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Neural correlates of high and craving during cocaine self-administration using BOLD fMRI

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Modern theories of drug dependence hold the hedonic effects of drug-taking central to understanding the motivation for compulsive drug use. Previous neuroimaging studies have begun to identify brain regions associated with acute drug effects after passive delivery. In this study, a more naturalistic model of cocaine self-administration (SA) was employed in order to identify those sites associated with drug-induced high and craving as measures of reward and motivation. Non-treatment seeking cocaine-dependent subjects chose both when and how often i.v. cocaine administration occurred within a medically supervised SA procedure. Both functional magnetic resonance imaging (fMRI) data and real-time behavioral ratings were acquired during the 1-h SA period. Drug-induced HIGH was found to correlate negatively with activity in limbic, paralimbic, and mesocortical regions including the nucleus accumbens (NAc), inferior frontal/orbitofrontal gyrus (OFC), and anterior cingulate (AC), while CRAVING correlated positively with activity in these regions. This study provides the first evidence in humans that changes in subjective state surrounding cocaine self-administration reflect neural activity of the endogenous reward system.
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Introduction

Understanding why humans compulsively seek and self-administer certain drugs remains central to developing adequate treatments for drug abuse. It has long been postulated that the positive affective property of cocaine is responsible for at least the initiation and perhaps the maintenance of drug taking (Wise and Bozarth, 1981). It has also been suggested that an addict's hedonic set-point changes over time such that drug-taking behavior reflects an attempt to alleviate a newfound negative state (Koob and Le Moal, 1997; Kreek and Koob, 1998). Another theory is that the desire to use drugs becomes, with experience, independent from the reinforcing outcome (Robinson and Berridge, 1993). These theories are predominately based on animal models of drug dependence. To contribute to the understanding of addiction, we present a naturalistic human model of self-administration (SA) behavior demonstrating the correlation of real-time subjective state reports with neural activation.

Previous human brain imaging studies have identified sub-cortical and cortical effects of acute cocaine administration, generally implicating limbic, orbitofrontal and striatal regions (Breiter et al., 1997), dopamine (DA) transporter binding (Logan et al., 1997), blood flow (Pearlson et al., 1993; Wallace et al., 1996), and D2 receptor availability in abusers (Volkow et al., 1997a,b). A generalized decrease in global metabolism has also been reported after an acute cocaine injection in polydrug abusers (London et al., 1990). One must, however, extrapolate these findings to the operant behavioral condition when abusers take drug. To do so, one must assume that a single, blinded, passive delivery of cocaine is significantly similar to an addict's repeated drug use on the street.

However, the preclinical literature suggests that neural activity within the mesocorticolimbic (MCL) DA system and related regions depends not only on the direct pharmacological actions

of the drug but also the behavioral and motivational state of the animal during drug administration. For example, using a yoked three-animal paradigm, one rat passively receives i.v. cocaine dependent upon its yoked peer's SA schedule. In this instance, the animal actively self-administering cocaine demonstrates a significantly greater increase in NAc DA levels than either the saline or passive drug yoked animal (Hemby et al., 1997). Similar results have been reported for amygdala DA and serotonin levels (Wilson et al., 1994). Such active/passive distinctions are especially significant since the MCL DA system is implicated during reinforcing stimulus processing (Wise and Rompre, 1989). As in the animal models, such differences are also likely in the human response to drugs, where a complex motivational context intertwines with addiction behavior.

A remaining question, one that is unanswerable from the animal literature, is the relationship between cocaine-induced neural activity and the subjective effects of cocaine. Previous human SA experiments (Fischman and Schuster, 1982; Foltin and Fischman, 1992, 1996; Ward et al., 1997) have used the ability of humans to report their subjective states, but have opted for self-report instruments that take several minutes to complete. These are, unfortunately, impractical for assessing moment-to-moment fluctuations in subjective state within a cocaine paradigm. Understanding this limitation and complementing the temporal resolution of blood oxygenation level-dependent (BOLD) fMRI, we developed a system of once per minute subjective state self-rating throughout a 1-h i.v. cocaine SA session.

To directly test the hypothesis that MCL regional neural activity correlates with self-reports of the subjective effects of cocaine and is distinct from that previously seen following single, passive cocaine administration, experienced cocaine users were allowed to self-administer intravenously delivered cocaine during fMRI. Throughout the SA scanning session, volunteers were asked to rate their behavioral responses along four axes: HIGH, CRAVING, RUSH, and ANXIOUS. In this design, we elucidate the minute by minute relationship between the subjective effects of self-administered cocaine and changes in neural activity. The utility of this study is that grounded in the current knowledge of the regional neurobiology of identified brain sites, better pharmacological and/or behavioral therapeutic strategies for drug dependence may be developed.

Materials and methods

Subject selection

Eight right-handed (Oldfield, 1971) males meeting DSM-IV criteria for cocaine dependence were recruited from the general population via local advertisements [mean ± SD (range) age: 36 ± 6.8 (23–41) years; 13 ± 1.1 (12–14) years education, and 11.2 ± 3.5 (6–15) years experience smoking crack cocaine]. All were exclusively crack cocaine users, 1-pack/day cigarette smokers, and none met criterion for any other Axis I or II psychiatric disorder. Subjects underwent a thorough medical and psychiatric screening that included full blood and urine chemistries and a 12 lead EKG to exclude potentially jeopardous medical conditions. Subjects were also excluded if they were positive for HIV, hepatitis, had concomitant or history of other drug dependence other than nicotine or had an IQ less than 80. All subjects were counseled regarding the dangers of cocaine use and offered but declined treatment. After complete description of the study, subjects

provided written informed consent to the MCW IRB approved protocol. Two subjects, however, displayed unacceptable head motion leaving six subjects for the imaging and behavioral analysis (see Image Post-Processing below).

Participants were 8–48 h abstinent from cocaine by self-report and positive for cocaine only (Triage®) upon admission. They performed the cocaine SA procedure on two occasions. The first was within the MCW General Clinical Research Center where they learned the procedure and experienced the drug in a controlled setting and where any emergency interventions could be applied in a timely fashion. The procedure was repeated approximately 1 week later during fMRI scanning. An Advanced Cardiac Life Support trained physician and emergency equipment were present and available at all times.

Self-administration procedure

Subjects had an i.v. catheter inserted into the left forearm for drug delivery and were given a two-button MR compatible joystick in their right hand. EKG and heart rate (HR) were monitored continuously and an auto-inflatable cuff monitored blood pressure at 2-min intervals. Prior to the experiment, subjects were instructed to press the button when they wanted cocaine and were informed they would receive the drug unless it was currently being administered or deemed medically unsafe by the monitoring physician. Unknown to subjects, cocaine was only made available on a fixed interval 5-min schedule (FI 5-min); they could receive cocaine no more frequently than once every 5 min. The cocaine dose (20 mg/70 kg injected over 30 s) and FI 5-min timing were chosen to (1) approximate the naturalistic pattern of cocaine SA, (2) enable subsequent comparison with previous non-imaging human SA studies (Fischman and Schuster, 1982; Fischman et al., 1990; Foltin and Fischman, 1992), (3) maintain subject safety, and (4) enable adequate time for image acquisition between drug injections.

