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Prevalence of Traumatic Brain Injury in Cocaine-Dependent Research Volunteers

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Abstract

Background—There is a high prevalence of traumatic brain injury (TBI) among those with substance dependence. However, TBI often remains undiagnosed in these individuals, due to lack of routine screening in substance use treatment settings or due to overlap in some of the cognitive sequelae (eg impulsivity, disinhibition) of TBI and cocaine dependence.

Methods—The prevalence of self-reported mild to moderate TBI in a group of cocaine-dependent ($n = 95$) and a group of healthy volunteers ($n = 75$) enrolled at the same facility was assessed. Additionally, the relationship between TBI and clinically relevant correlates, including impulsivity, cocaine use history, and treatment outcome in the cocaine-dependent group was also examined.

Results—A higher proportion of individuals with cocaine dependence (29.5%) reported having suffered a TBI in their lifetime compared to controls (8%) on a Closed Head Injury scale. Among cocaine users, the average age of sustaining TBI was significantly lower than the age of initiating cocaine use. Presence of TBI was not associated with higher impulsivity on the Barratt Impulsiveness Scale-11 or self-reported years of cocaine use. No differences were noted on treatment outcome for cocaine dependence as measured by treatment effectiveness scores (TES) between cocaine users with TBI and their non-TBI counterparts.

Conclusions—These results are the first to highlight the high prevalence of TBI among individuals with cocaine dependence. This study underscores the possible role of TBI history as a

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

risk factor for onset of cocaine use, however, more research is needed to determine the impact of co-morbid TBI as a complicating factor in the substance abuse treatment setting.

INTRODUCTION

Traumatic brain injury (TBI) and substance use disorders (SUD) commonly co-occur.¹⁻⁴ Mild traumatic brain injury (mTBI) or a concussion, occurs when trauma to the head is combined with one or more of the following symptoms: confusion or disorientation; loss of memory of events before or after the injury; and/or loss of consciousness lasting less than 30 minutes. On the other hand moderate TBI occurs when head trauma results in a loss of consciousness from 20 minutes to 6 hours which could lead to cognitive deficits including difficulties in attention, memory, concentration, impulsiveness, and other executive functions and possible impairments in speech, sensory-motor functions and social-emotional behaviors. Strikingly, mTBI accounts for almost 85% of all TBIs and remains largely undiagnosed.⁵ Patients with even a single mTBI can exhibit persistent emotional, cognitive, behavioral, and physical symptoms, alone or in combination, which may produce a functional disability.⁶ Consistent with that notion, studies from the literature highlight TBI as contributing risk factor for substance abuse.⁷⁻⁹ Previous studies underscore the impact of TBI (regardless of injury severity) on substance abuse, where a history of at least one TBI is associated with worsening abuse severity (primarily alcohol), greater number of prior treatment episodes, earlier onset of prior use, and poorer SUD treatment outcomes.¹⁰⁻¹² Conversely, individuals with a history of SUD are at a higher risk for sustaining TBI, possibly from increased risk-taking while under the intoxicating effects of substances.^{2,9,13} Furthermore, lifetime or current substance abuse, regardless of intoxication at the time of injury, may be a risk factor for escalation of drug use post-injury.^{1-3,14,15}

Increased impulsivity is common to both TBI and SUD. A frequent consequence of impulsivity is behavioral problems that may influence social and financial decision-making. In two studies by Wood and colleagues, subjects with TBI were compared to healthy age-matched controls across impulsivity measures including delayed reward tasks and the Barratt Impulsiveness Scale Version-11 (BIS-11) questionnaire. The results showed that rates of temporal discounting and BIS-11 scores were significantly higher amongst the TBI group.^{16,17} Temporal discounting is the tendency to discount rewards as the time to reward receipt becomes farther into the future and is a measure of impulsive choice. A study by RoCHAT and colleagues extended these findings using the UPPS impulsivity questionnaire and the stop-signal task demonstrating that subjects with TBI exhibited higher urgency, lack of premeditation, and poorer prepotent response inhibition.¹⁸ Prepotent response inhibition refers to inhibition of a response for which immediate reinforcement is available or has been previously associated with that response and is a measure of rapid response impulsivity. However, these observations of impaired impulsivity and decision-making were restricted to subjects with moderate to severe TBI, and the impact of mTBI on these behavioral measures remains unclear. Amongst those with SUD, it is well established that cocaine-dependent individuals reliably display higher impulsivity ratings compared to controls as measured by standard self-report instruments such as the BIS-11 as well as laboratory behavioral tasks.¹⁹⁻²¹ However, the impact of co-occurring TBI and cocaine dependence on impulsivity is unknown.

