Expectation Modulates Human Brain Responses to Acute Cocaine: A Functional Magnetic Resonance Imaging Study

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Background: Human expectation of psychoactive drugs significantly alters drug effects and behavioral responses. However, their neurophysiological mechanisms are not clear. This study investigates how cocaine expectation modulates human brain responses to acute cocaine administration.

Methods: Twenty-six right-handed non–treatment-seeking regular cocaine abusers participated in this study. Changes in blood oxygenation level-dependent (BOLD) signals were measured, and online behavioral ratings during cocaine expectation and acute cocaine administration were recorded.

Results: Distinct regional characteristics in BOLD responses to expected and unexpected cocaine infusions were observed in the medial orbitofrontal gyrus (Brodmann area [BA] 11), frontal pole (BA 10), and anterior cingulate gyrus regions. Active engagement in the amygdala and the lateral orbitofrontal cortex (OFC; BA 47) by unexpected but not expected cocaine infusion was discovered. Cocaine expectation did not change BOLD responses to acute cocaine administration in a set of subcortical substrates, the nucleus accumbens, ventral putamen, ventral tegmental area, and thalamus.

Conclusions: These results suggest that cocaine expectation modulates neural-sensitivity adaptation between the expected events and the actual outcomes but did not modulate the pharmacological characteristics of cocaine. In addition, the amygdala–lateral OFC circuitry plays an important role in mediating stimulus-outcome relations and contextual factors of drug abuse.

Key Words: Amygdala, cocaine, expectation, functional magnetic resonance imaging, human brain, orbitofrontal cortex

Human expectation of the effects of psychoactive agents—both therapeutic and abused—interacts significantly with the actual effects. Alcohol and marijuana have been reported to enhance subjective effects in dependent subjects after the presentation of predictive cues (1,2). Volkow *et al.* (3) reported that the expectation of the reinforcing effects of methylphenidate (MP) generally enhances the acute MP effect in cocaine addicts. Other studies demonstrated that expectation of drugs, as one of the conditioned responses, significantly contributed in decreasing drug effects or drug tolerance (4). However, the issue of how drug expectation affects human drug use behavior remains primarily unsolved.

Functional magnetic resonance imaging (fMRI) has been employed to investigate roles of expectation in relation to appetitive and financial rewards in humans, by measuring changes in blood oxygenation level-dependent (BOLD) signals during reward processing (5–7). Activation in the orbitofrontal cortex (OFC) and other anterior prefrontal areas has been recorded during anticipatory periods preceding pleasant (8) and aversive (9,10) sensory stimuli. The medial OFC has been associated with reinforcement stimuli and outcomes (11), whereas the lateral OFC has been linked to behavior modification on the basis of previous reward-related experiences (11–14). However, OFC BOLD responses were also modulated by uncertainty about the outcome of reward-predicting trials (15). These studies explain the functional roles of expectation of natural and financial rewards and their relationship to neural structures in a manner detectable by fMRI. However, caution should be exercised in applying these results to drug expectation, because drugs like cocaine might act on different parts of the reward system with varying levels of strength.

Previous fMRI human studies involving acute cocaine administration attempted to account for effects of drug expectation by using a double-blind design (16) or by informing the subjects of the nature of the drug administration (17,18). To date, no studies have explicitly investigated the effect of drug expectation on human brain responses to acute cocaine. The nature and extent of the contribution of expectation to human cocaine processing remains elusive.

Here, we describe an fMRI study in which the cocaine-addicted subjects expected either the delivery of a 20-mg/70 kg cocaine dose or a control dose of saline by a predictive visual message 4 min before infusion. It is hypothesized that concomitant cocaine-induced euphoria and craving (19) are likely derived from the interacting pharmacological effects and learned responses (20,21), and drugs of abuse purportedly invoke a strong expectation of reward, overactivating reward, and motivation circuitry while suppressing executive control.

Methods and Materials

Human Subjects and Drug Run-Up

Detailed inclusion and exclusion criteria as well as run-up procedures for the participants were described previously in the literature (17,22). In brief, 26 right-handed non–treatment-seek-

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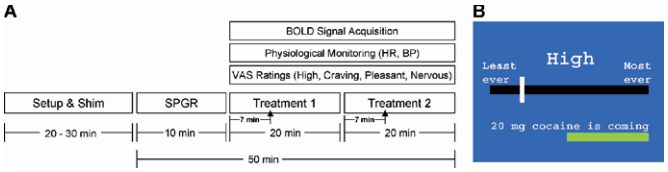

Figure 1. Experimental design. Schematic of the scanning sequence, including high-resolution anatomical scan and two functional magnetic resonance imaging (fMRI) runs each lasting for 20 min **(A)**. Treatments 1 and 2 were order-balanced either with cocaine infusion or saline infusion under expected or unexpected conditions. Only one cocaine infusion each day was conducted in the 2-day experiment. The physiological monitoring and the online visual analog scale (VAS) ratings were recorded during the fMRI runs. The total imaging time lasted for about 1.5 hours. **Figure B** is a representative of a visual stimulus during cocaine expectation.

ing regular cocaine abusers from the greater Milwaukee area participated in this study. A consent form approved by the Institutional Review Board was obtained from each subject before any experiments were conducted. During the consent process, participants were informed that they might receive either saline or cocaine administration during the experiment. Subjects were given an overnight stay at the hospital, ascertaining the 12-hour abstinence from cocaine before the fMRI experiment.