Prior to cocaine availability, a 5-min baseline period allowed subjects to acclimate to performing the continuous behavioral ratings (described below). Subjects were then presented an on-screen "Drug Available" message indicating that SA could be initiated at any time and which permanently disappeared with the first SA request (button press); no further external signal of drug availability or delivery was given. After each SA, subsequent injection requests were denied until the obligatory 5-min lockout interval had passed. The physician denied individual SA requests if the HR exceeded 131 beats/min (bpm,) diastolic blood pressure (DBP) was greater than 100 or systolic blood pressure (SBP) was greater than 170 mm Hg. For safety reasons, subjects were limited to 6 cocaine injections over the course of the 1-h data acquisition session (i.e., ≤120 mg/70 kg cocaine). Intervention protocols were in place and previously rehearsed in the event of medical complications. After each procedure, subjects underwent a brief physical exam and a second 12 lead EKG. They were discharged from 2 to 12 h post-procedure and only after their cardiovascular parameters returned to baseline, they were no longer experiencing any acute drug effects and they reported no residual drug craving.

Behavioral ratings and analysis

Subjects were instructed to rate their current level of high (while viewing the word "HIGH" through prism glasses on a back-projected screen), rush ("RUSH"), craving ("CRAVING"), and anxiety ("ANXIOUS") once every minute throughout the entire

experiment. They were instructed to use their common "street" definitions for these terms. Questions cycled in a fixed order and remained on screen until answered or for a maximum of 15 s. Subjects recorded their behavioral responses on a visual analog rating scale (VAS) by using a joystick to move a tab along a horizontal bar with anchors "Least Ever" and "Most Ever" at extrema. A joystick button was then pushed when the desired location was reached. The tab started at the subject's previous rating for each construct to facilitate comparison of the current state versus 1 min earlier. Since subjective experience ratings are not likely to be equivalent across individuals, it was assumed that changes in ratings were proportional. Thus, for each item, VAS scores were normalized relative to the minimum and maximum rating for each subject ($Y = [(Obs-Min)/(Max-Min) \times 100]$) and parsed into four 1-min bin periods before and after each SA event. Behavioral data were analyzed with a 3-factor, within-subject ANOVA design, which included the factors of Injection Number (1–5), Phase (pre- vs. post-injection), and Rating Time (four 1-min rating episodes, 1 min apart). Since only 2 subjects took all 6 possible injections, the first 5 injections were analyzed for both the fMRI and behavioral data. Significant interactions were followed by trend analysis at the pre- and/or post-injection phases.

Image acquisition

All experiments were performed on a GE 1.5 T Signa scanner (General Electric Medical Systems, Waukesha, WI) using a local gradient coil designed specifically for rapid gradient switching (Wong et al., 1991). A high-resolution SPGR sequence produced contiguous 1.1 mm thick axial anatomic images for subsequent spatial normalization and superimposition of functional signal (time to repeat (TR) of 24 ms, echo time (TE) of 5 ms and flip angle of 45°). These images were gathered immediately prior to the SA scan initiation (i.e., subjects began the SA protocol approximately 30 min after entry into the scanner). A whole brain gradient-echo, echo-planar image (EPI) pulse sequence was used with a TE 40 ms and TR 10 s. A 64×64 image was acquired with a field of view of 24 cm (3.75 mm in-plane resolution) in up to 19 contiguous 7 mm sagittal slices. Two sequential 30-min scans were acquired during each SA session, with a 1- to 2-min time-out for data storage.

Image post-processing

The AFNI software package (Cox, 1996) was used for all data analyses. Time series images were first registered to minimize motion artifact, concatenated across consecutive acquisitions to create one continuous time-course, and Gram-Schmidt orthogonalized to a step function to eliminate discontinuities during data acquisition breaks. Image series were visually examined for motion artifacts via cine viewing after 3D registration. Two of the 8 subjects had residual head motion (>3.75 mm movement in any direction) and were eliminated from further analysis.

Image correlation with behavior

Behavioral ratings were interpolated using a cubic spline and the interpolated curve was used to obtain the behavioral point corresponding to the 10-s image acquisition time. This on-line measurement of "state" was then used as a reference waveform in a voxel-wise cross-correlation analysis with the whole brain BOLD signal time-course (Bandettini et al., 1993). Voxel correlation

coefficients were transformed to z scores, spatially normalized (Talairach and Tourneaux, 1988) to 1 mm³ resolution and blurred using a 3-mm RMS Gaussian kernel. A t test of the z score for each voxel against the null hypothesis (of no significant correlation with the behavioral rating) was performed for each of the four behavioral measures and thresholded at $P \leq 0.01$. After individual voxel thresholding, a cluster-based analysis was incorporated (Forman et al., 1995) to account for multiple comparisons, assuming that true regions of activation will occur over contiguous voxels. Monte Carlo simulations revealed that a cluster size threshold of 185 mm³ in combination with the voxelwise threshold of $P \leq 0.01$ produced an overall alpha of $P \leq 0.05$. Since the OFC and NAc are located in regions of high BOLD contrast inhomogeneity, raw BOLD signal was examined in every subject to establish that signal was present and not near the acquisition limit (>1 voxel from edge of signal dropout).

With 6 subjects, we have a power of 80% to detect an expected effect size of 0.75% for an alpha level of 0.05 (Desmond and Glover, 2002). This is due to the relatively greater BOLD signal change (contrast) in pharmacological studies as compared to cognitive probes and the substantially smaller variance observed in within-subject studies. This allowed us to use the conservative approach of not smoothing the data over time, which can bias the correlation coefficients upward by as much as a factor of two.

Results

All subjects tolerated the SA protocol without any untoward effects or complications and rapidly learned the SA procedure. As expected, the greatest change in cardiovascular parameters occurred following the first cocaine injection. Although rapid tolerance to the cocaine-induced tachycardia and hypertension was seen with successive cocaine injections (Fig. 1), HR and BP levels remained elevated over baseline values throughout the session (mean increases of 10.5 ± 12 mm Hg SBP, 6.6 ± 8.2 mm Hg DBP, 10 ± 8.5 mm Hg MAP, and 16 ± 9.7 bpm HR from baseline to the end of the 1-h procedure).
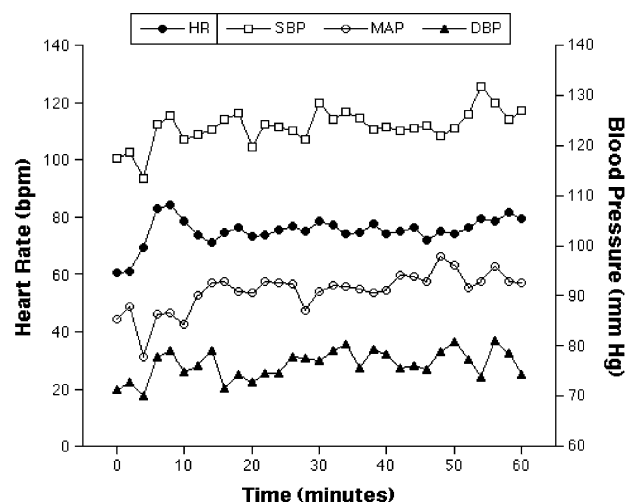

Fig. 1. Cardiovascular effects of cocaine self-administration. Mean heart rate (HR) in beats per minute, systolic (SBP), mean arterial pressure (MAP), and diastolic (DBP) in mm Hg for all six subjects over the 60-min self-administration procedure.

