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Self-reported paranoia during laboratory "binge" cocaine self-administration in humans

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Abstract

Cocaine-induced paranoia (CIP) has been extensively studied by retrospective interviews; however, only limited efforts have been made to further characterize CIP by human laboratory methods. We examined CIP in 28 healthy cocaine-dependent volunteers, who participated in 2-h, intravenous cocaine self-administration sessions at 8, 16, and 32 mg/70 kg doses, including 18 in a placebo-controlled design. Self-reports of paranoia showed significant main effects of cocaine dose ($p=0.0002$) and time ($p=0.0003$), and were statistically distinguishable from placebo at the two highest doses (16 and 32 mg). These effects were accounted for by a subgroup of vulnerable subjects in whom self-reports were consistent across dose and test–retest sessions. Subjects with CIP did not differ from those without CIP with respect to demographic, cocaine use, or cocaine self-administration variables. In conclusion, self-reports of CIP in the human lab are frequently endorsed, dose-dependent, and though variable between subjects, reproducible within subjects. Such methods may facilitate our understanding of the vulnerability to CIP in humans.

Keywords: Cocaine; Paranoia; Psychosis; Dependence; Self-administration

1. Introduction

Cocaine use can induce a range of transient psychotic experiences (Brady et al., 1991; Cubells et al., 2005), and cocaine-induced paranoia (CIP) is one of the most common symptoms associated with cocaine intoxication. Paranoia refers to an irrational belief that someone or something may cause harm to oneself, despite the fact that no such threat exists or that the perceived fear is out of proportion to the situation. As many as 50–80% of cocaine-dependent individuals endorse CIP during 'street' use of the drug (Bartlett et al., 1997; Brady et al., 1991; Cubells et al., 2005; Kalayasiri et al., in press; Rosse et al., 1994; Satel et al., 1991). CIP occurs almost invariably as a time-limited effect of cocaine (Brady et al., 1991; Satel et al., 1991) and resolves with sobriety. The positive symptoms of stimulant-induced psychosis, including paranoia, are indistinguishable from those seen in other primary psychoses, making it a valuable investigational model for idiopathic psychoses (e.g., schizophrenia). In addition, an understanding of CIP may have implications for understanding cocaine reward and aversion. For example, the clinical efficacy of disulfiram (i.e., Antabuse) in non-alcohol-dependent cocaine abusers (Carroll et al., 2004) has been hypothesized to result from its ability to increase the aversive effects (i.e., paranoia) associated with cocaine, thereby discouraging continued drug use. In this regard, an improved understanding of the vulnerability to CIP and its underlying neurobiology may facilitate medication development efforts for cocaine dependence.

Studies of CIP have most commonly relied upon retrospective self-report data obtained by interview (Bartlett et al., 1997; Brady et al., 1991; Cubells et al., 2005; Kalayasiri et al., in press; Rosse et al., 1994; Satel et al., 1991). In contrast, relatively few studies have examined CIP in a controlled

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experimental setting (Angrist, 1990; Addiction Research Center, NIDA; Muntaner et al., 1989; Sherer et al., 1988). The first laboratory demonstration of paranoid ideation occurred in a single subject administered intravenous cocaine (2 g) over a 12-h period (Addiction Research Center, NIDA). Subsequently, Sherer and colleagues reported evidence of "suspiciousness" in cocaine users ($n=8$) during a 4-h, continuous, intravenous (but not single bolus) administration of the drug as assessed by staff observations (Sherer et al., 1988). In contrast, Muntaner et al. (1989) found bolus cocaine injections (10–40 mg) capable of producing increases in self-reported 'suspiciousness' among chronic users of the drug ($n=8$). With these limited exceptions (3 studies, $N=17$ subjects), however, the vast majority of studies examining cocaine-induced subjective effects in the human laboratory (Cascella et al., 1994; Fischman and Schuster, 1982; Fischman et al., 1985; Foltin and Fischman, 1991; Foltin and Haney, 2004; Foltin et al., 2003; Kumor et al., 1989; Nagoshi et al., 1992; Van Dyke et al., 1978; Van Dyke et al., 1982; Ward et al., 1997a; Ward et al., 1997b), including studies examining the effects of anti-psychotic medications on cocaine administration (Evans et al., 2001; Gawin et al., 1996; Sherer et al., 1989) do not comment on the phenomenon.