While there is a small body of literature examining prevalence of TBI among those with SUD,^{4,12,22} even fewer studies have looked exclusively at occurrence of TBI amongst those with cocaine dependence. In parallel, the ADHD (attention deficit hyperactivity disorder) literature suggests that individuals who are at risk for cocaine dependence such as those with ADHD are also at risk for TBI.^{23,24} One study reported that treatment-seeking substance abusers with TBI were more likely to have used cocaine, however there was no information on cocaine use patterns or severity of TBI in these individuals.¹⁰ The overall lack of information is, in part, the result of the fact that TBI, especially mTBI, often remains undiagnosed in these individuals, as identification of brain injury in clinical treatment settings for substance abuse is not routine. Additionally, due to overlap in some cognitive sequelae of the two conditions, cocaine dependence may mask the presence of symptoms of TBI.

Thus, there is a need to better understand the relationship between TBI and cocaine use disorders. To achieve this goal, the prevalence of self-reported mild to moderate TBI in a group of individuals with cocaine dependence and a group of healthy volunteers was assessed. Healthy volunteers and cocaine-dependent subjects were recruited at the same research clinic. Cocaine users with and without self-reported TBI were compared on measures of impulsivity and cocaine use history. In the subgroup of treatment-seeking cocaine-dependent patients, the relationship between TBI and treatment outcome was examined. The overall hypotheses were that: (a) the prevalence of TBI would be higher in cocaine-dependent subjects compared to healthy controls; (b) the co-occurrence of cocaine dependence and TBI would be associated with higher impulsivity, greater length of cocaine use, and poorer treatment outcome.

MATERIALS AND METHODS

Subjects

The sample consisted of 75 healthy control subjects and 95 cocaine-dependent subjects recruited from previous treatment and non-treatment studies over the last ten years using the same diagnostic, psychometric, and advertising procedures. Subjects were recruited via newspaper advertisements, and were initially screened by a brief telephone interview. Individuals were excluded if they indicated significant psychiatric or medical conditions, including a self-reported history of severe brain injury. Following the phone screen, eligible subjects attended an in-person intake assessment session, where they were screened for psychiatric disorders using the structured clinical interview for DSM-IV (SCID-I),²⁵ and completed a medical history and physical examination. Information about the participants' demographic and drug use history was also collected at the intake interview. Drug use history included information about severity of cocaine use related to length of cocaine use. All subjects were tested for urine cocaine (benzoylecgonine), tetrahydrocannabinol (THC), opiates, amphetamine, methamphetamine, and benzodiazepines using integrated E-Z split key cup II (Innovacon Company, San Diego, CA) on each visit to the clinic. Eligible cocaine-dependent subjects met current DSM-IV criteria for cocaine dependence; did not meet DSM-IV current dependence criteria for abused drugs other than cocaine, marijuana, nicotine or alcohol; did not have current or past medical disorders affecting the central

nervous system; and did not have current axis I disorders other than substance abuse or dependence. The cocaine-dependent sample included subjects seeking treatment ($n = 42$) and not seeking treatment ($n = 53$). The treatment-seekers were part of studies in which they received manual driven cognitive behavioral therapy, and were randomized to either placebo or any one or combination of the following medications: levodopa/carbidopa, citalopram, mirtazapine, naltrexone, modafinil or dextroamphetamine. All data from treatment-seekers except treatment effectiveness scores (TES) were collected at intake prior to the start of medication or behavioral therapy.

Control subjects consisted of participants who did not have a positive drug screen and did not have any current or past DSM-IV axis I disorders (including substance dependence) or medical disorder affecting the central nervous system. Control subjects were recruited via similar advertising procedures as the cocaine-dependent subjects.

