Published in final edited form as:
Neuroimage. 2010 February 1; 49(3): 2536. doi:10.1016/j.neuroimage.2009.10.088.

Cognitive Control of Drug Craving Inhibits Brain Reward Regions in Cocaine Abusers

Nora D. Volkow, M.D.[1,2,*], **Joanna S. Fowler, Ph.D.**[3], **Gene-Jack Wang, M.D.**[3], **Frank Telang, M.D.**[2], **Jean Logan, Ph.D.**[3], **Millard Jayne, R.N.**[2], **Yeming Ma, Ph.D.**[2], **Kith Pradhan, M.S.**[3], **Christopher Wong, M.S.**[3], and **James M. Swanson, Ph.D.**[4]

[1] National Institute on Drug Abuse, Bethesda MD 20892

[2] National Institute on Alcohol Abuse and Alcoholism, Bethesda MD 20892

[3] Medical Department, Brookhaven National Laboratory, Upton NY 11973

[4] Child Development Center, University of California at Irvine, Irvine CA 92612

Keywords

brain imaging; nucleus accumbens; orbitofrontal cortex; insula; cingulate gyrus; conditioned responses; cognitive inhibition

Loss of control over drug taking is considered a hallmark of addiction and is critical in relapse. Dysfunction of frontal brain regions involved with inhibitory control may underlie this behavior. We evaluated whether addicted subjects when instructed to purposefully control their craving responses to drug-conditioned stimuli can inhibit limbic brain regions implicated in drug craving. We used PET and 2-deoxy-2[^{18}F]fluoro-D-glucose to measure brain glucose metabolism (marker of brain function) in 24 cocaine abusers who watched a cocaine-cue video and compared brain activation with and without instructions to cognitively inhibit craving. A third scan was obtained at baseline (without video). Statistical parametric mapping was used for analysis and corroborated with regions of interest. The cocaine-cue video increased craving during the no-inhibition condition (pre 3±3 post 6±3; $p<0.001$) but not when subjects were instructed to inhibit craving (pre 3±2 post 3±3). Comparisons with baseline showed visual activation for both cocaine-cue conditions and limbic inhibition (accumbens, orbitofrontal, insula, cingulate) when subjects purposefully inhibited craving ($p<0.001$). Comparison between cocaine-cue conditions showed lower metabolism with cognitive inhibition in right orbitofrontal cortex and right accumbens ($p<0.005$), which was associated with right inferior frontal activation ($r = -0.62$, $P < 0.005$). Decreases in metabolism in brain regions that process the predictive (nucleus accumbens) and motivational value (orbitofrontal cortex) of drug-conditioned stimuli was elicited by instruction to inhibit cue-induced craving. This suggests that cocaine abusers may retain some ability to inhibit craving and that strengthening fronto-accumbal regulation may be therapeutically beneficial in addiction.

*Correspondence: Nora D. Volkow, M.D., National Institute on Drug Abuse, 6001 Executive Boulevard, Room 5274, Bethesda, MD 20892, Tel. (301) 443-6480, Fax (301) 443-9127, nvolkow@nida.nih.gov.

In addicted individuals exposure to conditioned drug-cues (i.e., places, people and paraphernalia associated with the drug) usually elicits an intense desire for the drug. This subjective experience (described as craving) frequently triggers relapse (O'Brien et al., 1998). Dopamine (DA) is a neurotransmitter involved with reward and with prediction of reward (Wise and Rompre, 1989; Schultz et al., 1997), and DA increases in the nucleus accumbens (NAcc) are associated with the drug-seeking behavior that follows exposure to conditioned-cues (Phillips et al., 2003; Weiss et al., 2000). These DA responses are modulated by glutamatergic projections from the frontal cortex (You et al., 2007; Yun et al., 2004; Taber et al., 1995), including the orbitofrontal cortex (OFC), which signals the motivational value of the conditioned stimuli (Rolls, 1996) and from amygdala and ventral hippocampus (Grace et al., 2007). It has been proposed that disrupted function of frontal regions may contribute to the impaired control over drug taking that characterizes drug addiction (Kalivas, 2004).

However, addicted individuals may retain some level of purposeful control over craving, but to our knowledge this has not been specifically evaluated. Here we performed a proof-of-principle study to test the hypothesis that a simple cognitive control procedure could reduce the subjective report of cue-induced craving in cocaine abusers, and to test the linked hypothesis that this would be associated with objective measures of inhibition of activity in brain regions (NAcc and OFC) that are implicated in the responses to drug conditioned stimuli.

To test these hypotheses we used Positron Emission Tomography (PET) and 2-deoxy-2[^{18}F] fluoro-D-glucose (^{18}FDG) to measure brain glucose metabolism (marker of brain function) (Sokoloff et al., 1977) in 24 active cocaine abusers. Subjects were tested using a video of cocaine cues that was previously shown to induce the subjective report of craving and to increase objective measures of striatal DA in cocaine abusers (Volkow et al., 2006). The cocaine abusers were scanned during stimulation with the cocaine-cue video twice, both with instruction to try to purposefully inhibit craving (cognitive inhibition CI) and without instruction (no-inhibition NI). A third scan was obtained without the stimulation of drug cues, which was used as a measure of baseline brain metabolic activity. We hypothesized that if cognitive inhibition of craving occurred, then it would be accompanied by decreases in metabolic activity in NAcc (in which activity is associated with prediction of reward) and in OFC (in which activity is related to motivational value of conditioned cues). We also assessed if the inhibition in these brain regions was associated by activation of the right inferior frontal cortex (Brodmann area 44), which is a critical brain region for exerting inhibitory control (Aron et al., 2004).