Our group has recently developed a human laboratory paradigm of self-regulated cocaine administration under a fixed-ratio (FR1) schedule (Sughondhabirom et al., 2005). In that pilot study, we observed a modest and statistically significant effect of cocaine on visual analog scale (VAS) self-ratings of paranoia when compared to administration of placebo. However, the limited number of subjects ($n=8$) and the modest levels of paranoia precluded addressing questions about potential dose–response relationships and other factors that might account for vulnerability to the trait. Therefore, the current study focused on examining and characterizing CIP in an expanded sample ($N=28$) of cocaine users, who as part of several ongoing studies were allowed to self-administer cocaine in our laboratory "binge" self-administration paradigm.

2. Materials and methods

2.1. Subjects

Participants were 46 non-treatment seeking, cocaine-dependent volunteers studied as part of several ongoing inpatient studies (see below) conducted on the Clinical Neuroscience Research Unit (CNRU) and the Yale General Clinical Research Center (GCRC), New Haven, Connecticut. Subjects were between 18 and 45 (38.8±6.1), dependent on cocaine for at least 2 years, and actively using cocaine by a high potency, rapid onset route (i.e., smoking or intravenous; as confirmed by positive urine toxicology testing). Individuals with a primary psychotic disorder (e.g., schizophrenia) were excluded, as were individuals dependent upon alcohol, sedative-hypnotics, or opiates. Individuals were free of clinically significant medical (e.g., cardiac) and neurological (e.g., seizure) illness, as established by medical/psychiatric history and physical, neurological, and laboratory examinations (e.g., EKG, blood chemistries, hematology, and urinalysis). All subjects participated in a cocaine safety-eligibility screening session (Sughondhabirom et al., 2005). Nine of 46 individuals were excluded based on those criteria, resulting in the eligible study sample (i.e., $n=37$). Written informed consent was obtained from all participants, and studies were approved by the Yale Human Investigations Committee and the Yale GCRC General Advisory Committee. Demographic information (e.g., age, sex, race) and retrospective assessments of cocaine use history (e.g., age of onset of cocaine use, duration of cocaine use, average money spent for cocaine per day, days per week of cocaine use, and route of administration) were obtained by unstructured interview at the time of screening/enrollment.

2.2. Cocaine self-administration studies

As noted above, subjects participated in at least one of four ongoing/published inpatient studies in which self-administration procedures (see below) were the same, but study design and session number varied. Two were placebo-controlled validation studies, including, for reasons of subject safety, an initial escalating-dose, placebo-randomized design (four sessions total; 0, 8, 16, and 32 mg cocaine "binge" doses) (Sughondhabirom et al., 2005) and, for reasons of scientific rigor, a subsequent full randomized design (five sessions, 0–32 mg and 16 mg retest doses) (Lynch et al., in press). A third study examined the effects of binge cocaine and abstinence on sleep and cognition (three sessions, 32 mg, on consecutive days) (Morgan et al., in press). The fourth is an ongoing study examining the effects of acute placebo or disulfiram (250 mg) pretreatment on cocaine self-administration (three, placebo-pretreatment, sessions only; 8, 16, 32 mg cocaine doses). VAS data for paranoia have been previously presented in the former, but not latter, two studies. Subject data from all four studies are pooled in the current manuscript in order to maximize power for the chosen analyses (see below). In instances where subjects participated in more than one study, data from the first were used in examining demographic, cocaine use, and self-administration variables.

2.3. Cocaine self-administration sessions

All subjects participated in an identical "binge" paradigm of self-regulated intravenous cocaine administration under a FR1: 5-min timeout schedule. Sessions consisted of 2 h in which subjects had access to self-regulated, bolus infusions of placebo (0 mg) and/or active cocaine (8, 16, and 32 mg/70 kg body weight, hereafter referred to as 8, 16, and 32 mg; one dose condition per day), preceded/followed by 30-min baseline and 60-min washout periods, respectively. Except for the first 8 subjects (Sughondhabirom et al., 2005), in whom only the order of placebo was varied (see above), cocaine and placebo doses were randomized. Sessions were in all instances double-blind. Out of 37 eligible subjects, 28 successfully completed all study procedures without significant pump-withholding (i.e., cumulative threshold vital sign elevations in excess of 1 h; see below) [$N=5$ from Sughondhabirom et al., 2005; $N=13$ from

Lynch et al., in press; $N=10$ from ongoing disulfiram study, including 7 subjects prior to any disulfiram pretreatment, and 3 subjects a minimum of 2 weeks after acute disulfiram] including 18 from the initial two placebo-controlled validation designs ($N=5$ and 13, respectively).

