTS task was previously used with these animals to reveal deficits in visual working memory during active self-administration when tested drug-free 72 hours after the most recent cocaine exposure (Porter et al. 2011). In that version, there

was a choice between two images at the match stage. We altered the previous version of the task in order to make it more cognitively demanding due to omission of the longest delay previously used (40 sec). That delay was omitted because at higher delays animals would occasionally quit working and we wanted to ensure maximal performance on scan days.

Control task

The control task was designed to be analogous to the DMTS task with respect to sensorimotor demands and reward amount received. There was no intra-trial delay between the sample and match screen. Rather, a 12 second inter-trial interval was inserted to compensate for the lack of an intra-trial delay, thereby ensuring that animals performed an equivalent number of rewarded trials as on the DMTS task.

Cognitive training and acclimation to FDG-PET procedures

During the cognitive training period to introduce the DMTS task which differed slightly from that used previously (Porter et al. 2011), animals were initially trained on the control zero delay task, during which they were acclimated to procedures necessary for the PET scan such as accessing the vascular access port for radioligand administration. After that, the delay task was introduced. Total number of zero delay sessions were: control 50 ± 13.4 , cocaine 63.8 ± 7.8 $t_{(9)} = 0.93$, $p = 0.375$. Total number of sessions with delays were: control 15.4 ± 0.9 , cocaine 19.8 ± 7.2 , $t_{(9)} = 0.557$, $p = 0.591$. The control task was always performed on the initial FDG-PET scan day. Typically, control and DMTS task FDG-PET scans days were separated by 7–10 days.

FDG-PET scan procedures

On the day of the FDG-PET scan, animals were positioned in their primate chair, had an i.v. line placed in their vascular access port, and were placed into a sound attenuating chamber. After completing 5 trials of the task, animals received an injection of 7–10 mCi of FDG, followed by a 10 ml flush of sterile saline. Injections were done from outside the chamber with minimal disruption to the animal. Animals performed the task for 35 minutes before the sessions were terminated. Animals were then immediately anesthetized with ketamine (15 mg/kg, i.v.) and quickly transported to the PET center, where scans were initiated exactly 60 minutes after the FDG injection.

Scan processing and co-registration

PET images were acquired on a Siemens microPET P4 scanner (Siemens Medical Systems, Knoxville TN), which has a 7.8 cm axial field of view, a transaxial field of view of 19 cm, and a maximum intrinsic spatial resolution of 1.8 mm FWHM (Tai et al. 2001). CT images were acquired using a CereTom system (Neurologica, Inc., Danvers, MA), which is a clinical small-bore 8-slice (1.25 mm slice pitch) helical CT scanner designed for neuroimaging applications. The microPET and CereTom systems are aligned along a common isocenter, with a custom designed unified bed pallet servicing both PET and CT systems. This arrangement allows intrinsically co-registered PET and CT images to be acquired over a ~50 cm co-scan range. Prior to the acquisition of PET emission data, an axial CT scan was acquired (7 mAs, 120 kVp) over 15 cm (1 cm/sec). The resulting CT scan

was used both for positioning the animal in the microPET gantry and for the attenuation correction of PET emission data. PET emission data were acquired in list mode for 30 min commencing 60 min after the injection of [^{18}F] FDG and binned into a single 30 min static frame. The emission sinograms were reconstructed using filtered back projection with a 0.5^{-1}cm ramp filter and an image zoom of 1.5, resulting in PET image matrix of $256 \times 256 \times 63$ voxels with dimensions of $0.63 \text{ mm} \times 0.63 \text{ mm}$ (transaxial) $\times 1.21 \text{ mm}$ (axial). Co-registered CT images were segmented into air, brain tissue, bone, and bed pallet segments and converted to appropriate mass attenuation coefficients (μ) for the respective segments at PET photon energies (511 keV). The resulting μ -maps were forward projected into an attenuation sinogram for correction of PET emission data. Standard corrections for scatter, scanner dead time, and random coincidences were applied to the PET emission data.

Magnetic resonance imaging (MRI) scans were obtained for each subject prior to self-administration. MRI scans (0.5mm voxel size) were acquired using a Siemens 3T Allegra scanner with a custom-designed dual stereotaxic holder/secondary coil designed by Dr Seong Gi Kim and colleagues (Univ. of Pittsburgh). The MRI scans were warped using Statistical Parametric Mapping version 8 (SPM8) software (Ashburner et al. 1997) to a merged and fully segmented macaque monkey MR template, analogous to the Montreal Neurological Institute templates used in human imaging studies as described previously (Jedema et al. 2010). A 5 mm smoothing kernel was used during pre-processing of the MR image. Each monkey's reconstructed PET image was then co-registered to that monkey's warped MR image and transformed spatially to match the monkey MR template using the warping parameters previously determined, to produce normalized FDG-PET images. Regions of interest (ROI) were drawn on the MR template and used to sample the PET images in order to generate regional raw scanner measures for each monkey.