All subjects were free of alcohol at the time of testing as determined by a breathalyzer (Intoximeters, Inc., St. Louis, MO). Female subjects were excluded if they had a positive urine pregnancy test. All data were collected at the University of Texas–Houston, Center for Neurobehavioral Research on Addictions. All subjects were compensated for their participation. Subjects were fully informed of the nature of the research and provided written consent for their involvement in accordance with the Declaration of Helsinki. The studies from which subject data was included were approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston.

Closed Head Injury (CHI) Scale

The Closed Head Injury (CHI) scale was used to determine if the subjects had suffered any type of mild to moderate TBI in their lifetime. The CHI scale is a 13-item self-report measure designed by a member of the research team (Moeller). The CHI scale was developed to assist in patient recall of prior instances of head trauma, including number of head trauma instances, duration of loss of consciousness/confusion, posttraumatic amnesia, age of first injury, hospitalizations related to the injury, etc. For the purpose of the current study, subjects who answered “yes” to the question “Have you ever been hit in the head so hard, either by another person or in an accident, that it knocked you out or made you confused?” and responded “<30 minutes” and “30 minutes-1 day” to the question “What is the longest period of time that you were knocked out or confused?” as confirmed by the interviewer, were considered to have had suffered mild to moderate TBI. (For a copy of the complete scale, please contact the corresponding author).

Barratt Impulsiveness Scale (BIS-11)

The BIS-11 is a 30-item self-report scale with three oblique factors: attentional/cognitive, measuring tolerance for cognitive complexity, and persistence; motor, measuring the tendency to act on the spur of the moment; and non-planning impulsivity, measuring the lack of sense of the future.²¹ Impulsivity as measured by the BIS-11 is considered “trait-like” because the questionnaire focuses on “the kind of person you are,” in contrast to “state-like” measures of impulsivity using behavioral laboratory tasks. Items are rated from 1 (absent) to 4 (most extreme); scores range from 30–120 with non-psychiatric controls

generally scoring 50–60.²⁶ Several studies have shown that individuals with SUD including cocaine have higher total BIS-11 scores than controls.^{21,27,28}

Treatment Effectiveness Score (TES)

The TES is commonly used in pharmacotherapy trials as an objective measure of treatment efficacy. Typical treatment outcome measures include treatment retention, which is the number of outpatient sessions successfully attended by the patient, and drug use measured by urinalysis, as a biochemical measure of abstinence. However, individually these measures can be incomplete indices of treatment outcome, as retention can be independent of drug use and vice versa. The TES is a composite score that records the number of negative urine screens of the drug of choice over the length of treatment, with each “clean” urine earning a point on the TES.²⁹ In this way, the TES is influenced by retention and abstinence, and sample attrition does not directly affect this measure. For example, patients who attend clinic visits reliably and give negative urine samples for the drug being tested obtain high scores. On the other hand patients who attend clinic visits reliably but have positive urine drug screens would obtain low TES scores. The TES has been shown to correlate with traditional objective and subjective measure outcomes in cocaine medication trials as well as the Addiction Severity Index (ASI) drug subscales.^{30,31}

Statistical analysis

Differences in demographic variables between groups were compared using the non-parametric or student's *t*-test for continuous variables (after determining normality of data) and the chi-square test for categorical variables. Non-parametric *t*-tests were used if results were found to lack normal distribution as per the Shapiro-Wilk test. Logistical regression was used to include age, gender, education, co-morbid marijuana abuse, and alcohol dependence as co-variables while comparing occurrence of TBI between control and cocaine-dependent subjects. Differences between controls and cocaine-dependent subjects for BIS-11 scores were analyzed using non-parametric *t*-test. Among the cocaine-dependent participants, effect of TBI on impulsivity, severity of cocaine use and TES was compared using non-parametric *t*-test. It has been recommended that effect sizes be reported along with *p*-values to provide information about the clinical significance of an effect in addition to its statistical significance. Accordingly, the Cohen's *d* was calculated for the comparisons between TES for cocaine-dependent subjects with and without TBI.^{32,33} All data are presented as means ($\pm$ SD) and results were considered statistically significant when *p* values were ≤ 0.05 .