2.4. Vital signs

Vital signs (heart rate, HR; systolic blood pressure, SBP; diastolic blood pressure, DBP) were measured at 5-min intervals throughout. Cocaine self-administration was temporarily suspended (HR ≥ 75% of age-adjusted maximum, SBP ≥ 170 mm Hg, DBP ≥ 100 mm Hg), reinstituted (HR ≤ 75% age-adjusted maximum on two consecutive readings with the second more than 10 bpm less, SBP ≤ 160 mm Hg, DBP ≤ 100 mm Hg), or permanently suspended (HR ≥ 160 bpm, SBP ≥ 180 mm Hg, DBP ≥ 110 mm Hg) for corresponding threshold vital sign changes to ensure the safety of participants during cocaine administration. Sessions were conducted in the presence of basic life support (BLS)- and advanced cardiac life support (ACLS)-trained research staff.

2.5. Subjective effects ratings

Subject reports of cocaine-induced subjective effects, including paranoia ("I feel paranoid"), euphoria ("I feel high") and craving ("I want cocaine"), were assessed at 5-min intervals by visual analog scale [VAS; 0 (not at all) to 10 (most ever)] using a touch-screen laptop computer. For the current study, paranoia was defined for subjects according to Satel et al. (1991) as an intense fear that one will be "caught" or harmed in some way, despite knowing that these things cannot happen. Cocaine self-administration behavior (i.e., responses for cocaine, cocaine infusions, inter-infusion interval, and cumulative cocaine intake, mg/70 kg) was recorded for each subject.

2.6. Test–retest assessments

Out of the 28 subjects analyzed, nine participated in more than one study, including eight subjects who participated in three 32 mg self-administration sessions on three consecutive test days (i.e., as part of the aforementioned study of cocaine, sleep, and cognition) (Morgan et al., in press). Within-study data in these eight subjects provided test–retest assessments of paranoia self-reports over short-term (i.e., 24 h) intervals, while 'between-study' assessments in these eight and one additional subject provided stability estimates over longer and more variable intervals.

2.7. Data analysis

Data were checked for normality prior to analysis using normal probability plots and Kolmogorov–Smirnov test statistics. Normally distributed data were analyzed using mixed effects models or two-tailed *t*-test. Non-normally distributed data were either subjected to transformation (e.g., log for dollars spent for cocaine per day, responses for cocaine; reciprocal for inter-infusion interval) or, if transformations did not achieve normality, analyzed using a nonparametric approach for repeated data (Brunner et al., 2002), Mann–Whitney test, or Spearman's correlation. Categorical non-repeated measures data were analyzed using a two-tailed χ^2 test or Fisher's exact test. All available data were used for each subject. Repeated measures data (e.g., subjective effects, vital signs) were analyzed for the 2 h (0–120 min) during which subjects had access to cocaine/placebo. When statistically significant interactions or main effects were observed, Bonferroni corrected post-hoc tests were used to explain these effects. Outcome consistency/test–retest reliability were assessed by intraclass correlation and two-sided Fisher's exact test. Analyses were performed using SPSS 11.0 for Mac OS X or SAS Version 9.12.

3. Results

Paranoia time–activity curves for all subjects are depicted in Fig. 1. When analyzed as a function of time (0–120 min), cocaine self-administration (8, 16, and 32 mg; $N=28$) showed significant main effects of dose (ANOVA-type statistic (ATS) $=9.3$, $df=1.9$, $p=0.0002$) and time (ATS $=3.5$, $df=8.6$, $p=0.0003$), but no dose x time interaction (ATS $=0.75$, $df=24.8$, $p=0.81$) (Brunner et al., 2002).

Analogous comparisons of mean paranoia ratings (i.e., average from 0–120 min) for each of the active conditions (i.e., 8, 16, and 32 mg; $N=28$) showed a similar pattern (main effect of dose, ATS $=11.7$, $df=1.8$, $p<0.0001$; 8 mg vs. 16 mg, ATS $=8.7$, $df=1$, $p=.01$; 16 vs. 32 mg, ATS $=5.6$, $df=1$, $p=0.05$; and 8 vs. 32 mg, ATS $=18.7$, $df=1$, $p=0.0003$; Bonferroni corrected). These mean VAS data are depicted according to self-administration dose in Fig. 2. When analysis was restricted to subjects who also participated in a placebo day ($N=18$), the dose effect remained significant (ATS $=8.5$, $df=1.9$, $p=0.0003$), with both the 16 and 32 mg doses producing statistically higher levels of paranoia than placebo (ATS $=7.1$, $df=1$, $p=0.02$ and ATS $=13.4$, $df=1$, $p=0.001$ respectively; Bonferroni corrected).