METHODS

Subjects

Twenty four active cocaine abusers (21 M and 3 F; 46 ±5 years of age; 13 ±2 years of education) who responded to an advertisement were studied. Subjects fulfilled DSM- IV criteria for cocaine dependence and were active users for at least the prior 6 months (free-base or crack) with average cocaine use of 16 ±2 days per month; 2.2 ±1 grams/day; and 17 ±6 years of abuse. Exclusion criteria included current or past psychiatric disease other than cocaine or nicotine dependence (12 subjects were smokers); past or present history of neurological, cardiovascular or endocrinological disease; history of head trauma with loss of consciousness greater than 30 minutes; and current medical illness. Scores for the "drug" domain of the Addiction Severity Index (McLellan et al., 1992), corresponded to 8 ±1; scores for the Cocaine Selective Severity Assessment Scale (Kampman et al., 1998) corresponded to 23 ±13. Measures of verbal IQ (estimated using the WRAT reading scaled score) corresponded to 92 ±4 and average years of education corresponded to 13 ±2. The average days since last use of cocaine for the baseline condition was 2.5 ±2 days, for the NI was 3.2 ±2 days, and for the CI it was 2.8 ±2 days. Written informed consent was obtained from all subjects.

Behavioral Scales

To assess the subjective experience of craving we used an analog scale (1–10) for self-reports of "cocaine craving" and the brief version of the Cocaine Craving Questionnaire (CCQ) (Tiffany et al., 1993), which evaluates current cocaine craving on a seven-point visual analogue scale. These measures were obtained prior to (pre) and 30 minutes after (post) initiation of the video. We compared the pre versus the post measures and the corresponding time period for the baseline condition using repeated ANOVA.

Cardiovascular measures

Heart rate and blood pressure were measured throughout the study. For statistical purposes we compared the measures obtained prior to initiating the study to the average measured for the 30 minutes that followed the initiation of the cocaine-cues video or the corresponding time period for the baseline scan using repeated ANOVA. Post hoc t tests determined which measures differed from one another.

Scans

PET scans were conducted with a whole-body, high-resolution positron emission tomograph (Siemens/CTI ECAT HR+, with 4.6 × 4.6 × 4.2 mm NEMA (National Electrical Manufacturers Association) using ^{18}FDG. Details about the methods for scanning have been published (Wang et al., 1993). Briefly, a 20 minute emission scan was started 35 minutes after injection of 4–6 mCi of ^{18}FDG. Arterialized blood sampling was used to measure ^{18}FDG in plasma.

All subjects were scanned 3 times with ^{18}FDG under the following conditions: 1. Eyes open but no video exposure (baseline); 2. Cocaine-cue video with no instruction to inhibit craving responses (no-inhibition = NI); 3. Cocaine-cue video with the instruction to purposefully inhibit craving (cognitive inhibition = CI). For the latter condition subjects were told to try to inhibit the desire for cocaine when watching the cocaine-cue video and were instructed on how to practice cognitive inhibition. Specifically, prior to the initiation of the study for the CI condition, subjects were told to use anyone of the following strategies to help them ignore the craving: ignore thoughts about cocaine, don't let your thoughts recall how it felt to take cocaine, try to relax, shift attention away from the desire to take cocaine to identifying the clothes the subjects in the video were wearing, and/or on the type of objects that they were using. The scans for the CI and the NI conditions were performed on separate days and the order of the conditions was balanced across subjects so that for half the CI occurred before the NI and for the other half the NI occurred prior to the CI conditions. Videos were started 10 minutes prior to injection of ^{18}FDG and were continued for 30 minutes after radiotracer injection. Each subject was exposed to a different cocaine-cues video for each condition to ensure that the stimuli were novel to them. The videos were randomly assigned to ensure that for half of the subjects one of the videos was presented for the CI and for the other half for the NI condition. The cocaine-cues videos featured non-repeating segments portraying scenes that simulated purchase, preparation, and smoking of cocaine.

Image and data Analysis

The data were analyzed using Statistical Parametric Mapping 99 (SPM 99) (Friston et al., 1994) and findings were subsequently corroborated using regions of interest (ROI) analysis. The SPM analyses were performed on the normalized metabolic images. For purpose of normalization we first obtained the average metabolic activity for the whole brain and then computed the ratio of metabolic activity in each voxel to that in the whole brain to obtain the normalized measures. The images were spatially normalized using the template provided in SPM 99 and subsequently smoothed with a 16 mm isotropic Gaussian kernel. Paired samples t-tests were performed for the following comparisons: 1. baseline versus NI; 2. baseline versus

CI; 3. NI versus CI. Significance was set at $p < 0.005$ (uncorrected, > 100 voxels) for the a priori hypothesis that during CI as compared with NI metabolic activity would be lower in NAc and OFC. For other comparisons significance was set at $p < 0.001$ (uncorrected, > 100 voxels). Statistical maps were overlaid on an MRI structural image.

For ROI analysis, we extracted ROI using an automated extraction method based on the standard brain template from the Talairach atlas (Talairach and Tournoux, 1988). First, ^{18}FDG images were mapped into the Talairach brain using the spatial normalization package in SPM. The inverse mapping procedure was used to extract the Talairach coordinates of all voxels for a given anatomical region from the Talairach Daemon database (Collins et al., 1995; Lancaster et al., 2000). These anatomically defined ROIs were overlapped voxel by voxel onto the SPM normalized PET image. To compare metabolic values in the ROI we used a repeated measure ANOVA for the 3 conditions (baseline, NI and CI). Post hoc t-tests were used to assess which conditions differed from each other. We only consider significant findings that were corroborated both by SPM and ROI analysis.

