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Increased CSF Volumes Are Associated with Diminished Subjective Responses to Cocaine Infusion

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We evaluated the hypothesis that ventricular and cortical CSF volume increases are associated with reductions in the magnitude of euphoric effects produced by intravenous IV cocaine infusion in cocaine dependent (CD) individuals. Eleven CD patients participating in a cocaine-infusion study and eleven control subjects underwent magnetic resonance imaging (MRI). Two CSF regions of interest (lateral ventricles and frontal cortex CSF) and two comparison regions (third ventricle and posterior cortex CSF) were measured. Self-reported ratings of the intensity of euphoric response ("high") were obtained from the CD subjects at 3, 10, and 30 minutes after IV administration of cocaine. A significant negative correlation was observed between the volume of the lateral ventricles and subjective ratings of the "high" experienced at 3 minutes, but not at 10 and 30 minutes after cocaine infusion. In contrast, a significant negative correlation between frontal cortex CSF volume and the intensity of euphoric response was observed at 30 minutes after IV cocaine. No significant associations were observed between the volumes of the two comparison regions and any subjective ratings of "high." No significant volume differences were observed between the CD and control groups in any region. The results suggest larger lateral ventricular volumes are associated with a decrease in immediate euphoria while larger frontal cortex CSF volumes are associated with a decrease in the duration of the euphoria induced by cocaine infusion. The age-related brain volume reductions underlying the volume increase in these two CSF spaces may be the neurobiological basis of the age-related reduction in the rates of addiction.
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The relationship between brain variables and subjective effects of cocaine has not been extensively studied. Morgan et al. (1993), using non-contrast computerized tomography (CT), examined the association between ventricular brain ratio (VBR) and intensity of response to the effects of 40 mg of intravenous cocaine. They obtained subjective ratings of drug effect every minute for 30 minutes after the cocaine injection and observed a significant negative correlation ($r = -.53$, $p = .02$) between VBR and the average rating of drug response over the first 10 minute interval but no relationship over the last two 10 minute intervals ($r = -.22$ and $r =$

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−.06 respectively) (Morgan et al. 1993). This suggested that subjects with larger ventricles had reduced sensitivity to cocaine's immediate euphoric effects.

As part of a recent study investigating the possible attenuating effects of selegiline on cocaine-induced euphoria and brain metabolism (Bartzokis et al. 1999a), non-treatment seeking "crack" cocaine smokers were evaluated with magnetic resonance imaging (MRI) of the brain in order to identify patients with enlarged ventricles who may be less responsive to IV cocaine's euphoric effects. The total volume of the lateral ventricles was measured in order to evaluate the magnitude of the negative association between this volume measure and the experience of euphoria ("high") associated with cocaine infusion. The volume of the third ventricle was also measured in order to assess whether this structure/function association was specific to the lateral ventricles or a phenomenon associated with generalized ventriculomegaly.

In addition, the volume of the supracortical cerebrospinal fluid (CSF) in the frontal region of the cerebral cortex was measured in order to indirectly assess whether reduced frontal cortex gray matter observed in the polysubstance dependent (Liu et al. 1998) and alcohol dependent (Pfefferbaum et al. 1998) populations is also associated with a diminished intensity of cocaine infusion-induced euphoria. As with the ventricular volumes, we hypothesized that the volume of CSF in this cortical region will also correlate negatively to the cocaine infusion-associated experience of euphoria. Again, in order to assess whether this structure/function association was region-specific or due to a generalized atrophy of the cortex, we also measured the volume of the remaining (posterior) portion of cortical CSF.

Since cocaine dependence has been associated with increased rates of white matter lesions (Bartzokis et al. 1999b), we obtained the same volume measurements for a matched group of eleven normal control subjects.

METHOD

Subjects

Seventeen non-treatment seeking CD subjects who smoked "crack" cocaine and had prior IV drug use at some time in their past were recruited into an inpatient medication development study investigating the possible attenuating effects of selegiline on cocaine-induced euphoria and brain metabolism (Bartzokis et al. 1999a). The MRI evaluation was performed at admission. A group of eleven age-, gender-, and race-matched control subjects were also evaluated with the same MRI procedure. Written informed consent was obtained from all subjects prior to study participation.