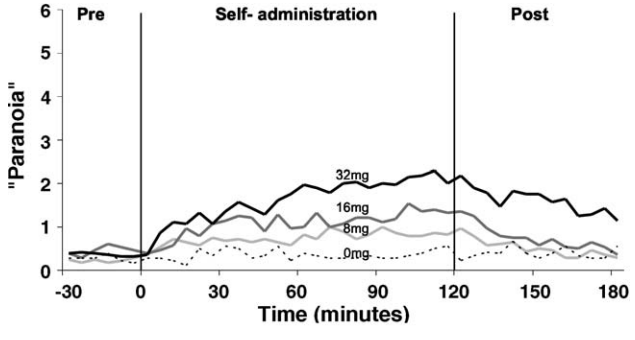

Fig. 1. Group visual analog scale (VAS; 0 = not at all, 10 = most ever) self-ratings of paranoia are depicted according to cocaine dose as a function of time (min). VAS time–activity curves show significant main effects of dose and time, but not a significant dose-by-time interaction for active–dose (i.e., 8, 16, and 32 mg; $N=28$; ATS $=9.3$, $df=1.9$, $p=0.0002$; ATS $=3.5$, $df=8.6$, $p=0.0003$; ATS $=0.75$, $df=24.8$, $p=0.81$, nonparametric mixed effects model). VAS self-ratings for placebo (0 mg) sessions ($N=18$) are included as a reference.

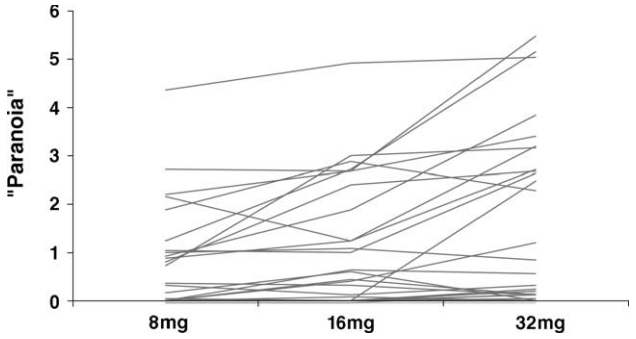

Fig. 2. Mean VAS self-ratings of paranoia are shown for individuals ($N=28$) as a function of cocaine dose (8, 16, and 32 mg). A significant main effect of dose (ATS = 11.7, $df=1.8$, $p<0.0001$, nonparametric mixed effects model) was observed. Pair-wise comparisons showed significant differences between individual doses (8 mg vs. 16 mg, ATS = 8.7, $df=1$, $p=0.01$; 16 vs. 32 mg, ATS = 5.6, $df=1$, $p=0.05$; and 8 vs. 32 mg, ATS = 18.7, $df=1$, $p=0.0003$; Bonferroni corrected). Consistency of within-subject response data was also observed after controlling for dose differences ($N=12$ subjects with the highest VAS paranoia scores at 32 mg; intraclass correlation coefficient = 0.62).

Visual inspection of the distribution of VAS ratings across active cocaine doses suggested two important features of these data, including 1) considerable between-subject variably in self-reported paranoia across all doses (Fig. 2), and 2) a skewed and seemingly discontinuous distribution in subjective paranoia at the 32 mg dose (e.g., in contrast to subjects' self-ratings of euphoria or 'high') (Fig. 3). Based on our interest in understanding factors that might underlie the observed variability in these data (Fig. 2), we divided subjects into two operationally defined groups, designated as 'paranoid' (i.e., mean VAS self-ratings of ≥ 2.0 during the 32 mg session; $N=12$) and 'non-paranoid' (mean VAS score ≤ 1.5; $N=16$). These groupings, though based initially upon the visual distribution of data from the 32-mg dose (Fig. 3), were indirectly supported by the within-subject consistency of response data at other doses (i.e., intraclass correlation coefficient for subjects in the paranoia group was 0.62, controlled for dose). Alternatively stated, 11 of the 12 subjects with the highest paranoia ratings at 32 mg (e.g., VAS score ≥ 2.0) also reported the most intense paranoia at the lower doses (i.e., 8 and 16 mg) (Fig. 2).