SPM was used to establish the voxel-wise correlation between metabolic activity during CI and the craving measures and between the metabolic activity during NI and the changes in craving (CI vs NI). Differences in the SPM results were considered significant ($p < 0.001$, cluster size > 100 voxels) when corroborated by the correlations obtained using the ROI. Pearson product correlations were also performed to assess the relationship between the difference in activation in brain regions that differed between the NI and CI conditions and the metabolic changes in right inferior frontal cortex. For this a priori hypothesis we set significance at $p < 0.005$.

RESULTS

Effects of cocaine video NI and CI on craving and on cardiovascular measures

The behavioral assessment comparing the pre versus the post video measures of craving revealed that the cocaine-cue video elicited significant increases in subjective reports of craving in the NI condition but not in the CI condition. There was no pre-post difference in self-reports of craving for the corresponding times of assessment during the baseline condition (Figure 1). Heart rate and blood pressure were significantly increased after watching the cocaine-cue video (NI and CI) whereas they did not differ for the baseline (Figure 1). Post hoc t tests showed that cardiovascular measures were higher for both cocaine-cue conditions than for baseline but that there were no differences between NI and CI.

Effects of the cocaine video with CI and NI on absolute metabolic measures

When compared with the baseline condition whole brain metabolism increased significantly with both cocaine-cues conditions corresponding for the left and right hemisphere respectively for NI to 9.43 ±14 % and 10.5 ±12 % increases; and for CI to 9.3 ±16 % and 9.2 ±16 % increases. The magnitude of the increases in whole brain did not differ between NI and CI nor was the laterality effect significant for the left right brain comparisons.

Effects of the cocaine video with CI and NI on relative metabolic measures

Exposure to the cocaine-cues video in both experimental conditions (NI and CI) significantly increased metabolism in occipital cortex when compared to the baseline condition (no video stimulation). The results for SPM are shown in Figure 2A and B (shown for $p < 0.001$). The occipital activation is consistent with the visual stimulation by the video. In addition, in the CI but not the NI condition, there were also significant decreases in metabolism in limbic regions (bilateral NAcc, right medial orbitofrontal cortex, right anterior cingulate and right posterior insula), and in left fusiform/parahippocampal gyrus when compared with the baseline condition

(Figure 2A and B, Table 1). These findings were corroborated by independently drawn regions of interest analysis (Table 2).

The comparison of the brain images between the two cocaine-cue video conditions showed significant decreases with CI relative to NI in right NAcc, and right medial OFC ($p < 0.005$) (Results for the SPM analyses are shown in Figure 3A, Table 1). There was no region where metabolism was higher for CI than NI. Analyses of independently drawn ROI corroborated these findings (Table 2). The region by hemisphere interaction was not significant neither for the NAcc nor for the medial OFC.

The CI versus NI difference in metabolism in the right NAcc (but not in right medial OFC) was negatively correlated with metabolic differences in the right inferior frontal cortex (BA 44; $r = -0.62$, $P < 0.005$; see Figure 3B).

Correlation between metabolic measures and craving measures

The SPM voxel-wise correlation between metabolism and the self-reports of craving for the NI condition showed a significant positive correlation ($p < 0.001$) with regions in the left and the right hippocampal gyrus (Talairach coordinates: −22, −40, −20 and 20, −54, −12 respectively) (Figure 4A). However, the independently drawn ROI did not corroborate significance for this correlation.

The SPM voxel-wise correlation between metabolism during CI and the changes in the self-reports of craving (CI vs NI) showed a significant ($p < 0.001$) positive correlation with the medial prefrontal cortex (BA 8 BA 10) (Talairach coordinates 6, 34, 58) (Figure 4B). However, the independently drawn ROI did not corroborate significance for this correlation.

The correlations on the changes in metabolism (differences between CI vs NI) in the ROI that differed between CI and NI (right NAcc and medial OFC) and the changes in craving were not significant.

DISCUSSION

Our findings provide evidence that when cocaine abusers purposefully inhibit craving when exposed to conditioned drug-cues, specific changes in brain regions that process reward and prediction of reward occur. Namely when subjects were instructed to inhibit cue-induced craving (CI), metabolic activity decreased in the right NAcc and in the right medial OFC (mOFC) when compared with the condition with no inhibition instructions (NI) or when compared with the baseline condition. The decrease with respect to the baseline condition indicates that the simple inhibitory control manipulation we used was associated with decreased activity in these regions and not just a relative change in activity with respect to the NI condition. In addition we also show that the decreases in right NAcc were correlated with changes in right inferior frontal cortex, which is a crucial brain region for inhibitory control (Aron et al., 2003; Aron et al., 2007) and our findings expand its involvement in the control of the responses to drug-conditioned stimuli.

Involvement of NAcc and mOFC in Conditioned Responses

The decreases in brain activity in NAcc and mOFC is consistent with the known role of these regions in processing conditioned responses (Parkinson et al., 1999; Cardinal et al., 2002). Since metabolic activity in a given brain region primarily reflects activity of its afferents as well as local processing (Schwartz et al., 1979), the metabolic changes in NAcc in the CI condition are likely to reflect activity from DA neurons projecting from VTA and from glutamate neurons projecting from prefrontal cortex (perhaps also amygdala) (Heimer et al., 1995; Yun et al., 2004; Rossetti et al., 1998; Taber et al., Both these systems are likely to

modulate the responses of the NAcc to the 1995). conditioned-cues; the midbrain DA neurons by processing signals predicting reward (Schultz et al., 1997; Bayer and Glimcher, 2005) and the glutamate neurons from prefrontal cortex by processing saliency of the conditioned stimuli (You et al., 2007). The negative correlation between the metabolic changes in NAcc and those in right inferior frontal cortex (BA 44), a crucial region for response inhibition (Aron et al., 2003; Aron et al., 2007), supports the contribution of this region in inhibiting the response of the NAcc to cocaine-cues in the CI condition. The metabolic changes in mOFC are likely to reflect projections both from subcortical (mesencephalon, striato-thalamic, amygdala) as well as gabaergic connections between cortical regions (including lateral OFC and prefrontal cortex) (Kringelbach and Rolls, 2004).