RESULTS

Subject Characteristics

Demographic data for 95 cocaine-dependent subjects and 75 control subjects included for analysis in the present study is represented in Table 1. Of the 95 cocaine-dependent subjects, 42 subjects were seeking treatment for their cocaine use, while the remaining 53 subjects were non-treatment seeking research volunteers. The cocaine-dependent subjects were more likely to be male, older ($t = -5.3$; $p < .01$), and to report fewer years of education ($p < .01$) compared to controls. Cocaine users and controls did not differ in ethnicity ($\chi^2 = 14.3$, $p = .$

08), but differed in gender distribution ($\chi^2 = 11.6$; $p < .01$) compared to controls. Cocaine-dependent subjects reported the age of first use of cocaine to be 23.0 ± 6.1 years with the duration of regular use to be 12.7 ± 8.0 years. Rates of lifetime (past or current) cannabis abuse and alcohol dependence in the cocaine-dependent groups were 40% and 37.9%, respectively, which is consistent with findings from previous studies.^{34,35} Within the cocaine-dependent subjects, the treatment and non-treatment seekers did not differ significantly with respect to age, years of education, or severity of cocaine, alcohol, and marijuana use (data not shown), and thus, all cocaine users were grouped together for further analysis.

Prevalence of TBI among Research Participants

Cocaine-dependent participants exhibited a significantly higher prevalence of TBI compared to controls ($\chi^2 = 12.079$; $p < .001$; Table 1). Furthermore, a logistical regression analysis showed that cocaine use predicted occurrence of TBI in this population while including age, gender, and alcohol dependence and marijuana abuse as co-variables ($p < .01$). Among the cocaine-dependent subjects, 29.5% ($n = 28$) reported having experienced TBI on the CHI scale, while only 8% ($n = 6$) of controls reported a TBI. Among cocaine users with TBI, 64.3% ($n = 18$) reported having experienced only one incident of brain injury, while the remaining 35.7% ($n = 10$) reported two or more TBIs. Cocaine users predominantly met criteria for mTBI (82%; $n = 23$) (as measured by loss of consciousness < 30 minutes) while a small percentage of cocaine users (18%; $n = 5$) indicated loss of consciousness > 30 minutes on the CHI scale indicative of moderate TBI. All control subjects ($n = 6$) met criteria for mTBI and suffered only one incidence of brain injury. Finally, among cocaine users with TBI, 60.9% and 31.6% of participants reported lifetime alcohol dependence and marijuana abuse respectively. Among cocaine users without TBI, 41.1% and 56.1% of participants reported lifetime alcohol dependence and marijuana abuse respectively. However, presence of alcohol dependence ($\chi^2 = 2.57$; $p = .109$; Table 1) or marijuana abuse ($\chi^2 = 3.34$; $p = .064$; Table 1) was not significantly associated with occurrence of TBI in this population.

Effect of TBI on Impulsivity

Of the 170 subjects, 169 had completed the BIS-11 self-report questionnaire. BIS-11 data was unavailable for one control subject. Consistent with previously published data, control subjects had significantly lower BIS-11 scores on all three sub-scales as well as the total score compared to cocaine-dependent subjects (Table 2). Within the cocaine-dependent population, BIS-11 scores of subjects with and without TBI were compared. Occurrence of TBI was not significantly related to scores on the BIS-11 motor ($p = .28$), attentional ($p = .50$), non-planning ($p = .31$) or total ($p = .37$) scores.

Impact of TBI on Cocaine Use and Treatment Outcome

Complete cocaine use history data was available for 87 (out of 95) cocaine-dependent participants. Occurrence of TBI was not significantly related to years of cocaine use ($p = .29$). Subjects with TBI reported using cocaine for 14.08 ± 7.76 years, whereas those without TBI had used cocaine for 12.24 ± 7.98 years. Notably, the age of sustaining the first TBI (16.32 ± 7.87 years) was significantly earlier ($t = 2.95$; $p < .01$; $n = 17$; Fig. 1) than the age