VAS data for paranoid and non-paranoid groups are depicted in Fig. 4. Paranoid subjects ($N=12$) showed significant main effects of time (ATS = 5.7, $df=6.3$, $p<0.0001$) and cocaine dose (ATS = 13.7, $df=2.0$, $p<0.0001$) on VAS self-ratings (but no dose x time interaction: ATS = 0.9, $df=11.9$, $p=0.60$), while the non-paranoid subjects showed no significant effects ($N=16$; time: ATS = 0.8, $df=7.2$, $p=0.59$; dose: ATS = 1.3, $df=1.9$, $p=0.27$; dose x time: ATS = 0.8, $df=11.3$, $p=0.68$). VAS paranoia self-ratings were stable in test–retest analyses of subjects receiving repeated 32 mg sessions over both short (i.e., 1 day; $N=8$; intraclass correlation coefficient = 0.94) and long intervening intervals (18–979 days, mean ± S.D. = 295 ± 354 days, median = 159 days; $N=9$; intraclass correlation coefficient = 0.92). Categorical analyses of group status (i.e., paranoid vs. non-paranoid) were also statistically significant (i.e., no individual experienced a change in classification over short or long intervals; $p=0.03$, and 0.008, respectively, Fisher's exact test two-sided), supporting the stability of our operational definitions (Fig 5).

Demographic, cocaine use, and laboratory self-administration data for 32 mg sessions were then compared for paranoid and non-paranoid subjects (Table 1). With the exception of race ($p=0.05$, Fisher's exact test two-sided) and baseline paranoia (averaged from −30–0 min; 32 mg session; Mann–Whitney $U=49.5$, $p=0.01$), paranoid subjects did not significantly differ from non-paranoid subjects with respect to demographic (age, gender), cocaine use (age of first use, duration of use, money spent, days per week), cocaine-induced subjective effects ("high", "want cocaine"), or vital signs (HR, SBP, DBP), or cocaine self-administration behavior (responses, infusions, inter-infusion interval, or total cocaine intake). Similarly, total cocaine intake was not significantly different between groups at any cocaine dose (i.e., 8, 16, or 32 mg). In addition, no correlation between cocaine intake and self-ratings were noted among vulnerable individuals (i.e., 8 mg: Spearman's rho = −0.3, $p=0.29$; 16 mg: Spearman's rho = −0.1, $p=0.79$; 32 mg:

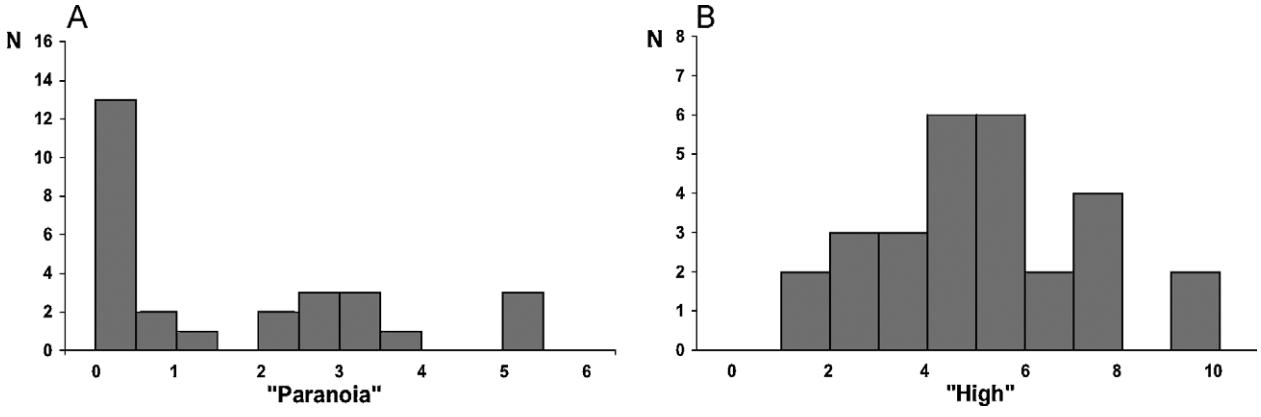

Fig. 3. Distributions of VAS "paranoia" (A) and "high" (B) ratings during cocaine (32 mg) self-administration are depicted. In contrast to a seemingly symmetric distribution of euphoria self-ratings, paranoia self-ratings were skewed and discontinuous.