Within the FI 5-min schedule, subjects administered an average of 4.5 injections/session (range 2–6), for a group total of 28 injections out of a theoretical maximum of 36 with a mean inter-injection interval of 7.4 (±3.5 SD) min. Subjects one through six injected 6, 6, 6, 5, 3, and 2 times during the 1-h scanning session, respectively. The sixth injection of subject three occurred immediately prior to session termination and was excluded from analysis. Injection requests were denied a total of only 3 times in 2 subjects when predetermined physiological parameters were exceeded mid-procedure. SA was permitted to continue 3 min later when parameters again fell within prescribed limits. Due to response recording error, button press data were not analyzable for the 3 subjects who took less than six injections. Subjects one through three pressed 130, 92, and 87 times, respectively. Fig. 2 is the first 45 min of the button press record for Subject #2 and is representative of the four subjects (6, 6, 6, 5) with the high press pattern. This subject self-administered all 6 injections within the first 35 min of the scanning period. For this group, their injection request behavior during MR scanning was consistent with other fixed-interval models of SA behavior.

Behavioral effects of cocaine SA

For each of the four constructs, changes in behavioral ratings followed the injection sequence in a clearly reproducible pattern. Examples from one subject are illustrated in Fig. 3. HIGH ratings approximated zero prior to the first injection and reached peak levels for each interval 1–3 min after cocaine SA. Over the course of the entire SA session, the HIGH rating tended to decline near the minimum value just prior to each subsequent injection. Not unexpectedly, RUSH ratings tended to parallel those of HIGH. In regards to CRAVING, baseline ratings were variable between subjects. Following the first injection, CRAVING ratings uniformly decreased, reaching a minimal level about 2–3 min after drug SA, but then increased prior to subsequent injections. Ratings of ANXIOUS were the least consistent, both within- and between-subjects, although they tended to increase prior to injections, peaked within seconds of cocaine delivery and fell immediately afterwards. These cyclic drug- and time-dependent behavioral patterns were consistently seen when averaged across all subjects.

Orderly effects of HIGH and CRAVING ratings were demonstrated relative to injection progression (Fig. 4). Not unexpectedly, there was an increase in peak HIGH with injection number, reaching a maximum after the fourth injection (Fig. 4A). Between the peak from each injection to the following one, subjects rated a decreasing value for HIGH over this interval, moving toward but not as low as the pre-injection HIGH rating. However, there was an increase in the slope of this decline as the subjects progressed through the injection series. CRAVING exhibited an increase prior to injection, however, unlike HIGH, post-injection CRAVING demonstrated no trend to be either suppressed or increased over time (Fig. 4B).

Using the previously described behavioral ANOVA, HIGH ratings were significantly greater after than before injection ($F_{[1,5]} = 39.94$, $P = 0.0015$, Fig. 4C) and were significantly different among the injections ($F_{[4,20]} = 11.04$, $P < 0.0001$, Fig. 4A) and among the individual rating time points ($F_{[3,15]} = 3.62$, $P = 0.04$). The significant Rating Time × Phase interaction ($F_{[3,15]} = 7.85$, $P = 0.002$) shows that there are different rates of change (slope) before and after injection; the Injection x Phase interaction ($F_{[4,20]} = 4.04$, $P = 0.01$) show that there are smaller differences among the injections after SA compared to before SA. Before SA, a linear trend analysis for Time showed that later injections were associated with greater overall HIGH ratings ($F_{[1,5]} = 38.25$, $P = 0.0016$) and a linear Injection by linear Rating Time interaction showed larger decreases in HIGH scores as rating time approached the SA ($F_{[1,5]} = 51.54$, $P < 0.0008$). More precisely, the slope of pre-injection HIGH decreased from 0 to -3.5 to -7.4 to -7.7 to -16.4 from injections one through five, respectively, indicating that pre-injection HIGH ratings tended to descend more rapidly with each successive injection. In contrast, post-injection increases in the quadratic trend (inverse-U) in HIGH ratings occurred with increasing injection number ($F_{[1,5]} = 27.37$, $P = 0.0034$), with the exception of injection 5 and, to a lesser extent, injection 3, deviating from the quadratic main effect pattern. Similarly, post-injection peak HIGH tended to significantly increase across injections ($t = 4.41$ with 60 d.f., $P < 0.0001$). In
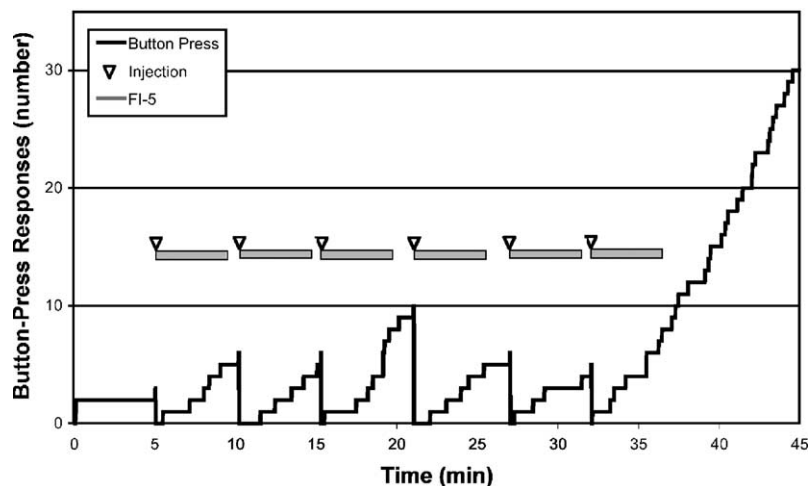