The metabolic decreases in right OFC and NAcc with CI were not correlated with decreases in craving. This could reflect the limited temporal resolution of brain metabolic measurements (averaged activity over 30 minutes). It is likely that the dynamic patterns of activation of NAcc and mOFC are important to the experience of drug craving. Indeed voltammetry studies of brain responses to conditioned-cues reveal that DA changes in NAcc are fast and of short duration (Stuber et al., 2005). Similarly fMRI studies show that the activation in NAcc and OFC during craving are not fixed, but instead show significant fluctuations (Breiter et al., 1997; Risinger et al., 2005). However, others have reported correlations between increases in craving and changes in metabolism as assessed with PET and FDG (Grant et al., 1996). Thus the failure to document an association could also reflect the unique roles that these regions play in the responses to conditioned-cues that may be distinct from the subjective experience of craving (conscious awareness of desiring the drug). Specifically the NAcc has been associated with the motivational drive to procure a reinforcer and its lesion prevents the behavioral responses to cue presentation (Corbit et al., 2001; Hall et al., 2001; de Borchgrave et al., 2002). In contrast the OFC has been associated with predicting the reward value in stimulus-reward associations (Gottfried et al., 2003; Rudebeck et al., 2008). Future studies that assess the motivational valence of drug cues (i.e., how much would the subjects pay to get the drug) may provide better prediction of metabolic changes in right NAcc and mOFC.

The decreases in the medial OFC could reflect deactivation of the medial prefrontal cortical component of the default network (Raichle et al., 2001). Since the medial prefrontal cortex is the component of the default network that is involved with processing the emotional value of internal and external stimuli it could be postulated that its deactivation during CI may be the mechanism by which the drug abusers inhibited craving. Indeed, the negative association between the activation of the right inferior cortex (region involved with inhibitory control) and the deactivation of the mOFC (region involved with salience attribution) supports this interpretation. This would imply that during craving the prefrontal component of the default network, which processes interoceptive signals is activated and that cognitive inhibition deactivates it.

Metabolic Decreases in Right Hemisphere with CI

The normalized metabolic measures showed that when compared with baseline CI resulted in relative decreases in right NAcc, right medial OFC, right ventral CG (BA 32, BA 25), and right insula (BA 13). The decreases in right CG (region involved with salience attribution) (Hare et al., 2008) and right insula, (region involved with interoception including awareness of craving) (Naqvi and Bechara, 2009) with CI, suggests that both the alteration in salience to the cues and in interoceptive awareness were involved in the cognitive inhibition of craving. The predominant location of the effects of CI to the right hemisphere is consistent with imaging findings that suggest inhibitory mechanisms (including emotion suppression) are predominantly lateralized to the right hemisphere (Garavan et al., 1999; Aron et al., 2004; Depue et al., 2007). However, since the region by hemisphere effect was not significant we

can not rule out that low statistical power rather than a true laterality effect is responsible for the lack of significant effects of CI in left brain regions.

Clinical Implications

The frontal mediation of a neural circuit involved in the craving response provides a target for top-down cognitive interventions that may be therapeutically beneficial. Interventions that strengthen a weakened but still functional fronto-accumbal circuit may increase the ability of cocaine abusers to block or reduce the drug craving response. In most therapeutic programs, interventions are included that help addicted individuals predict exposure to conditioned cues, but the emphasis of this strategy is to avoid the anticipated situations. Our findings suggest another strategy would be to train cocaine abusers to use self-instruction to inhibit the craving response when the exposure to conditioned cues occurs. In real-world settings, the addicted person is likely to be exposed to conditioned drug-cues that are unexpected as well as expected. Since exposure is likely even when avoidance is attempted, the acquisition of the ability to exert cognitive control may decrease relapse rates. Our findings (and that of others) identify the frontal cortex as a target region for strengthening inhibitory control (Friedman and Miyake, 2004). Indeed addicted individuals exhibit impairment in response inhibition (Chambers et al., 2009) and research suggests that this may operate as a bidirectional etiological factor, since chronic drug use can impair response inhibition but also impulsivity can predispose to drug addiction (Verdejo-Garcia et al., 2008). Findings from a recent imaging study showing that an individual's level of intelligence influenced the strategy used to perform cognitive tasks (Graham et al., Epub ahead of print) highlights the importance of tailoring cognitive interventions to control craving to an individual's cognitive capacity.

Our addicted subjects reported a decrease in craving in the CI compared to the NI condition, but there was no difference in the cardiovascular response in these two conditions. This indicates that there is dissociation between the autonomic responses to cocaine-cues and the subjective awareness of craving. For the experimental conditions of our study, the autonomic responses were not amenable to the simple manipulation of cognitive control. Further work is required to assess if it is possible to train an addicted individual to alter these autonomic response.