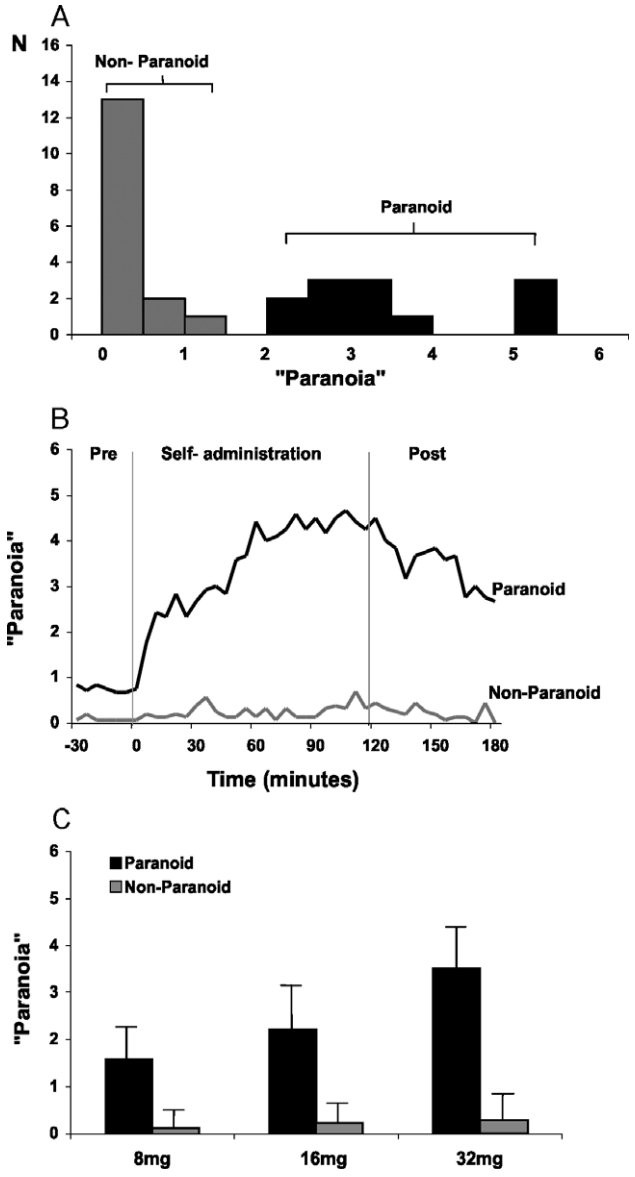

Fig. 4. VAS self-ratings of paranoia during cocaine (32 mg) self-administration for operationally defined groups of paranoid (N=12, black) and non-paranoid (N=16, grey) (A). Significant main effects of time and dose were observed in the paranoid (ATS=5.7, df=6.3, p<0.0001 and ATS=13.7, df=2.0, p<0.0001), but not the non-paranoid group (ATS=0.8, df=7.2, p=0.59; ATS=1.3, df=1.9, p=0.27) (B and C).

Spearman's rho=0.1, p=0.75). Notably, the observed effects of race and baseline paranoia did not withstand correction for multiple comparisons (p<0.003 threshold by Bonferroni).

4. Discussion

Our data shows that chronic cocaine users endorse subjective paranoia in response to repeated, bolus, drug self-administration in the human laboratory. Cocaine produced subjective responses that were dose dependent and distinguishable from placebo. Self-ratings of paranoia were highly variable across individuals, suggesting a spectrum of vulnerability to the trait. CIP was time-limited in all instances and required no clinical intervention/treatment. Categorical analyses showed that our findings were accounted for by a consistently (across doses and sessions) vulnerable subset of subjects. Interestingly, no other demographic, cocaine use, cocaine-induced subjective effect, vital sign or cocaine self-administration variable distinguished paranoid and non-paranoid groups. These data suggest that the self-reported susceptibility to cocaine-induced paranoia, at least under the experimental methods employed, may be primarily influenced by "intrinsic" (i.e., genetic, neurodevelopmental) factors.