ROI Analysis

Raw scanner numbers (counts/s/pixel over the period 60–90minutes after injecting FDG) were used to generate standard uptake value (SUV; average counts*scanner calibration factor*monkey weight/injected dose), a relative measure of metabolic activity. The final outcome used for comparison was the SUV ratio (or SUVR), which is simply the regional SUV referenced to the whole brain metabolic activity.

Previous neuroimaging studies have identified cognition related brain activity using a subtraction method (Posner et al. 1988; Smith and Jonides 1997) and this was applied herein. Because the control task was designed to engage all the task component processes except working memory, the subtraction method can be used to isolate metabolic activity associated with working memory. For each ROI, the control task SUVR was subtracted from the delay task SUVR for each subject in order to generate a difference score.

In order to maximize statistical power, a limited number of brain regions was selected *a priori* for comparison of standard uptake values. A spherical ROI was drawn on the MR template cerebellum, which encompassed cruz 1 and lobule 6, regions shown to be involved in working memory (Stoodley 2012; Stoodley and Schmahmann 2009; Strick et al. 2009). Previous work showed that during early cocaine abstinence, cerebellar activity correlated with working memory performance (Tomasi et al. 2007). Garavan and Hester also reported

an increase in cerebellar activity in active cocaine users (Hester and Garavan 2004). The second region that we focused our analysis on was the dorsolateral prefrontal cortex (DLPFC), corresponding to combined areas 9 and 46. The DLPFC was selected given previous work showing the role of DLPFC in working memory (Goldman-Rakic 1987) and because prior PET studies in healthy, drug free, non-human primates performing a DMTS task have shown the brain areas most activated to be the DLPFC, medial temporal lobe and dorsal striatum vs. non-task conditions (Deadwyler et al. 2007; Porrino et al. 2005). In addition, we conducted an exploratory analysis to compare between groups differences in the M1 (motor cortex) orbitofrontal cortex, and ventral, and dorsal striatum.

A two-way repeated measures ANOVA with factors: ROI (cerebellum and DLPFC) and group (cocaine vs. control) was conducted in order to examine metabolic activity differences between groups. Follow-up t-tests were conducted to determine what factor was contributing to the significant interaction.

Whole brain voxel comparison

As a follow-up to the targeted ROI analysis of the PET data, a parametric approach was conducted for the whole-brain voxel-level statistical analysis. The normalized FDG-PET scans for each subject acquired following the control and delay tasks were used to create a subtraction image representing change in regional cerebral metabolism between the working memory task and the control task (scans from the working memory task minus the control task). The results reflect the process of working memory by subtracting out the motor and visual components that are identical in the control and working memory tasks. A between-group comparison of the subtraction images was conducted using a two-sample t-test within SPM8. Between-session variations in global signal were adjusted using proportional scaling.

Behavioral analysis

The behavioral parameters examined were accuracy (correctly choosing the sampled stimulus) and mean response time for both the control and delay task. Although response time distributions are known to be skewed (Heathcote et al. 1991), the mean of that distribution is the most widely used metric for the present purpose which was to determine if there were any group differences in task engagement or motivation. Two way repeated measures ANOVA was used to examine whether there were main effects of delay on accuracy, or group by delay interactions on the DMTS task, and also to determine any task and/or group differences in response time. A t-test was used to compare performance on the no-delay control task between the cocaine and control groups.

Results

Behavior

During the training period to establish task performance, there were no between groups differences in accuracy on the control task ($t_{(9)} = 0.72$, $p = 0.49$) (Fig 1A, mean of 10 sessions). On the DMTS working memory task, there was a main effect of delay ($F_{(9,3)} = 48.5$, $p < 0.001$), but no group by delay interaction ($F_{(1,3)} = 0.729$, $p = 0.935$, Fig 1B, mean of 5–8 sessions). On PET scan days, performance matched the established training

performance indicating that animals were appropriately engaged in the task during isotope accumulation. As during training, there were no between groups differences in accuracy on the control task ($t_{(9)} = 0.43$, $p = 0.68$, (Fig 1C). On the DMTS task there was a main effect of delay ($F_{(9,3)} = 14.6$, $p < 0.001$) but no group by delay interaction ($F_{(1,3)} = 0.231$, $p = 0.642$, Fig 1D). Response times showed a main effect of task in which response times were increased during the DMTS task ($F_{(1,1)} = 24.9$, $p < 0.001$), but no group by response time interaction ($F_{(1,1)} = 0.2$, $p = 0.64$). Mean response times (msec) $\pm$ SEM were: control task, cocaine, 893 ± 72 ; controls, 959 ± 65 ; DMTS, cocaine 1163 ± 125 ; controls 1287 ± 24).