Fig. 2. Cumulative button-press responses during each injection interval. Injection attempt (button-press) behavior from one representative subject is shown for the first 45 min of the scanning session. The count begins at zero and increments with each button press until drug injection. Each drug injection (triangle) is followed by the FI-5 lockout period (gray bar). After each injection, the counter is reset to zero (vertical lines) for clarity. This subject self-administered all 6 injections within the first 35 min of the scanning period.
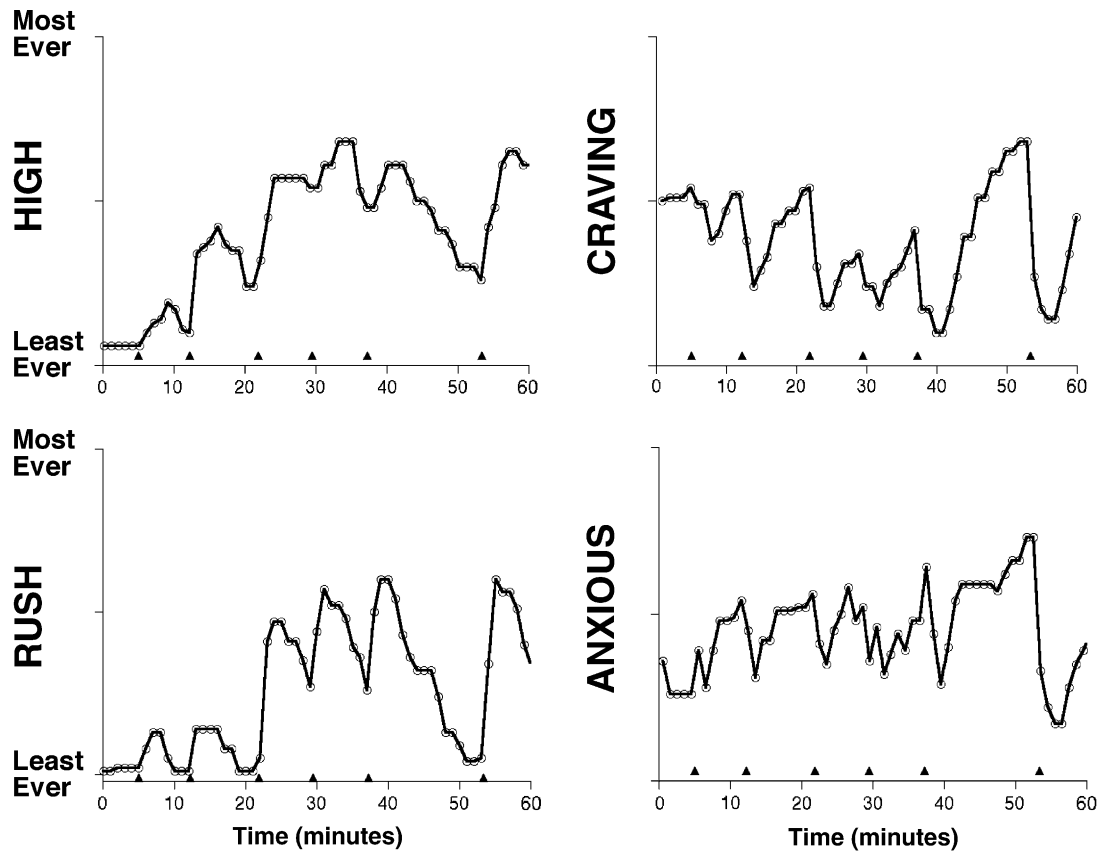
Fig. 3. Behavioral effects of cocaine self-administration. Behavioral data from subject number two performing the visual analog scale ratings of (clockwise from top left) HIGH, CRAVING, ANXIOUS, and RUSH during a 60-min cocaine self-administration session. Solid lines illustrate cubic spline interpolations of ratings acquired each minute, with an open circle at the timepoint of rating. Arrowheads indicate cocaine injection times.

sum, HIGH ratings, which reached their peak 2–3 min after SA, successively increased with each cocaine injection for the first 4 injections. Further, the rate at which they returned towards baseline increased as a function of repeated injections.

Collectively, subjects rated CRAVING as maximal just prior to requesting a cocaine injection, with drug administration resulting in a rapid decrease in CRAVING ratings (Fig. 4C). The 3-factor repeated-measures ANOVA revealed that mean CRAVING ratings were significantly greater before than after injection ($F_{[1,5]} = 129.61$, $P < 0.0001$) and were significantly different among the individual rating time points ($F_{[3,15]} = 13.22$, $P = 0.0002$, Fig. 4B). While the main effect of Injection Number, the Injection Number × Phase, and the Injection Number × Rating Time interactions were not significant, the Phase × Rating Time ($F_{[3,15]} = 16.30$, $P < 0.0001$) and the 3-way interaction term was significant ($F_{[12,60]} = 3.45$, $P = 0.0007$). Pre-injection analyses of trend in Injection Number showed that later injection numbers were associated with lower overall CRAVING ratings ($F_{[1,5]} = 25.11$, $P = 0.0012$) and linear × linear trend tests showed greater increases in the slope of the CRAVING scores as rating time approached the SA response ($F_{[1,5]} = 43.91$, $P = 0.0012$). In other words, as the injection number increased, the rate of change (slope) in CRAVING became more steeply upward, while the rate of change (slope) in HIGH became more steeply downward. As expected, post-injection decreases in the quadratic U-shaped CRAVING ratings occurred with increasing injection number ($F_{[1,5]} = 25.21$, $P = 0.004$); only injection five deviated from the quadratic main effect pattern ($F_{[12,60]} = 1.97$, $P = 0.043$). There

was, however, no trend of successive injections suppressing craving ($F_{[1,5]} = 2.66$, $P = 0.16$), nor did the post injection minimum CRAVING change significantly with repeated injections ($t = -1.05$ with 60 d.f., $P = 0.3$). Except for injection five, CRAVING ratings tended to peak 1 min prior to each injection and then immediately decreased to nadir in 2 min; they rose again before the subsequent injection. Group behavioral ratings of ANXIOUS and RUSH relative to each injection were quite variable within and between subjects and were not further analyzed.

Neural correlates of cocaine's subjective effects

Based upon a voxel-wise whole brain correlation analysis of the entire 1 h SA session BOLD time-course data with individual behavioral ratings, a number of brain regions correlated with ratings of HIGH ($n = 19$), followed by those of CRAVING ($n = 13$), RUSH ($n = 6$), and ANXIETY ($n = 3$), with the majority of these significant clusters localized to the right hemisphere (Table 1). Several clusters significantly correlated with self-reports of both HIGH and CRAVING, and as these constructs tended to be inversely related, an inverse relationship was also seen between the constructs and brain activity.

Structures correlating with HIGH

Several limbic, paralimbic, and mesocortical clusters correlated significantly with HIGH (Table 1, Fig. 5). In general, more inferior limbic and frontal regional activity was negatively related
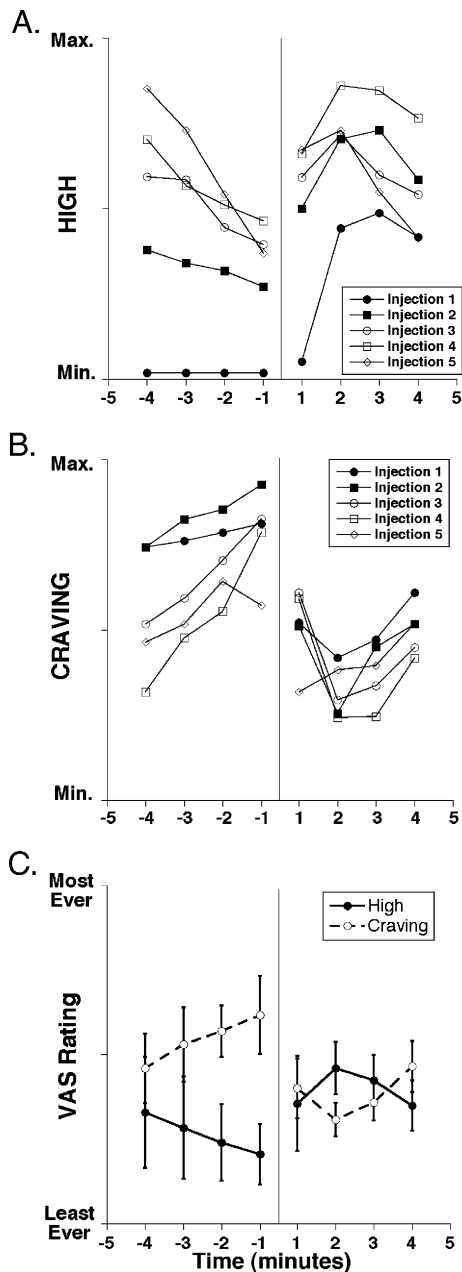
Fig. 4. Group behavioral ratings relative to cocaine injections. (A) Mean HIGH and (B) CRAVING ratings averaged 4 min before and after cocaine injections. For both, data were normalized and are plotted as a function of injection number. (C) Mean ± SEM VAS ratings of HIGH and CRAVING averaged 4 min before and after all 5 cocaine injections for 4 subjects.