All CD subjects met DSM-IV criteria for cocaine dependence and had smoked an average of at least 1/2 gram (quantified as $50) of "crack" cocaine per week for more than six months (assessed by self-report and a positive urine benzoylecognine test within two weeks prior to entering the study). Cocaine was the primary current drug of abuse, though subjects reporting use of alcohol without meeting DSM-IV criteria for alcohol dependence were included. Two CD patients reported a past history (greater than 12 months prior to evaluation) of alcohol dependence and one CD patient reported a history (greater than 12 months prior to evaluation) of opiate dependence. Females were included only if they were unable to conceive.

Cocaine dependent subjects were excluded for: age under 21 or over 50 years; dependence on other substances of abuse besides tobacco; report of opiate abuse or urine positive for opiates within the past month; participation in more than two other research protocols involving cocaine administration in the past year; history of previous medically adverse reaction to cocaine; stroke, epilepsy, or psychiatric illness other than cocaine dependence; untreated or clinically significant heart disease or hypertension; significant abnormalities detected on physical exam, laboratory examination, EKG, or EEG; positive HIV test or positive pregnancy test (for females).

The CD subjects consisted of 10 males (nine African-Americans and one Caucasian) and one female (African-American), with a mean age of 41.3 years (SD = 4.4 years, range 34-47) and a reported mean duration of cocaine dependence of 12.3 years (SD = 7.2, range 4-28). The group of eleven normal control subjects was recruited from the community and hospital staff. They were subjected to the same exclusion criteria as the CD patients; in addition, they had no history of current or past psychopathology or substance dependence and no history of first degree relatives having been treated for a major psychiatric disorder. The control group was matched to the CD group in mean age (39.6 vs. 41.3 respectively, $t = -0.59$, $p = .56$), gender (10 males and one female for both groups), and race ($\chi^2=1.22$, df = 1, $p = .27$).

Cocaine Infusion Procedure

The medication development study involved two phases, a placebo phase followed by an active medication phase. Data obtained in the first (placebo) phase was used to evaluate the relationship between CSF volumes and the subjective euphoric effects of cocaine infusion or "high." Urine toxicology screens were obtained daily to assure that the subjects received only the cocaine administered to them as part of the protocol. For safety reasons, all subjects were administered two test doses of IV cocaine hydrochloride (20 mg followed by 40 mg) prepared as 1 mg cocaine/1 ml saline and administered at 1 mg/sec IV (i.e., over 20 and 40 seconds respectively). Saline infusion was given as a control for

each of the test doses of cocaine in order to ensure that the subjects did not exhibit a placebo response, which would result in exclusion from the study. These test doses were given on the first and second study day respectively on days 4 and 5 after admission into the study. Six subjects were excluded during this part of the study for medical reasons (cocaine-induced hypertension, arrhythmia, etc.). Subjects not excluded during the test dose administration sessions continued in the placebo phase and received 40 mg cocaine hydrochloride 72 h later. This last time point was chosen for data analyses (8 days from admission into the study and the last day the subjects received placebo). This time point is most similar across all subjects since everyone had the same procedures performed, had the same experimentally controlled exposure to cocaine over the preceding week, and the same amount of time withdrawn from cocaine.

At approximately 3, 10, and 30 min after each cocaine infusion, the participants' subjective responses to cocaine were ascertained by verbally rating, on a 1 to 10 scale, the extent to which they felt "high." Subjective ratings were also performed during the initial two test dose infusions so that the subjects could learn to be consistent in their responses and become thoroughly familiar with the procedures by the time of the last cocaine infusion in the placebo phase (the data point used in the current analyses).