Imaging

Our *a priori* hypothesis was that we would see metabolic differences between the groups in the cerebellum and DLPFC. A two way-repeated measures ANOVA revealed a group X region interaction ($F_{(1,9)} = 8.085$; $p = 0.019$, Figure 2). A follow up t-test revealed that cerebellar activation was significantly different between the groups ($t_{(9)} = 2.61$, $p = 0.028$). In the cocaine group, the cerebellum showed greater metabolic activity during the DMTS task (relative to the control task) compared to the control group. There was also a trend towards a significant difference between the groups in DLPFC activity ($t_{(9)} = 2.21$, $p = .054$), with the cocaine group showing lower DLPFC metabolic activity during the delay task than the control group. By itself, the control group showed a clear activation in that the DMTS task – control task mean value was 0.029 with a 95% confidence interval of 0.0123. The cocaine group DMTS – control task mean was -0.0256, with a 95% confidence interval of 0.048. Thus, zero was just outside the latter 95% confidence interval, limiting potential interpretations as to whether that group showed decreased metabolic demand in DLPFC with working memory, or alternatively, there was just not a consistent metabolic change there in the cocaine group.

We conducted a follow up analysis to determine the specificity of our results by doing a between groups analysis comparing M1 (motor cortex), orbitofrontal cortex, dorsal striatum and ventral striatum metabolic activity. We did not observe any between groups differences in any of these areas. The post hoc exploratory analysis of the entire brain also did not reveal between groups differences in metabolic activity at our chosen level of significance ($p < 0.05$) and contiguous voxel threshold value of 100.

Discussion

The aim of this study was to assess neurobiological differences between monkeys with a history of chronic cocaine self-administration and drug naive controls. FDG-PET in combination with a visual working memory task was employed to examine regional metabolic brain differences in cocaine monkeys that were drug free for 20 months and controls. There were no between groups differences in working memory performance as measured by accuracy and response time. However, the cocaine group showed greater metabolic activity in the cerebellum while the DLPFC trended toward less activation compared to the control group.

FDG-PET imaging in monkeys reveals increased metabolic activity in DLPFC during a working memory task (Deadwyler et al. 2007; Porrino et al. 2005), and PET imaging has

revealed hypoactivity in cortical areas of abstinent cocaine abusers (Volkow et al. 1991). More recently, during early abstinence, fMRI studies have shown decreased cortical activity in early cocaine abstainers performing a working memory task (Moeller et al. 2010a; Tomasi et al. 2007). We were able to use FDG-PET to observe a trend toward a decrease in cortical metabolic activity in cocaine monkeys, even after 20 months of being drug free.

Although previously there were cognitive impairments in the cocaine group relative to controls when examined (across multiple sessions) 72 hours post-cocaine (Porter et al. 2011), at the time of the present study, frank behavioral deficits on the DMTS task were not apparent. However, in clinical studies, despite a lack of group differences in cognitive performance, cocaine users (Li et al. 2008; Moeller et al. 2010a) can show differences in function (BOLD signal) despite behavioral equivalence to controls. The potential interpretive value of functional differences between performance matched groups is revealed by significant correlations between functional activation and treatment response (Moeller et al. 2010a). It should also be pointed out that latent cognitive deficits not apparent under standard conditions can exist. For example, with these same monkeys, we previously demonstrated that reversal impairments that had normalized upon cessation of cocaine re-emerged when attentional distractors were added to the task (Porter et al. 2013).

