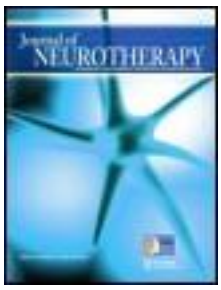

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Attentional Bias to Drug- and Stress-Related Pictorial Cues in Cocaine Addiction Comorbid with Posttraumatic Stress Disorder

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Attentional Bias to Drug- and Stress-Related Pictorial Cues in Cocaine Addiction Comorbid with Posttraumatic Stress Disorder

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ABSTRACT. *Introduction*. Cocaine addiction places a specific burden on mental health services through its comorbidity with other psychiatric disorders. Treatment of patients with cocaine abuse is more complicated when addiction is co-occurring with posttraumatic stress disorder (PTSD). This study used dense-array event-related potential (ERP) technique to investigate whether the patients with this form of dual diagnosis display excessive reactivity to both trauma and drug cues as compared to neutral cues. Cue reactivity refers to a phenomenon in which individuals with a history of drug dependence exhibit verbal, physiological, and behavioral responses to cues associated with their preferred substance of abuse. This study explores ERP differences associated with cue-related responses to both drug and trauma cues in a three-category oddball task using neutral, drug-related, and trauma-related pictorial stimuli.

Methods. The study was conducted on 14 cocaine dependent participants, 11 participants with cocaine-dependence comorbid with PTSD, and 9 age- and gender-matched control subjects. A 128-channel Electrical Geodesics EEG system was used to record ERP during the visual three-category oddball task with three categories (neutral, drug, stress) of affective pictures.

Results. Patients with cocaine dependence and PTSD, as compared to patients with only cocaine addiction and control participants, showed excessive cue reactivity to both drug- and

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trauma-related visual stimuli. Most profound differences were found in the amplitude and latency of frontal P3a, and centro-parietal P3b ERP components. Group differences were found as well between patients with cocaine abuse (both addiction-only and dual diagnosis groups) versus controls on most ERP measures for drug-related cues.

Conclusion. We propose that the employed ERP cue reactivity variables could be used as valuable functional outcome measures in dually diagnosed drug addicts undergoing behavioral treatment.

KEYWORDS. Cocaine addiction, cue reactivity, stress, ERP, P300, PTSD

INTRODUCTION

Comorbid posttraumatic stress disorder (PTSD), which is highly prevalent among cocaine abusers, is known to be associated with poorer treatment outcomes because of aggravation of factors contributing to cocaine addiction development.

Cocaine addicts with co-occurring PTSD have a more persistent illness course and are more refractive to treatment than those without dual diagnosis (Brown, Recupero, & Stout, 1995; Brown & Wolfe, 1995; Coffey et al., 2002; Evans & Sullivan, 2001; O'Brien et al., 2004). In dually diagnosed patients, symptoms of both disorders are in complex relationships where one disorder serves to sustain another (Chilcoat & Breslau, 1998; Jacobsen, Southwick, & Kosten, 2001; Saladin et al., 2003; Shiperd, Stafford, & Tanner, 2005).

There are different approaches to explain high rate of co-occurrence of PTSD and cocaine addiction (Stewart, Pihl, Conrod, & Dongier, 1998), including those based on concepts from the cognitive neuroscience field (Sokhadze, Stewart, & Hollifield, 2007). Preoccupation with drug and drug-related items is a typical characteristic of addicted individuals. Several research studies provided support for the hypothesis that the process of alteration of attention takes place in addicts (Hester, Dixon, & Garavan, 2006; Lyvers, 2000; Robinson & Berridge, 1993), so-called attentional bias (Franken, 2003; Franken, de Haan, van der Meer, Haffmans, & Hendriks, 1999; Franken, Kroon, & Hendriks, 2000), and drug-related cues attain greater salience and motivational significance (Cox, Fadardi, & Pothos, 2006) Cue reactivity refers to a phenomenon in which individuals with a drug dependence exhibit excessive verbal, physiological, and behavioral responses to cues associated with their preferred substance of abuse (Carter & Tiffany, 1999; Childress et al., 1999; Drummond, Tiffany, Glautier, & Remington, 1995). Furthermore, in cocaine abusers cue reactivity has been shown to be dependent on cue type and modality (Johnson, Chen, Schmitz, Bordnic, & Shafer, 1998). One of the cognitive components of cue reactivity in substance abusers is the preferential allocation of attentional resources for items related to drug use (Lubman, Peters, Mogg, Bradley, & Deakin, 2000) or to alcohol use (Stormark, Laberg, Nordby, & Hugdahl, 2000). It has been proposed that conditioned sensitization in neural pathways associating incentives with stimulus items may be responsible for cue reactivity (Franken, 2003; Weiss et al., 2001).

Several neuroimaging studies have reported effects associated with drug cue-related responses and craving in cocaine addiction (Childress et al., 1999; Garavan et al., 2000; Hester et al., 2006; Kilts et al., 2001; Kilts, Gross, Ely, & Drexler, 2004). PTSD in persons with cocaine abuse is associated with more severe drug dependence; on the other hand, the neurotoxic effects of cocaine abuse can aggravate PTSD (Brown et al., 1995; Najavits, Weiss, Shaw, & Muenz, 1998; Ouimette, Ahrens, Moos, & Finney, 1997; Ouimette, Finney, & Moos, 1999). Only a few studies have examined mechanisms by which PTSD might exert an adverse effect on the course of addiction (Ouimette & Brown, 2003; Stewart et al., 1998). In substance use disorder (SUD) and PTSD comorbidity research, one of the main challenges is to obtain knowledge of

cognitive processes that correlate with both cue reactivity and PTSD symptoms.