In contrast to a prior laboratory study of 'suspiciousness' induced by continuous cocaine infusion (Sherer et al., 1988), subjects in our study self-reported paranoia without difficulty and at moderate rates and levels. Our findings are consistent, however, with positive self-report data from at least two prior laboratory studies of the trait (Addiction Research Center, NIDA; Muntaner et al., 1989) and our initial observations in a small subset of the current cohort (Sughondhabirom et al., 2005). Just recently, Mooney and colleagues also showed measurable self-reports of paranoia from single doses of smoked cocaine (Mooney et al., in press). One major difference between the Sherer study and ours was the use of a regimen of repeated drug boluses, a pattern that more closely mimics 'street' use and may more robustly elicit CIP (Gawin, 1991; Post and Kopanda, 1976). Alternatively, more rapid rates of consumption (i.e., roughly comparable cumulative doses over 2 instead of 4 h) may also be a factor. Certainly, rate-dependent effects of cocaine are well-established (Balster, 1988; Nademanee, 1992; Samaha and Robinson, 2005) and may pertain to paranoia, as well. Future studies that more directly compare patterns of administration, while controlling for dose and route, will be informative in this regard.

We cannot exclude the possibility that subjects' self-ratings of paranoia constitute 'false-positive' endorsements (unlikely) or, alternatively, misspecification of other cocaine-induced subjective effects as psychosis-spectrum (e.g., anxiety). Prior studies have noted a correlation between measures of trait anxiety and CIP self-reports (Rosse et al., 1995). Operational definitions of 'paranoia' were specifically employed with subjects to guard against such misspecification. Moreover, anecdotal accounts of symptoms by subjects following self-administration sessions were consistent with the kind of paranoid ideation commonly reported by subjects during 'street' use (e.g., fear of being discovered, caught, tracked-down by others, etc.) (Bartlett et al., 1997; Brady et al., 1991; Harris and Batki, 2000; Manschreck et al., 1987; Mitchell and Vierkant, 1991; Rosse et al., 1994; Satel et al., 1991; Serper et al., 1999). Nonetheless, future prospective studies will benefit from a more complete characterization of the nature and severity of such symptoms using recently developed and validated scales for cocaine-induced psychotic symptoms (Cubells et al., 2005). Alternatively, in the absence of more objective methods of assessment, reductions in paranoia self-reports by pharmacologic agents with known antipsychotic properties and/or association of such symptoms with other vulnerability factors (e.g., allelic variants associated with CIP) (Cubells et al., 2000; Gelernter et al., 1994) would be indirectly corroborative.

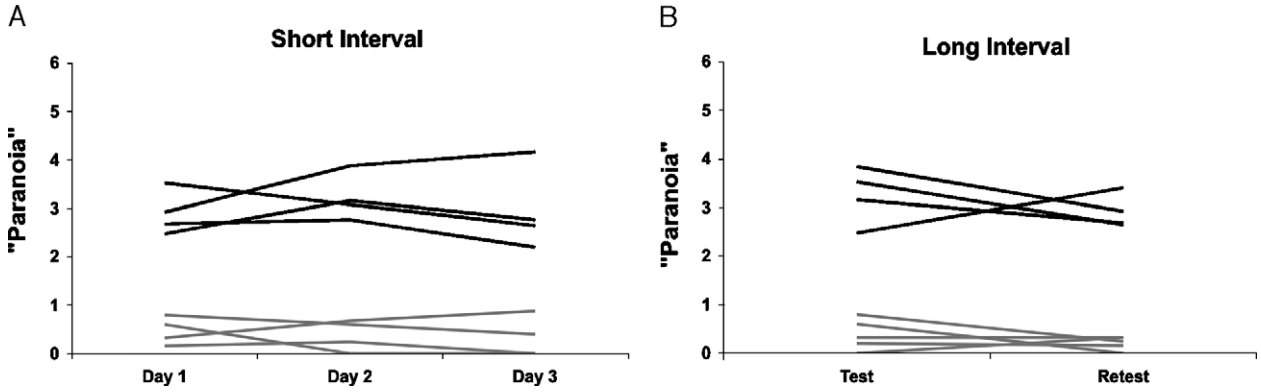

Fig. 5. Paranoia self-ratings during cocaine self-administration (32 mg dose) are shown for short (24 h; A; $N=8$; intraclass correlation coefficient = 0.94) (one subject in paranoid group had no cocaine infusion on day 2), and long intervening intervals (18 to 979 days; median 159 days; B; $N=9$; intraclass correlation coefficient = 0.92) (black line = paranoid; grey line = non-paranoid, as defined in Fig. 4). Group categorizations were statistically stable over these same intervals (i.e., $p=0.03$ and $p=0.008$, respectively; Fisher's exact test two-sided).