Study Limitations

In this study we did not find a correlation between the changes in metabolism and the changes in craving using a paradigm that we had shown resulted in significant increases in dopamine in striatum that were associated with increases in drug craving (Volkow et al., 2006). Thus the failure to see activation of the craving network and correlated behavioral changes is unlikely to reflect the inadequacy of the paradigm but rather that the changes in brain metabolism, which average activity over 30 minutes may lack the temporal sensitivity to identify the dynamic changes in brain activity elicited by cue exposures as detected with fMRI (as discussed above). Another limitation is the use of an experimental setting to assess the effects of purposeful control on craving, which may not faithfully mimic cue-elicited craving in real-world situations. An unavoidable limitation is that the experimental manipulation of cognitive control does not allow for the evaluation of the purposeful control manipulation under double-blind conditions. We cannot rule out the possibility that the changes in the subjective reports of craving may be attributed to the demand characteristics of the study, but the significant effects for objective measures of brain activation (decreases in activity in right NAcc and mOFC) suggest otherwise. Another limitation was that we did not record eye tracking nor did we require responses during the video exposure that would have assured us that the subjects were attending to the video. However the fact that the subject's heart rate and blood pressure increased while they watched the cocaine-cues video indicates that the subjects were attending to the stimuli.

Summary

This study suggests that when cocaine abusers report purposeful control over craving when exposed to conditioned cocaine-cues, specific changes in regional brain metabolism occur, including decreases in metabolic activity in right NAcc and mOFC that are modulated in part by the right inferior frontal cortex. The identification and improved understanding of the underlying brain circuitry of cue-elicited craving may direct therapeutic interventions that could strengthen these responses and help prevent relapse.

Acknowledgments

We thank David Schlyer, David Alexoff, Don Warner, Paul Vaska, Colleen Shea, Youwen Xu, Lisa Muench, Barbara Hubbard, Pauline Carter, Karen Apelskog, Linda Thomas for their contributions. Research supported by NIH's Intramural Research Program (NIAAA), by DOE (DE-AC01-76CH00016).

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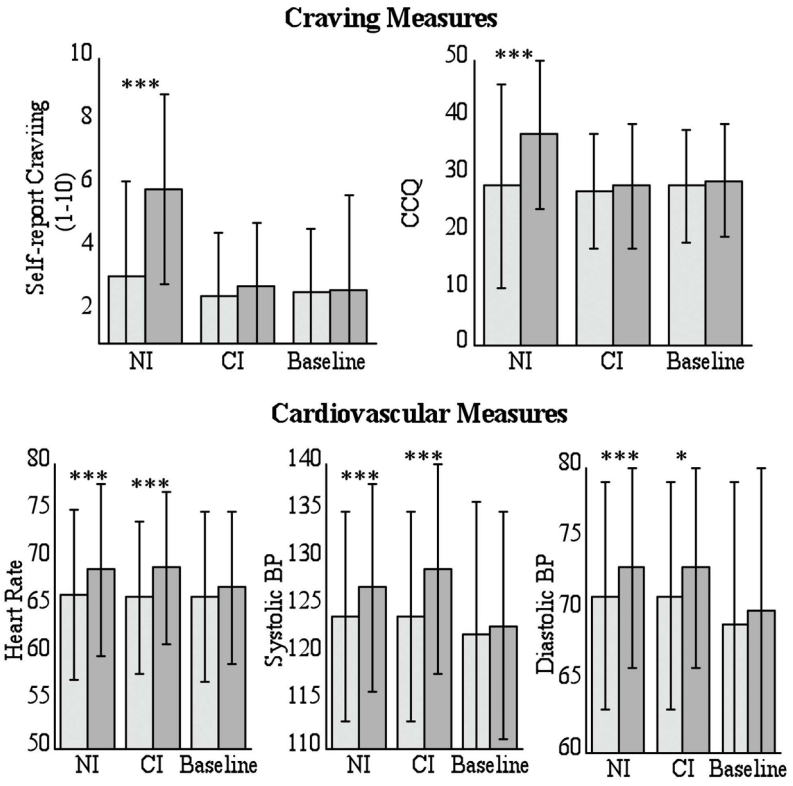
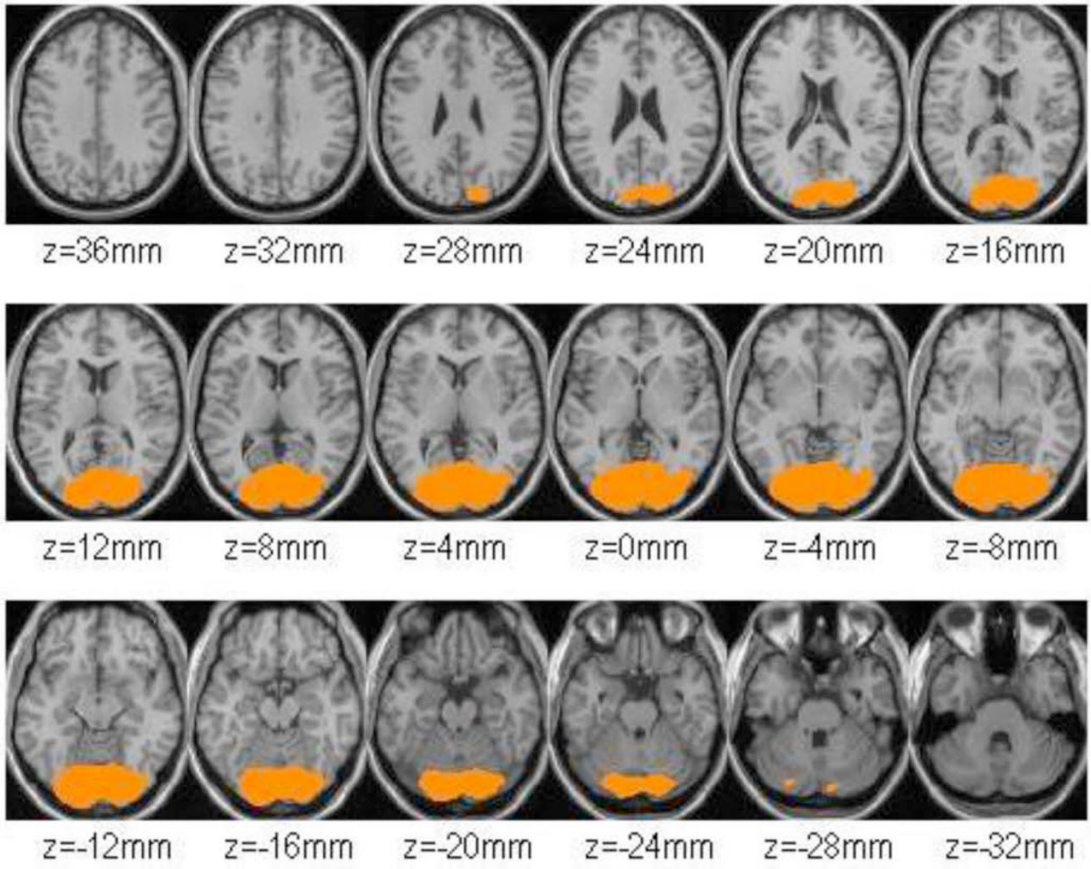