Imaging Procedures

MRI Protocol. The MRI examination used a Picker 1.5 Tesla instrument. Coronal and sagittal MRI pilot sequences were obtained to specify the location and spatial orientation of the head and the position of the axial image acquisition grid (Bartzokis et al. 1993). All MRI data were derived from the subsequent axial sequence which used two repetitions, 256 x 192 view matrix and slices, a transverse asymmetric dual spin-echo Carr-Purcell-Meiboom-Gill sequence (TR = 2500, TE = 20,90) that acquired interleaved 3 mm thick contiguous slices. This data was used to produce transverse relaxation time (T_2) images with very high CSF-brain contrast that makes measurements of CSF volume extremely accurate (Bartzokis et al. 1993).

Image Analysis. Imaging measures were obtained using a Macintosh configured image analysis workstation that read compact disks containing the original MRI data stored in digital format. The regions of interest (ROIs) were quantified by a single rater who was blind to the clinical data.

Regions of Interest

Ventricular System. The lateral and third ventricles were separately quantified. The rater manually traced a rough contour surrounding the bright pixels of ventricular CSF while maintaining the cursor on the darker brain matter pixels. All the brain matter pixels (defined as pixels with a T_2 less than 130 ms.) were then eliminated from the ROI using the "shrink image" function as described in Bartzokis et al. (1993). The resulting ROI contained only ventricular CSF pixels. To obtain the volume, the same procedure was repeated on each slice that contains the structures.

Frontal Cortex CSF. The largest brain slice was identified and the frontal region was defined as the anterior one-half of the entire brain length. The rater traced a rough contour surrounding the frontal cortex CSF and again used the "shrink image" function to eliminate all pixels with a T_2 less than 130 ms so that only CSF pixels remained in the ROI (Bartzokis et al. 1993). The same line used to separate the frontal region from the rest of the brain was used for all subsequent slices which spanned the brain from the slice where the anterior temporal lobe appears separated from the frontal lobe by the Sylvian fissure to the highest available slice.

Intracranial Volume. For all slices on which measurements were obtained for ventricular structures and cortical CSF, total brain and total cortical CSF volume were also quantified. Summing the volumes of total brain tissue, total cortical CSF, and total ventricular volumes produced the intracranial volume measure.

Data Analysis

The association between ventricular and cortical CSF regions and self-rated "high" was evaluated with Spearman's rank-order correlational analysis because the data were not normally distributed and the relatively small sample. Robust age-related increases in frontal cortex CSF volumes were observed in the CD group ($r = 0.77$, $p = .006$) and the normal control group ($r = 0.54$, $p = .09$); therefore, for all significant correlations, the age-adjusted results are also reported (partialling age). Similarly, in order to ensure that variations in head size would not influence the results, all significant correlations were also adjusted for intracranial volume measures (partialling intracranial volume). Duration of cocaine use was not statistically correlated with any of the CSF volume variables ($p > .13$). The formulated hypothesis of a negative relationship between lateral ventricle and euphoric response was based on the results reported by Morgan et al (1993). Negative associations were also hypothesized between frontal cortex CSF and ratings of "high" based on studies by Liu et al. (1998), Pfefferbaum et al. (1998), and Bartzokis et al. (2000); therefore, all the reported results (p-value) are one-tailed. One-way analysis of variance was performed to compare CSF volumes between CD patients and a control group.

RESULTS

In support of the hypothesis, the data revealed a significant negative association between the volume of lateral ventricles and rating of euphoria verbalized by the CD subjects at the 3-minute time point (Table 1). This relationship remained significant after statistically controlling for age and intracranial volume ($r = -0.70$, $p = .02$). This association was not present at 10 or 30 minutes (Table 1). The correlation coefficient between lateral ventricle volume and rating of "high" was significantly larger at 3 minutes when compared to the same volume vs. "high" association at the 10 minute ($t = -1.94$, $p = 0.045$) and 30 minute ($t = -2.50$, $p = .019$) assessment of euphoric response. The volume of the third ventricle (examined as a control region) was not significantly correlated with the subjective ratings of "high" at any of the time points (Table 1).