of initiation of cocaine use (22.97 ± 6.06 years). Overall, 84% of cocaine-dependent participants suffered TBI at a younger age than initiation of cocaine use. In order to determine the relationship between TBI and treatment outcome, TES scores were computed for treatment-seeking cocaine participants ($n = 34$) for whom urinalysis results were available. TES scores were not significantly different ($p = 0.13$) between cocaine users with TBI (2.62 ± 3.40 ; $n = 13$) compared to those without TBI (6.81 ± 8.22 ; $n = 21$). Since the sample size of the subjects with TBI who were in treatment was relatively small, effect size was calculated in order to estimate the sample size that would be needed to detect an effect of TBI on treatment outcome. The calculated effect size based on the differences between these two groups was in the medium effect size range (Cohen's $d = 0.61$). Based on a medium effect size, to have a power of 0.8 to detect a difference between groups at an alpha of 0.05 would require 64 subjects per group,^{32,33} suggesting the study was underpowered for TES score differences, and that a history of TBI could be statistically significant in a larger group.

DISCUSSION

Relative to healthy controls, a significantly higher rate of TBI was observed among cocaine users. Overall, approximately 30% of cocaine users reported sustaining at least one TBI in their lifetime. While previous literature has shown that moderate to heavy drinkers are more prone to TBI,⁸ this is the first study examining a similar association with cocaine dependence. On the other hand, despite higher prevalence amongst cocaine users, occurrence of TBI was not significantly related to length of cocaine use or treatment outcome. Cocaine subjects with TBI had overall greater number of years of cocaine use and lower TES scores but these were not significantly different from cocaine subjects without TBI. Additionally, while BIS-11 scores of cocaine users were significantly higher than those of control subjects, they did not differ amongst cocaine users with and without TBI. Thus, these data suggest that lifetime occurrence of TBI may not be related to cocaine use severity.

The study featured several limitations related to the sample characteristics. First, the cocaine users were significantly older than control subjects; however, the mean age of sustaining TBI was similar in the two groups. Thus, all subjects sustained TBI at a much younger age compared to the age at which they participated in the study. Next, we had a relatively small number of treatment-seeking subjects and subsequently a smaller sample of those with TBI. While TES scores for treatment-seekers with TBI was higher than those without, it is possible that the lack of statistical significance in the group comparison was related to the small sample size. Finally, there were also limitations with regard to the specifics of the TBI (eg, injury characteristics and recovery). The CHI scale, a new, previously unpublished brain injury scale, was the only measure of brain injury used to assess occurrence of TBI. Inclusion of validated measures of TBI screening such as the OSU TBI scale may yield more accurate assessments of TBI characteristics and sub-types in our subject population.

The lack of association between TBI, cocaine dependence, and impulsivity measures could be attributed to methodological issues, specifically, the exclusion of subjects with moderate to severe TBI, and those with neurological impairments or severe physical or psychiatric conditions. However, cocaine-dependent subjects were part of studies examining cocaine

dependence as the primary area of interest; therefore any other psychiatric or neurological co-morbidities were exclusionary. Previous studies have shown that increased impulsivity is a distinguishing feature of moderate and severe TBI,^{16–18} but not necessarily mTBI, which accounted for majority of our sample. However, it also possible that elevation of impulsivity due to TBI may be masked by deficits produced by cocaine dependence (although TBI could also further increase the likelihood of impulsive behavior). Another shortcoming is the use of a single measure of impulsivity, the BIS-11 questionnaire, which is a measure of self-reported, trait-like impulsivity, and it may not be the optimal choice as the only impulsivity measure for this subject population. On the other hand some of the other relevant cognitive symptoms of mild to moderate TBI include deficits in attention, concentration, perception, memory, speech/ language, or executive functions. It may be advantageous in future work to include a battery of behavioral measures that examine attention and memory in studies on the effects of TBI in individuals with SUD.