Figure 1.

Measures for self-reports of craving and for the Cocaine Craving Questionnaire and for the cardiovascular measures (heart rate, systolic and diastolic blood pressure) obtained prior to (lighter bars) and 30 minutes after initiation of the video (darker bars) or for the corresponding time period for the baseline. Craving measures were higher for cocaine-cue no inhibition (NI) than for cognitive inhibition (CI) or for the baseline condition whereas cardiovascular measures significantly increased for both NI and CI but not for baseline. *** $p < 0.005$, * $p < 0.05$.



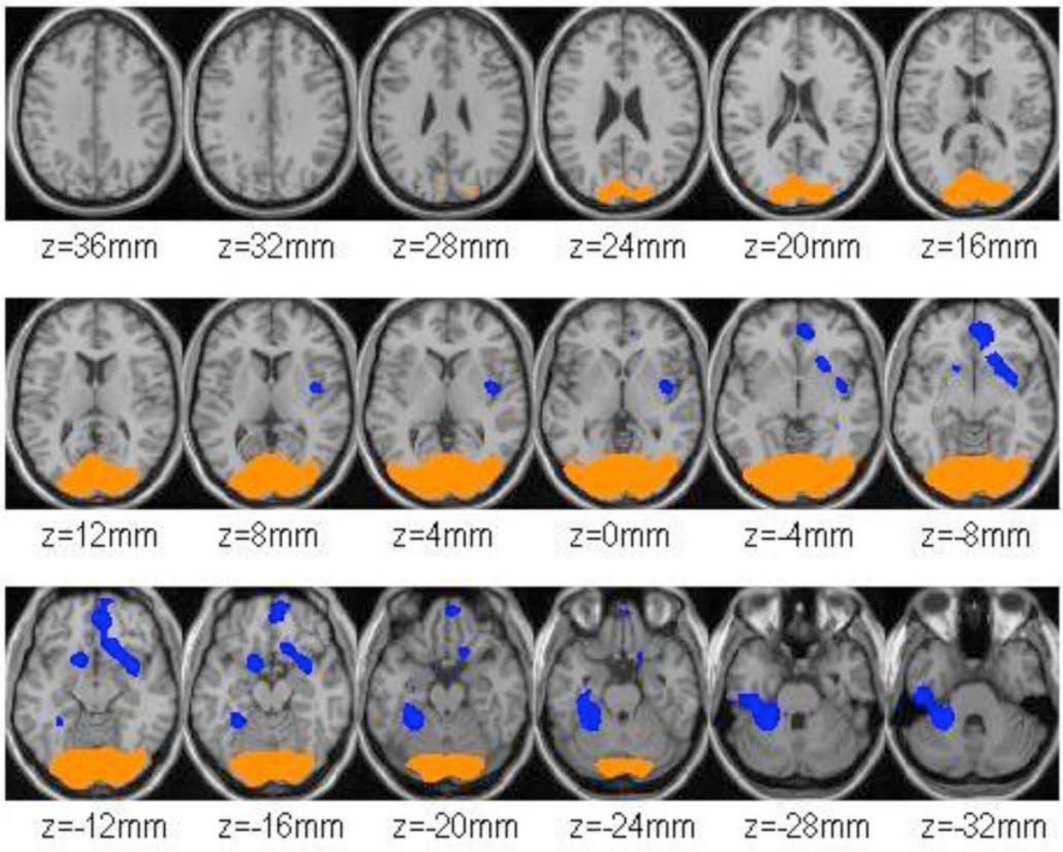


Figure 2.

A. SPM results for the comparison of the baseline (no video) versus the cocaine-cue video with no-inhibition (NI) conditions. **B**. SPM results for the comparison of the baseline versus the cocaine-cue video with cognitive inhibition (CI) conditions. The cocaine-cue video for both conditions induced relative increases in metabolism in occipital cortex. In addition the cocaine-cue video with CI induced relative decreases in right cingulate gyrus, right medial orbitofrontal cortex (OFC), right and left nucleus accumbens (NAcc), right posterior insula, and left fusiform gyrus (BA 28, BA 36). Significance corresponds to $p < 0.001$ not corrected, cluster > 100 voxels.