As hypothesized, the frontal cortex CSF volume was robustly negatively associated with the "high" rating. The association grew stronger as time elapsed from the initial cocaine infusion and reached statistical significance at the 30-minute assessment (Table 2). The relationship at 30 minutes remained significant after partialling out age and intracranial volume ($r = -0.62$, $p = .04$). A composite score consisting of the average of the ratings of "high" at the three time points was also significantly correlated with the frontal cortex CSF volume ($r = -0.52$, $p = .049$) and the association was unchanged after partialling out age and intracranial volume. In contrast, no significant relationship was found between the composite score and volume of lateral ventricles ($p > .50$) or the cortical CSF control region (cortical CSF volume posterior to the frontal cortex) ($p = .31$).

No significant differences were found between the normal control group and the CD group in the volumes of any of the regions ($p > .05$). When age, years of education, or intracranial volume were statistically controlled as covariates, these differences remained nonsignificant.

Table 1. Spearman rank-order correlations* of Ventricle Volume vs. Ratings of "High" at 3, 10, 30 Minutes after Cocaine Infusion

Region	3 Minutes		10 Minutes		30 Minutes	
	r	*p*	r	*p*	r	*p*
Lateral Ventricle	−0.64	.018	0.13	.354	0.38	.125
Third Ventricle	−0.30	.188	0.15	.334	0.014	.484

*All *p*-values are one-tailed.

Table 2. Spearman rank-order correlations* of Cortical CSF Volume vs. Ratings of "High" at 3, 10, 30 Minutes after Cocaine Infusion

Region	3 Minutes		10 Minutes		30 Minutes	
	r	*p*	r	*p*	r	*p*
Frontal	−0.32	.169	−0.51	.053	−0.64	.018
Posterior	0.14	.337	−0.12	.364	−0.18	.303

*All *p*-values are one-tailed.

DISCUSSION

The current study demonstrated a significant negative association between the subjective rating of "high" obtained at 3 minutes after cocaine infusion and the total volume of the lateral ventricles, supporting the relationship between subjective effects of cocaine infusion and VBR reported by Morgan et al. (1993). In fact, the association was of greater magnitude ($r = -.63$) than that observed by Morgan et al. (1993) ($r = -.53$) and quickly disappears (becomes non-significant and changes direction) as time from the cocaine-infusion elapses (Table 1).

Although a similar negative association was observed between the CSF volume of the frontal cortex and the rating of "high", the effect of time-from-infusion on the relationship was different from the effect observed in the lateral ventricles. Unlike the findings in the lateral ventricles, robust negative trends were observed between cortical CSF volume of the frontal cortex and subjective ratings of "high" at the 3 and 10 minute assessment ($r = -0.32$; $r = -0.51$, respectively), with the association reaching statistical significance at the 30 minute assessment (Table 2). A composite score consisting of the average of the three ratings of "high" was also significantly negatively correlated with the frontal cortex CSF volume but not with the volume of the lateral ventricles.

These observations suggest that the volume of the lateral ventricles are related to the intensity of the "high" experienced immediately after administration of cocaine while the volume of the frontal cortex CSF is more closely associated with the duration of the cocaine-induced "high." The third ventricle and the remaining cortical CSF (posterior to the frontal cortex) volumes were not significantly associated with the ratings of "high," indicating that, in contrast to the lateral ventricles and the frontal cortex, the volumes of these two comparison regions are not as closely associated with cocaine-induced euphoria. These observations suggest that the relationships between the CSF volumes and the subjective euphoric response to cocaine are not global and may instead be regionally specific.

Several limitations of the study must be acknowledged before further interpretation. First, the sample size was small and only one female and one Caucasian addict were included in the study, thus limiting the generalizability of the results. Second, the age range of the subjects is limited and inferences on age-related changes in CSF volumes must be derived primarily from the literature. However, the literature consistently indicate that CSF volumes of the lateral ventricles and frontal lobe CSF increase with age (Coffey et al. 1992; Jernigan et al. 1990; Matsumae et al. 1996; Pfefferbaum et al. 1994; Wahlund et al. 1990). Third, the statistical analyses did not correct for multiple comparisons; however, the analyses were conducted with clear hypotheses in mind. Finally, the observed associations between the intensity of cocaine-induced euphoria and CSF volumes presume that the associations are occurring with the underlying brain. The brain volumes were not directly measured. However, in adults, both brain and CSF are contained within the fixed and rigid bony enclosure of the skull; therefore, CSF volumes serve as very sensitive detectors of small reciprocal changes in the much larger brain compartment (Matsumae et al. 1996).