Our demonstration that laboratory self-ratings of CIP are dose-dependent is consistent with retrospective reports suggesting that the amount of cocaine use is a significant risk factor for CIP (Brady et al., 1991; Kalayasiri et al., in press). However, this effect was only observed among 'vulnerable' individuals. Specifically, individuals defined as 'non-paranoid' by our operational study criteria did not use less cocaine during laboratory sessions, nor did they report less 'street' cocaine use than 'paranoid' individuals.

Two other findings merit brief mention. We observed an increased risk for CIP among African-American (AA) subjects prior to statistical correction for multiple comparisons. This finding is potentially consistent with a published literature in non-drug dependent individuals (Blazer et al., 1996; Cohen et al., 2004; Griffith and Baker, 1993). However, several retrospective self-report studies in cocaine dependent populations have previously pointed to either opposite trends (i.e., increased risk among European American subjects) (Brady et al., 1991; Kalayasiri et al., in press) or negative associations (Bartlett et al., 1997; Satel et al., 1991). Similarly, prior to correction, VAS self-ratings of baseline paranoia (i.e., prior to cocaine) were also increased, raising the intriguing possibility that the subject's preexisting state, might predict susceptibility to subsequent drug response (e.g., consistent with prior reports of trait anxiety predicting CIP vulnerability) (Rosse et al., 1995). Such a possibility warrants further investigation.

Table 1
Demographic, cocaine use, and self-administration data in subjects with and without self-reported cocaine-induced paranoia (32 mg sessions)

	Paranoid ($N=12$)	Non-paranoid ($N=16$)	p-value
Age	40.1±5.2	37.3±6.5	0.20
Gender	8 M, 4 F	11 M, 5 F	1.0
Race	10 AA, 2 EA	7 AA, 9 EA	0.05 [a]
Age of first cocaine use (years)	20.4±4.9	19.2±3.1	0.44
Duration of cocaine use (years)	19.7±5.8	19.0±5.1	0.75
Money spent for cocaine per day	138±99	152±135	0.79
Days per week of cocaine use	5.8±1.6	5.5±1.8	0.76
Baseline "Paranoia" (VAS score)	0.7±1.0	0.1±0.3	0.01 [a]
"High" (VAS score)	4.0±1.9	4.1±1.8	0.91
"Want cocaine" (VAS score)	4.3±2.0	3.4±2.1	0.30
Heart rate (bpm)	102±10	100±13	0.66
Systolic BP (mm Hg)	136±11	142±13	0.20
Diastolic BP (mm Hg)	78±8	81±7	0.41
Responses (i.e., button presses)	30±50	89±216	0.74
Infusions	7.8±3.7	7.6±2.6	0.92
Inter-infusion Interval (min)	20.2±10.8	20.3±15.9	0.97
Cocaine intake (mg)			
32 mg session	248±119	244±84	0.92
16 mg session	152±67	154±66	0.94
8 mg session	88±32	95±33	0.58

[a] Not significant after Bonferroni correction ($p<0.003$ threshold).

Several limitations of the current study merit discussion. Though large for a laboratory study, issues of sample size may still have resulted in false negative findings with respect to demographic, cocaine use, and/or cocaine self-administration variables. Similarly, false-negative self-reports might have influenced our findings as well. Consistent with this possibility, rates of CIP (43%) in our laboratory study are low in comparison to data from retrospective surveys (50–80%). Several factors could account for these reduced rates. For example, the legal and authorized consumption of cocaine in a safe, hospital setting may have attenuated subjects' paranoid feelings. Alternatively, insensitivity of our primary rating scale and/or the lack of corroborative clinician ratings by research staff could have led to false negative results in some individuals (e.g., we are aware of one research subject that endorsed paranoia after the session that was not reflected in VAS self-ratings during the session), and our study did not elicit information about other positive psychotic symptoms (e.g., hallucinations). Finally, some subjects may not have had the chance to express their vulnerability to the trait by virtue of limitations of the experimental context (e.g., limits on cumulative cocaine consumption, session length, etc.).

In spite of these limitations, the frequency and intensity of paranoia observed suggest that CIP is amenable to laboratory study. Improved and objective methods for studying cocaine-induced psychotic symptoms will be of value for

understanding their neurobiologic and genetic bases initially, and their implications for the treatment of cocaine dependence, ultimately.

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