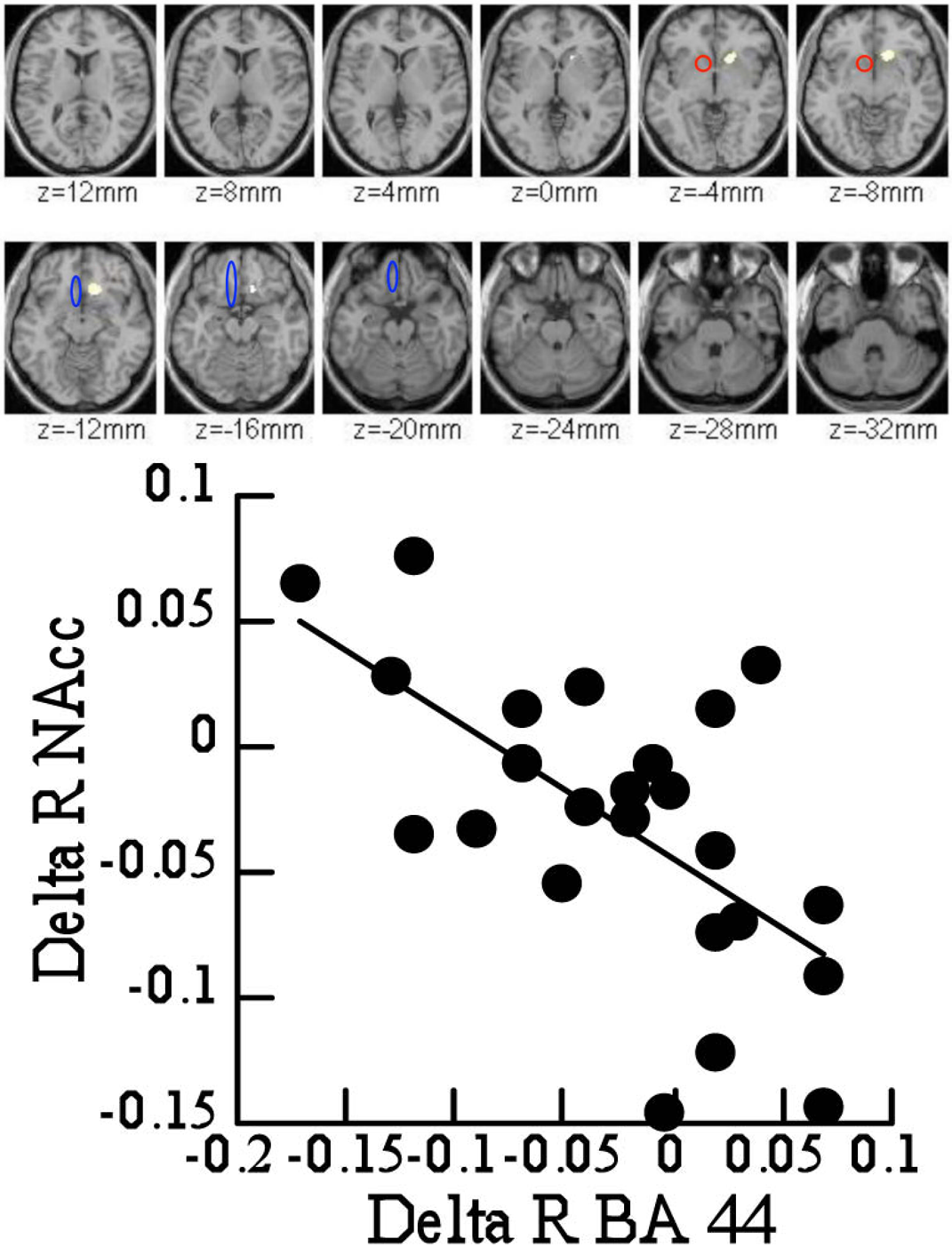


Figure 3.

A. SPM results for the comparison of the cocaine-cue video with cognitive inhibition (CI) versus the cocaine-cue video with no-inhibition (NI) and location of the ROI for the NAcc (red circles) and the medial OFC (blue oval) shown for the contralateral hemisphere. The SPM showed significantly lower metabolism in right NAcc and right medial OFC (mOFC) in CI when compared with NI, which was corroborated by ROI analysis. There were no areas where metabolism was higher for CI versus NI. Significance corresponds to $p < 0.005$ not corrected,

cluster > 100 voxels. **B.** Regression slope for the differences in metabolism between CI versus NI in right NAcc and in right inferior frontal cortex BA 44 ($r = -0.62$, $p < 0.005$).