Drug use, or the lifestyle associated with it, may accelerate the process of age-related brain atrophy (Liu et al. 1998; Pfefferbaum et al. 1998; Bartzokis et al. 1999b). In our sample, the CD group did not differ from the normal control group in any of the CSF volume variables. It is possible that people starting out with low CSF volumes are over-represented in the substance dependent population because they are more likely to become addicted if their "high" is more intense and therefore more reinforcing. If the rate of age-related increase in their CSF volumes is augmented by the drug use itself (Liu et al. 1998; Pfefferbaum et al. 1998), then in a cross-sectional study, a chronically addicted population may have CSF volumes similar to the ones of normal controls.

The current cross-sectional data cannot address the question of whether these brain CSF volumes are related to cocaine addiction, predate the addiction, or are simply the result of normal variance in CSF volumes. Regardless, this data supports the possibility that decreasing subcortical and cortical brain volumes (whether accelerated by drug use or not) may be associated with a reduced ability to experience cocaine-induced euphoria. Since the CSF volumes related to these brain regions are known to increase with age (Coffey et al. 1992; Jernigan et al. 1990; Matsumae et al. 1996; Pfefferbaum et al. 1994; Wahlund et al. 1990; Bartzokis, unpublished data) it is possible that with age, the ability to achieve cocaine-induced euphoria diminishes. This may result in age-related reductions in drug use.

Epidemiological data support this possibility and show that while the prevalence of the diagnosis of illicit drug dependence is 3.5% among all ages, the breakdown by age group is striking. Rates are highest among the young (17% for ages 18-29), considerably less in middle age (4% for ages 30-59), and virtually non-existent in those over 60 (Miller 1991). While such figures may represent the "wisdom" commonly associated with aging, they may also reflect age-related brain changes (Bartzokis et al. 2000; Coffey et al. 1992; Gottfries et al. 1983; Jernigan et al. 1990; Lepage et al. 1985; Lim et al. 1992; Matsumae et al. 1996; Pfefferbaum et al. 1994; Raz et al. 1998; Sullivan et al. 1995; Wahlund et al. 1990; Wang et al. 1996), which alter the balance between the addicting versus the aversive effects of cocaine by diminishing the euphoric experience of drug intoxication. Consequently, the tendency to develop a dependence syndrome decreases and the capacity to discontinue use increases (Miller 1991; Cook and Harrell 1987; Facy et al. 1991; Bartzokis et al. 1999b,c).

Individuals without brain atrophy (as evidenced by smaller CSF volumes) experience increased sensitivity and/or longer duration of the "high" induced by cocaine. Thus, the data replicate previous associations between anatomic brain measures and brain function, as assessed by its pharmacologic response to cocaine infusion (Morgan et al. 1993). The existence of such an association is supported by functional imaging studies, which have demonstrated changes in the frontal lobe of cocaine addicts (Volkow et al. 1992, Tumeh et al. 1990, Strickland et al. 1993). These functional changes may have structural underpinnings consisting of reduced frontal lobe gray matter (Liu et al. 1998; Pfefferbaum et al. 1998) and lower dopamine levels and dopamine transporter receptors in the frontal cortex (Hitri et al. 1994; Little et al. 1996).

Whether the association between CSF volumes and subjective effects of cocaine has clinical implications is unknown. The possibility that the rates of addiction, likelihood of abstinence, and possibly the success of treatment programs may be related to specific brain measures, is quite significant and amenable to further study given the wide availability of MRI instruments and the reliability of CSF measures (Bartzokis et al. 1993). If shown to have clinical implications, such measures can provide valuable clues as to which brain regions are most promising for pharmacotherapeutic intervention.

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