In the present study, the average age of sustaining TBI was lower than age of onset of cocaine use and 84% of individuals reported sustaining a TBI before initiation of cocaine use. These findings suggest that in most individuals, TBI preceded initiation of cocaine use and could be considered as a contributing risk factor for CUD. Given that majority of the subjects suffered mTBI, an important point to consider is that only 12–15% of subjects with mTBI exhibit any kind of persistent long-term cognitive and behavioral deficits >1 year post-injury. On the other hand 66% of those with moderate and 100% of those with severe TBI display some variety of cognitive disability post-injury.³⁶ Thus timing appears to be key when evaluating risk for SUD amongst those with TBI. Consistent with that hypothesis, a recent retrospective study in military personnel found that those with mTBI were at a greater risk for SUDs compared to non-TBI injury controls within the first 30 days of sustaining injury, with the risk for alcohol dependence remaining up to 6 months post-injury.³⁷ On another note, the majority of our sample with TBI consisted predominantly of cocaine users who had reported only one mTBI in their lifetime, while a small proportion had suffered multiple injuries. A study by Sacks and colleagues suggests that sustaining multiple TBIs may increase risk and significantly lower age of onset of substance abuse.¹⁰ Due to sample size limitations ($n = 10$) we were unable to examine this relationship in our population. Future studies may consider exploring similar measures in a population with multiple TBIs or closely observing cocaine use patterns shortly after brain injury, which may predict cocaine dependence later in life.

In conclusion, the current study found that, like other SUDs, cocaine users have a proportionally higher incidence of TBIs, predominantly mTBI. These findings suggest that treatment providers would benefit from inclusion of TBI screening as part of the clinical screening. The cognitive sequelae of cocaine dependence may mask symptoms of TBI, thus treatment of such a dual-diagnosis population becomes increasingly challenging. Future studies need to better elucidate the relationship between co-morbid TBI and cocaine abuse, and its impact on treatment outcome in this distinct population.

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FIGURE 1.

Comparison between age of sustaining TBI and age of first use of cocaine. Mean age of sustaining TBI is significantly younger from mean age of first cocaine use. Connecting line represents information from the same participant.

TABLE 1

Demographic characteristics of study participants

	CONTROLS (n = 75)	COCNT (n = 53)	TR-COC (n = 42)	ALL COCAINE USERS (n = 95)
Age (years)	33.3 ± 9.2	40.2 ± 7.2	41.1 ± 9.8	40.6 ± 8.4 *
Sex (M/F)	47/28	47/6	33/9	80/15 *
Race (B/W/H/O)	47/13/6/9	33/14/5/1	21/12/7/2	54/26/12/3
Years of education	14.7 ± 2.2	12.9 ± 1.6	12.3 ± 1.7	12.7 ± 1.6 *
Years of cocaine use	—	14.0 ± 8.3	11.3 ± 7.5	12.7 ± 8.0
Age of 1st cocaine use (years)	—	22.8 ± 5.6	23.2 ± 2	23.0 ± 6.1
Marijuana abuse	—	22(41.5%)	16(38.1%)	38(40%)
Alcohol dependence	—	21(39.6%)	15(35.7%)	36(37.9%)
Subjects with TBI	6(8%)	14(26.4%)	14(33.3%)	28(29.5%) *
Age of 1st TBI	20.33 ± 13.98	16.0 ± 6.93	16.85 ± 9.30	16.41 ± 8.0

Data are presented as means (± SD) or as frequency. Sex is indicated as female (F) and male (M); race is indicated as Black (B), White (W), Hispanic (H), or Other (O).

COCNT, non-treatment seeking cocaine-dependent subjects; TR-COC, treatment-seeking cocaine-dependent subjects; TBI, traumatic brain injury.

* $p < .01$ v/s control subjects.

TABLE 2

BIS-11 scores of control and cocaine-dependent subjects

	Motor	Attention	Non-planning	Total
Controls	20.8 ± 4.03	14.15 ± 4.19	20.8 ± 4.46	54.93 ± 10.41
Cocaine	24.11 ± 5.14 *	15.58 ± 4.12 *	27.29 ± 5.41 *	67.31 ± 12.31 *
Cohen's d (effect size)	0.72	0.34	1.31	1.11
Cocaine + TBI	24.71 ± 4.53	16.07 ± 3.74	28.11 ± 3.91	69.25 ± 9.60
Cocaine w/o TBI	23.85 ± 5.39	15.37 ± 4.28	26.96 ± 5.92	66.49 ± 13.26

Data are presented as means (± SD).

TBI, traumatic brain injury.

*
 $p < .01$ v/s control subjects.