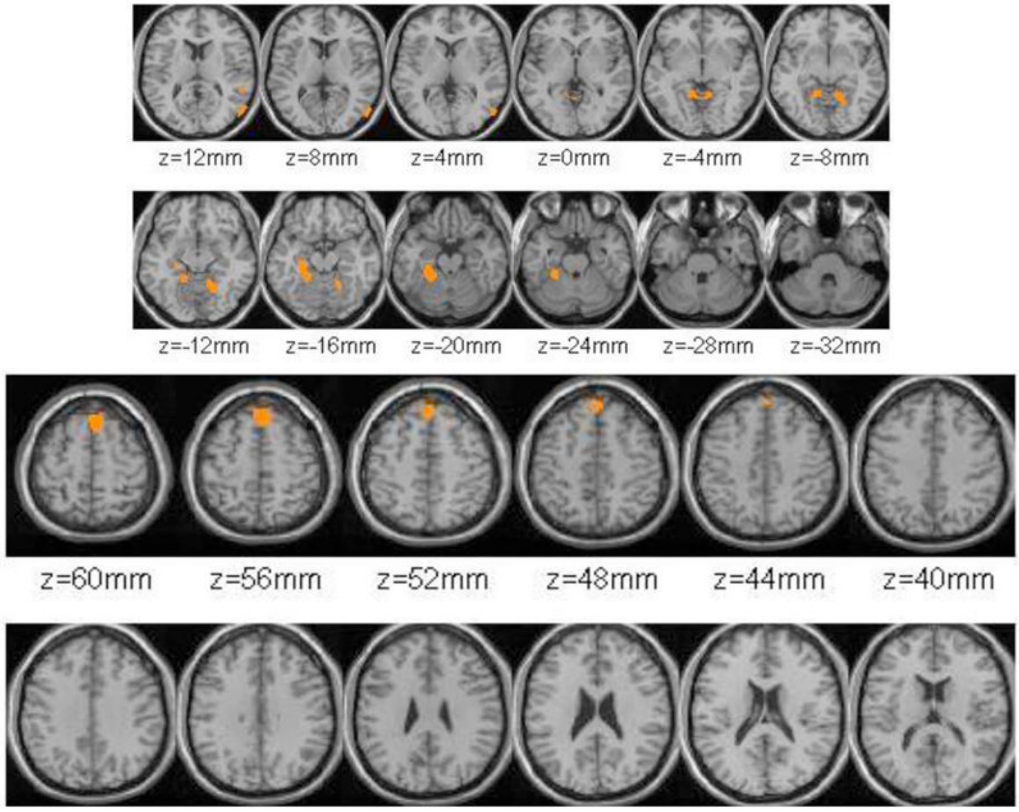


Figure 4.

A. SPM results for the voxel-wise correlations between metabolic activity during NI and the self-reports of craving ($p < 0.005$, cluster size > 100 voxels). B. SPM results for the voxel-wise correlation between metabolic activity during CI and the changes in the self-reports of craving (CI vs NI).

Table 1

Areas where SPM 99 showed significant differences between the baseline and the cocaine-cue condition with no inhibition (NI) and with cognitive inhibition (CI) and for the comparisons between the cocaine-cue CI versus cocaine-cue NI. We also show the size of the clusters (number of voxels), the Brodmann areas (BA) included in the clusters, the location of the center of the cluster with respect to the Talairach coordinates (x= left-right direction, y = anterior-posterior direction and z = top-bottom direction) and the significance levels for the cluster (T). The SPM level of significance was $p < 0.001$ (uncorrected, cluster > 100 voxels) for comparisons with the baseline condition and $p < 0.005$ (uncorrected, cluster > 100 voxels) for comparison between CI versus NI. L = left, R = right, OFC = orbitofrontal cortex, NAcc = nucleus accumbens.

Cocaine-Cues NI versus Baseline		**# Voxels**	**x**	**Y**	**z**	**T**
Cluster #1	*Increase metabolism*	12 706	4	−80	−4	7.7
L Occipital	BA 17, 18, 19					
R Occipital	BA 17, 18, 19					
Cocaine-Cues CI versus Baseline						
Cluster # 1	*Increase metabolism*	12630	−8	−74	−2	6.8
L Occipital	BA 17, 18, 19					
R Occipital	BA 17, 18, 19					
Cluster # 2	*Decrease metabolism*	1582	−28	−42	−30	4.9
L Fusiform	BA 28, 36					
Cluster # 3	*Decrease metabolism*	1709	8	48	−8	4.1
R Cingulate gyrus	BA 32					
R Insula	BA 13					
R medial OFC	BA 25					
R Ventral Striatum	NAcc					
Cluster # 4	*Decrease metabolism*	216	−12	12	−12	3.8
L Orbitrofrontal	BA 25					
L Ventral Striatum	NAcc					
Cocaine-Cues CI versus NI						
Cluster #1	*Decrease metabolism*	492	22	20	−10	3.5
R Medial OFC	BA 25					
R Ventral Striatum	NAcc					

Table 2

Relative metabolic measures from the region of interest (ROI) analysis done to corroborate the findings identified by SPM and results for repeated ANOVA (F and p).

	Baseline	Cocaine-cue NI	Cocaine-Cue CI	Repeated ANOVA F and p
R Cingulate	1.45 ±0.09	1.42 ±0.09*	1.39 ±0.09*	F = 8, p < 0.001
R Medial OFC	1.29 ±0.20	1.29 ±0.13	1.22 ±0.15*†	F = 3.8, p < 0.03
R Insula	1.29 ±0.15	1.26 ±0.15	1.23 ±0.16*	F = 3.3, p < 0.05
R NAcc	1.24 ±0.10	1.23 ±0.13	1.20 ±0.14*†	F = 4.8, p < 0.05
L NAcc	1.34 ±0.10	1.33 ±0.13	1.30 ±0.13*†	F = 5.5, p < 0.01
L Fusiform	1.33 ±0.11	1.26 ±0.12*	1.21 ±0.09*	F = 10, p < 0.0005
L Occipital	1.32 ±0.08	1.43 ±0.08*	1.44 ±0.08*	F = 39, p < 0.0001
R Occipital	1.31 ±0.08	1.46 ±0.08*	1.45 ±0.07*	F = 64, p < 0.0001

*Post hoc t tests showing significant differences with respect to the baseline condition p< 0.05.

†Post hoc t tests showing significant differences between the cocaine-cue video with no-inhibition (NI) versus the cocaine-cue video with cognitive inhibition (CI) p< 0.05.