to HIGH ratings, whereas BOLD signal in more posterior–superior limbic and motor-related regions was positively correlated with HIGH. The largest negatively correlated clusters were located in the NAc, ventral putamen and AC, extending inferiorly to mesial subcallosal cortex. The ventral putamen activation extended anteriorly into the medial AC and ventrally following the inferior rostral orbitofrontal gyrus, with its most posterior extent ventral to the anterior commissure and lateral to the orbitofrontal radiation of the anterior commissure in a region identified as accumbens centrolateral division (Mai et al., 1997). In order to determine correlation coefficients for specific regional

compartments, this large cluster was subdivided into individual anatomical regions based on the anatomic locations of functional signal prior to further analysis. After subdividing, 8 of the 19 brain regions were negatively correlated with HIGH, including the AC (BA 32), NAc, putamen, inferior frontal–orbitofrontal area, inferior temporal gyrus, precentral gyrus, and cerebellum. In contrast, positive correlations with HIGH were seen in the insula, cingulate gyrus (BA 24), middle frontal gyrus, frontal operculum, red nucleus-substantia nigra, caudate, thalamic pulvinar nucleus, retrosplenial-posterior cingulate, and cerebellar culmen.

Structures correlating with CRAVING

CRAVING correlated positively with neural activity in the AC, NAc, putamen, and inferior frontal–orbitofrontal region, while clusters in these same areas correlated negatively with HIGH (Table 1, Fig. 6). Likewise, negative BOLD correlations with CRAVING were seen in the middle cingulate gyrus (BA24) and pulvinar nucleus while these same regions correlated positively with HIGH. Finally, activity in the superior temporal and the parietal supramarginal gyri only negatively correlated with CRAVING.

Structures correlating with RUSH and ANXIOUS

Subjective ratings of RUSH or ANXIOUS were correlated with relatively few brain regions, although, not surprisingly, several regions correlating with RUSH overlapped with those correlating with HIGH, including the AC, the inferior temporal gyrus, and contiguous portions of the cerebellum. Ratings of RUSH were uniquely and inversely related to BOLD activity in the middle temporal gyrus. Despite high variance, ratings of ANXIOUS were related to two main brain regions, the left and right precuneus (positive correlation) and the middle temporal gyrus (negative correlation).

Discussion

Using a more naturalistic laboratory model of human drug abuse than previously available, this study provides the first direct evidence that the same MCL regions implicated in preclinical models of cocaine reinforcement (Wise and Rompre, 1989) are also engaged during human drug-taking behavior. When behavioral ratings were used as reference waveforms in a correlational analysis, cocaine SA-induced HIGH correlated with neural activity in a number of limbic, paralimbic, and mesocortical regions. These correlations were positive in the middle frontal gyrus and retrosplenial cingulate and negative in the NAc, OFC and AC. In contrast, CRAVING correlated positively with activity in the AC, NAc, inferior frontal–orbitofrontal and middle frontal regions and inversely with cingulate and thalamic activity in a topography that closely approximated HIGH.

Behavioral responses during cocaine SA

When combined across all injections, behavioral ratings of HIGH declined before and increased after cocaine SA, while CRAVING ratings increased before and transiently decreased immediately after SA (Fig. 4C). Our findings would support

Table 1
Neural (BOLD Signal) correlates of behavioral ratings

Region	Hemisphere	Correlation (Mean ± SD)	Volume (mm³)	BA	Talairach coordinates		
					R–L	A–P	S–I
High							
Inferior frontal/orbitofrontal gyrus	Right	−0.290 ± 0.117	463	47	26	23	−4
Putamen	Left	−0.280 ± 0.168	236	–	−22	16	2
Anterior cingulate	Bilateral	−0.274 ± 0.037	1717	32	5	32	−5
Putamen/nucleus accumbens	Right	−0.271 ± 0.090	827	–	14	10	−4
Inferior frontal gyrus	Right	−0.246 ± 0.100	295	47	39	35	−7
Precentral gyrus	Left	−0.155 ± 0.046	228	6	−7	−19	73
Inferior temporal gyrus	Left	−0.126 ± 0.050	185	37	−49	−66	−17
Cerebellum	Left	−0.103 ± 0.019	268	–	−45	−57	−23
Insula	Right	0.215 ± 0.087	298	13	38	8	17
Insula	Right	0.119 ± 0.043	†179	13	40	−13	1
Frontal operculum	Right	0.197 ± 0.071	582	6	48	−6	8
Red nucleus/substantia nigra	Right	0.189 ± 0.085	203	–	9	−25	−2
Middle frontal gyrus	Right	0.187 ± 0.083	†154	–	35	7	24
Cingulate gyrus	Left	0.136 ± 0.047	285	24	−7	−15	41
Cingulate gyrus	Left	0.134 ± 0.047	675	24	−3	5	35
Caudate, body	Right	0.161 ± 0.056	302	–	9	0	21
Thalamic pulvinar	Right	0.158 ± 0.049	717	–	18	−28	8
Retrosplenial cingulate	Left	0.137 ± 0.030	309	–	−10	−36	12
Cerebellar culmen	Right	0.122 ± 0.038	262	–	12	−38	−14
Craving							
Anterior cingulate	Bilateral	0.260 ± 0.040	919	32	7	34	−5
Anterior cerebellar dentate	Right	0.231 ± 0.020	327	–	18	−47	−25
Anterior cerebellar culmen	Left	0.110 ± 0.009	185	–	−18	−46	−13
Putamen/nucleus accumbens	Right	0.216 ± 0.025	241	–	16	9	−2
Inferior frontal gyrus	Right	0.197 ± 0.014	240	13	30	29	12
Inferior frontal/orbitofrontal gyrus	Right	0.167 ± 0.016	†152	47	37	33	−4
Middle frontal gyrus	Right	0.207 ± 0.030	200	10	30	62	11
Middle frontal gyrus	Right	−0.207 ± 0.015	247	9	41	12	30
Superior temporal gyrus	Right	−0.217 ± 0.032	†155	41	52	−25	3
Superior temporal gyrus	Right	−0.200 ± 0.032	†162	41	52	−37	9
Thalamic pulvinar	Right	−0.165 ± 0.017	†169	–	20	−31	8
Parietal supramarginal gyrus	Left	−0.141 ± 0.006	253	40	−62	−34	35
Cingulate gyrus	Left	−0.122 ± 0.008	240	24	−2	−9	34
Rush							
Anterior cingulate, ventral division	Right	−0.285 ± 0.042	493	1232	1	29	−8
Middle temporal gyrus	Left	−0.146 ± 0.011	190	37	−61	−63	1
Inferior temporal gyrus	Left	−0.133 ± 0.012	231	37	−51	−70	−16
Inferior temporal gyrus	Left	−0.103 ± 0.014	333	37	−61	−56	−14
Posterior cerebellar declive	Right	0.145 ± 0.015	660	–	7	−66	−20
Anterior cerebellar culmen	Right	0.141 ± 0.011	241	–	8	−35	−22
Anxiety							
Precuneus	Right	0.105 ± 0.018	253	7	6	−74	50
Precuneus	Left	0.128 ± 0.021	†168	7	−8	−69	52
Middle temporal gyrus	Left	−0.100 ± 0.019	252	21	−41	−5	−20