We observed a long lasting alteration in the cerebellum following chronic cocaine self-administration. Whereas in the control group a decrease in cerebellar metabolic activity was seen with the DMTS, in the cocaine group, metabolic activity was increased. The cerebellum has long been considered mainly involved in motor function but, over recent years, neuroimaging studies have shown that the cerebellum may also be involved in executive function (Owen et al. 2005; Parkins 1997; Schmahmann and Sherman 1998). In the functional neuroimaging literature, verbal working memory reliably activates areas of the cerebellar cortex (Chen and Desmond 2005; Desmond and Fiez 1998; Fiez 1996) and patients with cerebellar damage are impaired in verbal working memory (Desmond et al. 2005; Ravizza et al. 2006; Silveri et al. 1998). Increased cerebellum activity is seen using fMRI in active cocaine users performing a Go/No-Go task with (Hester and Garavan 2004) and without (Connolly et al. 2012) increasing memory load. Similarly, greater activation in the cerebellum with increasing working memory load is seen in early abstinence cocaine users (Tomasi et al. 2007), and with a Stroop task (Moeller et al. 2012). The increase in cerebellum activity that we observed is consistent with the clinical literature and suggests that cocaine does in fact alter the cerebellum, and that the observations from the clinical imaging literature do not reflect pre-existing differences between groups.

Given the cerebellum and DLPFC's role in working memory, the hypothesis that the cerebellum works in a compensatory mechanism to improve working memory is plausible. In the current study, working memory performance was equivalent between the cocaine and the control group. Gould et al. conducted a study in nonhuman primates with an extensive history of cocaine exposure (Gould et al. 2012) and showed initial impairments during self-administration but after 30 days of abstinence, working memory performance improved. One conclusion based on Gould's work and our current study is that there are improvements of working memory impairment over periods of abstinence. The lack of a

between groups difference in behavior in combination with increased cerebellar metabolic function is consistent with a compensatory mechanism that supports performance.

Anatomical and imaging studies strongly support an interaction between the cerebellum and DLPFC in working memory. Using rabies virus as a transynaptic tracer in cebus monkeys, Kelly and Strick demonstrated that regions of the cerebellar cortex that receive input from DLPFC are the same as those that project to DLPFC, suggesting a cerebrocerebellar circuit (Kelly and Strick 2003). In healthy human subjects, increased activation in cerebellar regions that are interconnected with DLPFC was observed when subjects performed a working memory task (Desmond et al. 1997). Functional connectivity studies conducted in healthy subjects also support a prefrontal-cerebellar linkage (Krienen and Buckner 2009).

Thus, the literature and our data support the idea that an increase in cerebellar activity might compensate for reduced DLPFC metabolic function. It can be hypothesized that during active cocaine use the cerebellum is not capable of compensating enough to normalize working memory to control levels. With longer periods of abstinence, the cerebellum might then be able to compensate, thereby improving working memory and/or attention. Consistent with this hypothesis, a compensatory mechanism has also been proposed in an alcoholic population with equivalent working memory performance to controls (Desmond et al. 2003) in which there were relative increases in the right cerebellar regions and reduced activity in the DLPFC with increasing task demands relative to controls. While the effect we observed in DLPFC was at the trend level ($p=0.054$), we believe the overall consistency with clinical observations supports an interpretation that the changes were meaningful, and given our experimental control, that clinical observations are likely due to drug effects rather than preexisting differences. This conclusion is tempered by a weakness of the current study, namely that it is lacking in statistical power.

Our data demonstrate long-term changes in metabolic function in cocaine monkeys that were drug free for 20 months. We hypothesize that the increased cerebellar activity may reflect a compensatory mechanism necessary to maintain efficient working memory performance in cocaine abusers in the face of decreased cortical activation. Future studies in long-term abstainers are needed to determine more detailed roles of the DLPFC and cerebellum in complex cognitive processes. It would be of great interest to look at functional and structural connectivity of the cerebellum and DLPFC in cocaine users and abstainers, to investigate the compensatory mechanism we are hypothesizing in this current study. An increase in functional connectivity relative to active users or controls would support the current compensatory mechanism hypothesis. The underpinning biology supporting this mechanism would also be important to examine, and these data suggest that measuring changes in cerebellar activity as part of treatment development efforts may be informative of mechanism.

Acknowledgments

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Figure 1.

Established and scan day task performance. Top panel shows established performance on control task (A), and the DMTS working memory task (B). Bottom panel shows scan day control task (C) and DMTS task (D). There were no between group differences in accuracy on the two tasks, and both groups showed a decrease in accuracy with increasing delay interval on the DMTS task ($p < 0.001$) during established performance, and on scan days. Cocaine $n=6$, control $n=5$.

Figure 2.

Relative metabolic activity (DMTS task – control task, referenced to whole brain) for cocaine and control animals in cerebellum and DLPFC. Two way repeated measures ANOVA revealed a group X region interaction ($p = 0.019$), with follow up t-tests indicating a significant difference in cerebellum (*, $p = 0.028$) and a trend (#, $p = 0.054$) in DLPFC.