Although 26 right-handed, non–treatment-seeking cocaine-dependent individuals were recruited, 22 subjects completed experimental procedures in the 2-day study; 4 were eliminated, owing to apparent gradient problems with the imaging apparatus. Of these 22 subjects, 9 were eliminated owing to the presence of motion artifacts in their datasets (translational motion more than 1.5 mm of base value in any direction, rotational motion not more than 1.5° from base position when not corrected by volume registration and regression), and 13 yielded useable BOLD data for all four fMRI runs. Of these 13 subjects, 7 experienced the expected cocaine (EC) and expected saline (ES) runs on the 1st day and unexpected cocaine (UC) and unexpected saline (US) runs on the 2nd day. The other 6 experienced UC and US runs on the 1st day and EC and ES runs on the 2nd day. As a result, subjects received order-controlled treatments of cocaine or saline.

Of the 13 subjects whose data were fully analyzed, 9 were male and 12 were black (1 Hispanic). The age (40 ± 7.5 years), education level (12 ± 1.3 years), history of cocaine use (14.5 ± 5.3 years, 4.2 ± 2 times/week), and estimated expenditure on cocaine (190 ± 170 dollars/week) of the analyzed subjects did not significantly differ from the entire population of recruited individuals.

Cocaine and Saline Infusion

As illustrated in Figure 1A, each subject received two separate scanning runs, one cocaine run and one saline run on each of the 2 days. Each run lasted for 20 min. After 4 min of a baseline scan while subjects watched a cross point at the center of a blue screen, a green bar appeared across the bottom of the screen with the message "20 mg cocaine is coming" or "saline is coming." It gradually shrank from left to right (Figure 1B). At 7 min into the 20-min scan, when the green bar vanished, a single 20-mg/70 kg dose of cocaine in 10-mL saline volume or 10 mL saline was infused intravenously over 30 sec. In expected cocaine runs, the message "20 mg cocaine is coming" was followed by a cocaine infusion of a 20-mg/70 kg dose (the EC run). The message "saline is coming" was followed by a 10-mL saline infusion (the ES run). In unexpected cocaine runs, the message "saline is coming" was followed by a cocaine infusion of a 20-mg/70 kg dose (the UC run), and the message "20 mg cocaine is coming" was followed by a 10-mL saline infusion (the US run). The four runs were performed in counterbalanced order (Figure 1A). This cocaine dosage of 20 mg/70 kg has a comparable dopamine transporter (DAT) occupancy in humans as a 42-mg/70 kg dose (23), which was used in the intravenous treatment in the previous acute cocaine fMRI study (16). In addition, the 20-mg/70 kg dose of cocaine was used to minimize the confounding systemic effects of cocaine on the cerebrovascular system (24), although the peripheral blood pressure changes do not significantly affect the BOLD signals in the human brain (25).

Physiological monitoring and behavioral measurements were performed, as described previously (17). The heart rate and blood pressure did not significantly change after infusion during the saline runs. Among the 13 subjects who provided useable fMRI data collection, 11 successfully furnished online behavioral data during the fMRI experiments (2 subjects had difficulty operating the joystick while in the scanner). For behavioral data analysis, mean pre-infusion visual analog scale (VAS) scores were compared with mean post-infusion scores for each of the rating types ("high," "craving," "pleasant," "nervous," and "sour") by two-sample *t* tests.

fMRI Data Acquisition

All experiments were performed on a GE Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, Wisconsin) with the multiecho segmented echo-planar imaging (EPI) with z-shimmed background gradient compensation (MESBAC) pulse sequence (26). The detailed data acquisition procedures and imaging parameters for implementing the MESBAC pulse sequence (17) to obtain reliable BOLD-weighted fMRI signals in the regions of the OFC, amygdala, and nucleus accumbens (NAc) were provided previously. In this study, each run lasted for 20 min, during which four axial slices of the inferior brain (relative to the anterior commissure) were imaged every 8 sec with the MESBAC pulse sequence (240-mm field-of-view, flip angle = 50°, echo time = 30 msec, 150 reps, 128 × 64 matrix with 5-mm slice thickness). The four MESBAC slices were interleaved with single-shot EPI acquisitions of 16 slices encompassing the rest of the brain with the same imagine parameters as the MESBAC sequence except the 64 × 64 matrix. Dummy echoes were obtained within each repetition-time interval to obtain steady-state longitudinal magnetization. After the functional imaging runs, high-resolution (.94 mm × .94 mm in-plane, 1-mm slice thickness) T_1-weighted whole-brain anatomical images were obtained with a spoiled gradient recalled acquisition in the steady state (GRASS) pulse sequence (27).

fMRI Data Analysis

Statistical analysis of the 13 fMRI datasets was performed with Analysis of Functional Neuroimages (AFNI) software, as described previously (17,28). The BOLD responses of the cocaine and saline runs were fitted with a nonlinear least-squares simplex algorithm to a difference-of-exponents model based on the single-dose single-compartment pharmacokinetics of cocaine (29). The area between the fitted curve and the baseline for each voxel was calculated by numerical integration and normalized, using the area between the baseline signal and zero. The resulting quotient was expressed as a percentage (AUC%), associated with each brain voxel. The voxelwise AUC% maps were transformed into a common Talairach space for analysis