These regions were identified as clusters of significant correlation across all subjects for HIGH, CRAVING, RUSH and ANXIETY ratings. Correlations represent the mean correlation coefficient from the identified region sampled across all subjects. All clusters correlated at $P \leq 0.01$ but regions of volume <185 mm³ are of marginal significance († overall $0.05 \leq P \leq 0.08$) when accounting for multiple comparisons. BA = Brodmann area; R–L = Right–Left; A–P = Anterior–Posterior; I–S = Inferior–Superior.

several explanations of phenomena driving drug-seeking and drug-taking behavior in chronic cocaine addicts.

Repeated cocaine SA increased peak HIGH ratings for the first four injections, suggesting a cumulative hedonic effect early within a SA session. This is somewhat surprising in light of clinical observations of the first "hit" of a session being the most intense, perhaps related then to the common description of

"chasing the high" (Wise and Bozarth, 1987). Although most human cocaine SA studies do not report enhanced HIGH ratings over time (Fischman et al., 1985, 1990; Foltin et al., 1995; Ward et al., 1997), three studies, one using crack and two i.v. cocaine, reported maximal HIGH ratings 4 min after the second or subsequent doses (Dudish et al., 1996; Foltin and Fischman, 1992, 1996). The observed reduction in HIGH immediately prior
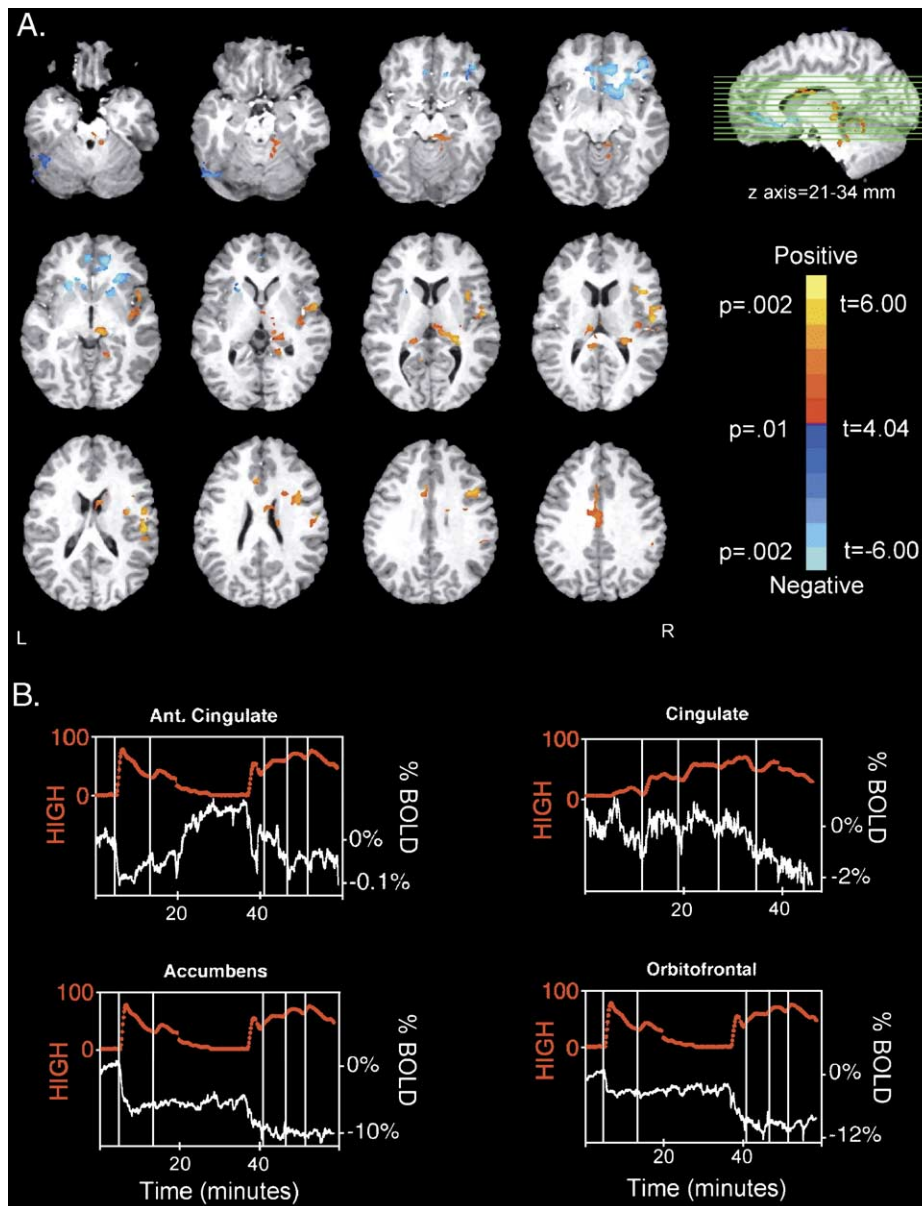
Fig. 5. Neural correlates of HIGH during cocaine self-administration. (A) Regions of significant ($P < 0.01$) group correlation with the VAS ratings of HIGH, both positive (yellow) and negative (blue), superimposed upon one grayscale anatomical image warped into Talairach coordinates. (B) Plots of VAS ratings (top tracing in red in each graph) and % change BOLD (bottom tracing in white) represent raw data from single subjects, averaged across the indicated ROI. The 4 single-subject plots were comprised of data from 2 separate subjects representative of the group. Vertical lines represent injection events. HIGH ratings were anchored at 100 = "Most ever," and 0 = "Least ever." %BOLD change is displayed relative to the initial 5-min baseline period.

to SA has generally not been reported in human studies (Foltin and Fischman, 1992). This may be due partially to the comparatively naturalistic design and rapid behavioral sampling employed in this study.

While peak ratings increased, HIGH ratings tended to decrease more rapidly with each successive injection, possibly due to a more rapid decline in drug effect (Fig. 4A). The accelerated rate of decline in HIGH with injection suggests that SA may be related to the slope, which dramatically demonstrates a more rapid loss of HIGH with injection order. Corroborative data are unavailable from other human SA paradigms, which typically measure subjective effects less frequently (Fischman and Schuster, 1982; Fischman et al., 1990). An overall increase in cumulative HIGH,

while simultaneously speeding the loss in HIGH, would seem to suggest that in the face of a cumulative hedonic response there is yet a simultaneous desensitization to the duration of HIGH and one possible explanation of the driving force behind repeated use.

Similar to previous reports and in contrast with HIGH, subjects reported pre-injection CRAVING that increased up to the point of the next injection, but then decreased immediately after cocaine administration (Fischman and Schuster, 1982). Consistent with our study, others have also reported an increase in cocaine craving or "wanting" 4 min after SA (Ward et al., 1997). With the exception of injection 5, which had the smallest number of subjects and thus the largest variance, absolute pre-injection cocaine CRAVING levels tended to decrease with each injection; the slope of this
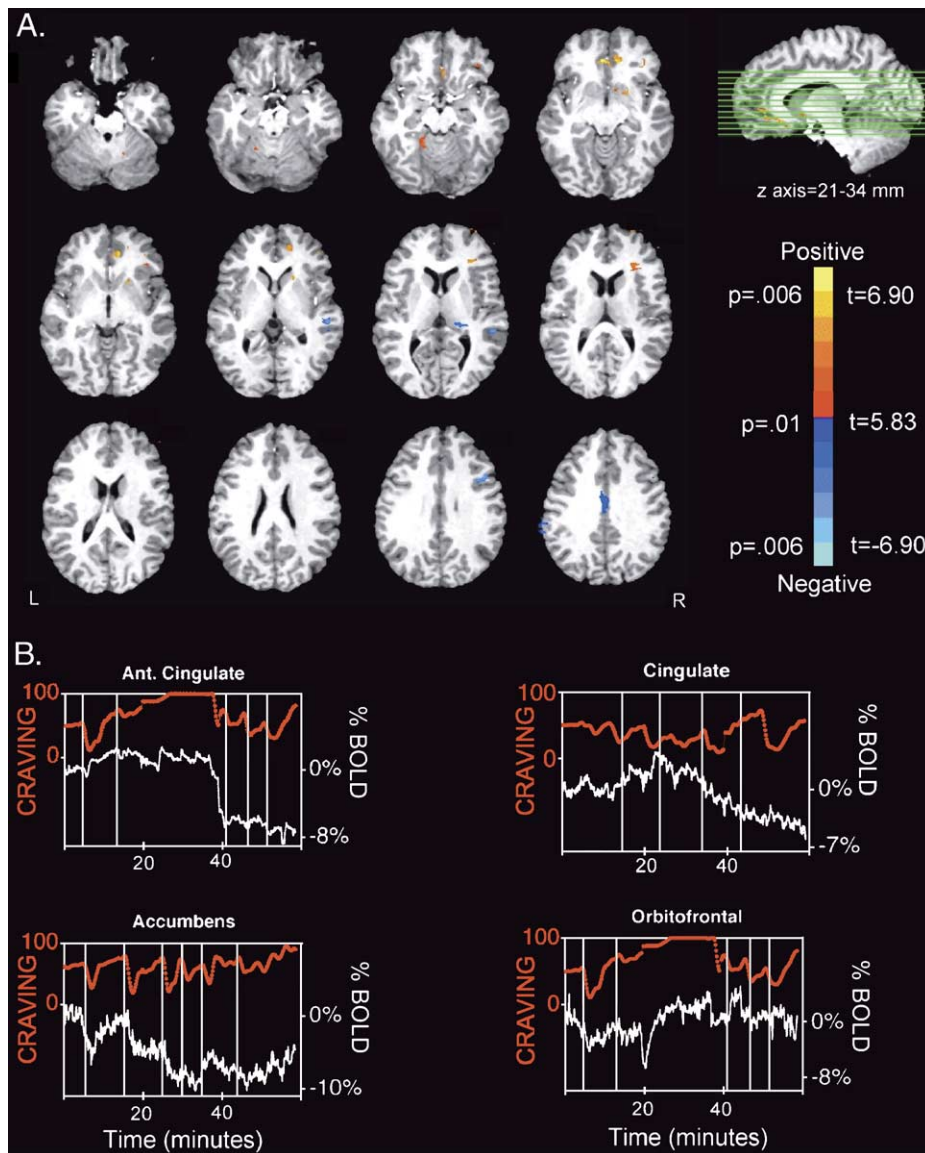
Fig. 6. Neural correlates of CRAVING during cocaine self-administration. (A) Regions of significant ($P < 0.01$) group correlation with the VAS ratings of CRAVING, both positive (yellow) and negative (blue), superimposed upon one grayscale anatomical image warped into Talairach coordinates. (B) Plots of VAS ratings (top tracing in red in each graph) and % change BOLD (bottom tracing in white) represent raw data from single subjects, averaged across the indicated ROI. The 4 single-subject plots were comprised of data from 3 separate subjects representative of the group. Vertical lines represent injection events. CRAVING ratings were anchored at 100 = "Most ever," and 0 = "Least ever." %BOLD change is displayed relative to the initial 5-min baseline period.

construct increased linearly with injection order (Fig. 4B). If craving is similar to Robinson and Berridge's drug 'wanting' and high is similar to drug 'liking' (Robinson and Berridge, 2001), then our data partially support their theory: if an increasing rate of CRAVING indicates desire for drug, an increase in the slope of pre-injection CRAVING supports the hypothesis that drug wanting drives behavior rather than drug liking (Berridge and Robinson, 1998). However, it is not clear if there is an interactional point where increasing craving and falling high effect the motivation to take cocaine.

Neural correlations with behavioral ratings

Correlations of HIGH and CRAVING with BOLD activity were seen within several MCL regions and their projections including the NAc, thalamus, anterior and middle cingulate, and OFC. These data are consistent with the known anatomical projections of the ascending MCL DA system and with previous human neuro-imaging findings in general. While the AC, NAc, regions of the inferior and middle frontal gyrus, anterior cerebellar structures, and OFC positively correlated with CRAVING, activity in middle cingulate, thalamic pulvinar, and superior temporal gyri negatively correlated with this subjective state. Most of these regions are part of, or receive inputs from, the MCL system. A number of recent imaging studies have begun to map cocaine craving to specific brain regions. Using presentation of directed affectively-laden stimuli, cue-induced cocaine craving has been shown to be associated with activity in the AC (Childress et al., 1999; Garavan et al., 2000; Grant et al., 1996; Wexler et al., 2001), mediodorsal thalamus (Childress et al., 1999; Garavan et al., 2000; Grant et al.,

1996), and middle, frontal and retrosplenial cingulate regions (Garavan et al., 2000; Grant et al., 1996).

This group of structures is identical to our reported correlational topography of CRAVING during cocaine SA. In addition, the association of CRAVING with NAc and cingulate activity is similar to that of Breiter et al. (1997) who reported NAc, anterior and posterior cingulate activation which correlated with maximum ratings of CRAVING more than RUSH following both cocaine and placebo injections. Increasing but still limited research in this area has precluded a full understanding of the neurochemical mechanisms underlying this pattern of activity in humans. In one study addressing this question, dopamine transporter (DAT) blockade after a single injection of cocaine was shown to correlate with high (Volkow et al., 1997b,c). However, repeated methylphenidate administration found DAT occupancy alone to be insufficient to account for the high (Volkow et al., 1996). These authors postulated that suppression of NAc firing represents the underlying neurobiological substrate associated with euphoria, whether due to increasing DA levels, downregulation of DA receptors, or reduced cortical excitatory input (Volkow et al., 1996). Our data support this concept in that NAc activity decreased with cocaine SA as subjects reported increased euphoria (increased HIGH).

Interestingly, while subjects in the only previous BOLD fMRI study also reported euphoria after cocaine administration, the NAc activity in that study increased after drug was received (Breiter et al., 1997). However, we have observed NAc suppression repeatedly (Mu et al., 2001; Dirckx et al., 2003), and several methodological differences between the two designs should be considered. The major difference between the two studies is that Breiter et al. used a single-blind, passive injection paradigm that administered one randomized cocaine or saline injection per session compared to active self-administration of multiple injections. A second important difference is that their subjects reported no craving at baseline while ours reported variable amounts. The statistical analyses of the two studies were also treated differently, thus disparate underlying assumptions ambiguate a direct comparison. Any of these differences, or some combination, could have led to the opposite directions of NAc activity.

The OFC plays an important role in reward, emotion and affect, decision-making, and compulsive behaviors (Bechara et al., 2000; London et al., 2000; Lyons et al., 1996; Rolls, 2000). For example, OFC neurons in rat (Schoenbaum et al., 1998; Schoenbaum et al., 1999) and monkey (Rolls, 2000), fire during the anticipation and experience of reward, suggesting OFC plays a role in learning the association between stimulus and reinforcement (Rolls, 2000). While others have suggested that repeated exposure to cocaine disrupts striato-thalamo-orbitofrontal (STO) circuitry and contributes to drug taking behavior (Volkow and Fowler, 2000), the present data are the first functional demonstrations of such associations in a repeated SA design. As predicted, we show evidence of hedonic correlation with MCL-related regions, specifically OFC, with respect to the presumably binge-like activity modeled in this design. Although not addressed in this analysis, we expect that SA alters neural activity in regions responsible for learning operant associations, and such alterations may drive the redirection of goal-related regions toward drug acquisition.

The current published data lack comparable temporal resolution or contain methodological limitations such as SA prompting, variable or intermittent reinforcement schedules, or relatively long time lags between request and dosing. Perhaps, the most appropriate comparison for the present data is with clinical observation. Clinical studies have generally not found craving to be associated with relapse rates (Fischman et al., 1990; Miller and Gold, 1994), but one problem is that abusers and researchers alike have yet to agree on a common and specific definition of craving. A functional definition of craving might therefore allow a more focused search into its underlying neural correlates, providing a baseline against which pharmacological and cognitive interventions for relapse may be measured.

Limitations

Several factors necessitate caution in the interpretation of these findings. First, the HIGH and CRAVING constructs appear not to be independent. The inverse correlation between HIGH and CRAVING, even across all subjects, suggests that during SA these states may have become patterned and impossible for subjects to disentangle, or the measurement method itself caused their apparent interaction. This interrelation may account for the partial overlap of brain regions in their correlational topography. Similarly, it is possible that the very act of introspective self-report may alter neural activity (Phan et al., 2003). With this design, it is not possible to discriminate between introspective demand and the potential interactions of drug with the self-rating task. However, since no single region correlated with all behaviors this would suggest that introspective demand did not consistently vary between ratings or across time. Also, we know of no data that suggest cocaine alters the performance of self ratings.

Second, since some subjects did not take all available doses, this paradigm may not have engendered compulsive drug use. However, all subjects took at least two injections and the majority of all possible injections were taken (28/36). Interestingly, subjects were not informed of the total number of injections possible, which would attest that subjects were freely self-administering drug when they so desired. In addition, participants might still have been in a loading phase or acclimatizing to the drug effects. Several injections may have been required to achieve the anticipated effect. Animal SA studies (Carelli and Deadwyler, 1994) reliably observe an initial loading phase whereby the initial injection frequency is high and then stabilizes to become more regular. Due to the safety issues inherent in human studies, we were not able to directly address this question in extended SA sessions. Certainly, the clinical phenomenology of cocaine abuse supports disparate patterns of use. That some volunteers failed to take all available doses suggest several possibilities: subjects were sated for different time periods, possessed different sensitivities or perhaps differed in refractory period to SA. As far as the subjects reported, this small group was fairy homogeneous in its drug use history. Due to the group averaging nature of fMRI, however, we cautiously state that there may be the unintended effect of diluting differences in subpopulations which have not yet been described.

Third, the number of subjects was limited. However, it has been demonstrated that for a within-subjects study, increasing the number of subjects merely increases the spatial extent of regions identified as 'activated' around the original center of mass, rather than changing the location of the center of mass (Huettel and McCarthy, 2001; Saad et al., 2003).

Lastly, but importantly, the potential exists for a direct effect of cocaine on the cerebrovasculature, bringing into question the above neuronal-based interpretations. Cocaine has been suggested to induce global, large vessel vasoconstriction in humans (Herning et al., 1999; Johnson et al., 1998; Kaufman et al., 1998) and a 21–37% decrease in absolute rCBF across many regions following a passively-administered 40 mg cocaine dose has also been demonstrated (Wallace et al., 1996). In spite of these global flow decreases, little data exist to suggest this is also true for the coupling processes between neuronal activity and blood flow (functional hyperemia) which mostly relies on regulating small vessel diameter. For example, after a relatively high (0.6 mg/kg) single i.v. dose of cocaine, which was more than double a single dose in our study, the BOLD signal response to visual stimuli remained unchanged despite modest decreases in global CBF (Gollub et al., 1998). To control for this potential confound, we measured BOLD activation of bilateral motor cortex induced by finger tapping both before and after acute cocaine administration and observed no decrement (Mu et al., 2001). Additionally, this study and others in this lab (Dirckx et al., 2003) clearly identify bidirectional BOLD signal changes following cocaine doses, again suggesting the lack of confounding global or non-specific vascular drug effects.

Conclusions

We demonstrate that drug-induced high and craving for cocaine are related to neural activity in MCL regions which are known from animal studies to be critical for the acquisition and maintenance of drug self-administration. Animal models of compulsive drug use repeatedly implicate these areas. However, with this design, we were able to correlate neural activity with behavioral self-reporting that is exclusive to human studies. This study may enable the vast animal literature to be interpreted more directly into changes in the human subjective experience, reflecting patterns of entrained neural activity surrounding cocaine SA. Finally, a functional definition of craving along with targeting these reward regions for modulation may well lead to more efficacious pharmacological and clinical interventions.

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