It has been shown that emotional abnormalities are typical for addicts (Fukunishi, 1996; Handelsman et al., 2000). Addicted individuals could be affected by a dysregulation associated with changes in emotional reactivity to natural positive reinforcers (Volkow, Fowler, & Wang, 2003). Sensitization to drugs and counteradaptation are hypothesized to contribute to dysregulation of both hedonic homeostasis and observed brain reward abnormalities (Koob, 1999; Koob & Le Moal, 2001; Koob et al., 2004). Emotional disturbances are also common for patients with PTSD. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event is a core feature of PTSD (American Psychiatric Association, 2000; Vasterling & Brewin, 2005). Research findings have consistently demonstrated that individuals with PTSD produce heightened physiological responses (e.g., startle, heart rate, skin conductance response, etc.) to stimuli related to traumatic events (Blanchard, 1990; Shalev, Orr, & Pitman, 1993; Orr & Roth, 2000; Prins, Kaloupek, & Keane, 1995). This heightened arousal has been found across a variety of psychophysiological measures during presentation of trauma-related auditory or visual cues and during personal imagery of traumatic events (Blanchard et al., 1996; Casada, Amdur, Larsen, & Liberzon, 1998; Orr et al., 1998; Sahar, Shalev, & Porges, 2001). Because physiological reactivity on exposure to cues related to traumatic events is common for PTSD, physiological assessments using electroencephalographic (EEG) measures such as event-related potentials (ERP) in PTSD co-occurring with cocaine addiction can provide valuable practical and theoretical insight.

The P300 component (300 to 600 msec poststimulus) is the most widely used ERP measure in psychiatric and other clinical applications (Polich & Herbst, 2000; Pritchard, 1981, 1986; Pritchard, Sokhadze, & Houlihan, 2004). The amplitude of P300 reflects the allocation of attentional resources, whereas the latency is considered to reflect stimulus evaluation and classification time (Katayama & Polich, 1996; Polich, Pollock, & Bloom, 1994). The P300 is usually obtained in oddball paradigm, wherein two stimuli are presented in a random order, one of them frequent, (standard) and another one rare (target; Polich, 1990). A modification of the oddball task has been used where a third, also rare stimulus (distracter) is presented along with standard and target stimuli. It was reported that these infrequent distracters elicit a fronto-central P300, so-called P3a, whereas the rare targets elicit a centro-parietal P300, so called P3b (Katayama & Polich, 1998). The P3a is recorded at the anterior scalp locations and has been interpreted as reflecting frontal lobe activity (Friedman, Simpson, & Hamberger, 1993; Knight, 1984). Whereas the P300 in general is thought to represent ''context updating/closure'' (Donchin & Coles, 1988), in three-stimuli oddball task the P3a is interpreted as ''orienting'' and the P3b as an index of an ability to maintain sustained attention to target (Naatanen, 1990; Potts, Patel, & Azzam, 2004; Wijers, Mulder, Gunter, & Smid, 1996). The anterior P3a indexes the contextual salience of the rare stimuli, whereas posterior P3b is indexing task-relevance of the stimuli (Gaeta, Friedman, & Hunt, 2003). The three-stimulus category oddball paradigm provides possibilities for delineating the cognitive processes engaged in this task when motivational salience of novel distracter stimuli is manipulated.

Most of the studies on PTSD report abnormalities in P300, which provide presumptive evidence for impaired cognitive processing in this disorder (Attias, Bleich, Furman, & Zinger, 1996; Blomhoff, Reinvang, & Malt, 1998; Charles et al., 1995; Felmingham, Bryant, Kendall, & Gordon, 2002; Karl, Malta, & Maerker, 2006; Kimble, Kaloupek, Kaufman, & Deldin, 2000; Stanford, Vasterling, Mathias, Constans, & Houston, 2001). Studies finding attenuated P300 attribute their results to concentration impairment (McFarlane, Weber, & Clark, 1993) or attention deficits (Charles et al., 1995; Metzger, Orr, Lasko, McNally, & Pitman, 1997; Metzger, Orr, Lasko, & Pitman, 1997). Increased P300

amplitude was explained as due to altered selective attention (Attias et al., 1996) or heightened orientation to threatening stimuli (Kimble et al., 2000). Several studies emphasize that P3a enhancement in PTSD is expressed when distracters are either trauma related or novel stimuli in oddball tasks (Bleich, Attias, & Furman, 1996; Drake, Pakalnis, Phillips, Pamadan, & Hietter, 1991; Felmingham et al., 2002; Weinstein, 1995). Increased P300 amplitude in PTSD is thought to reflect attentional bias toward threat stimuli, and reduced P300 amplitude is thought to reflect a consequent reduction in attentional resources to nonthreatening stimuli.

Acute and chronic use of cocaine exerts neuropharmacological effects on amplitude and latency of ERPs (Bauer, 1997; Biggins, MacKay, Clark, & Fein, 1997; Fein, Biggins, & MacKay, 1996; Kouiri, Lukas, & Mendelson, 1996). Longer P300 latency without abnormalities in amplitude has been reported in several studies on cocaine withdrawal (Bauer & Kranzler, 1994; Herning, Glover, & Guo, 1994; Noldy & Carlen, 1997). The majority of ERP studies aimed to assess cortical dysfunctions have used P3b tasks, and there are only few studies of P3a in addiction. Understanding contribution of frontal ERP components is important considering increased evidence of frontal dysfunctions in drug abuse, and specifically in cocaine abuse (Hester & Garavan, 2004).

According to the attentional biasing concept, patients with cocaine addiction with co-occurring PTSD in an attention task with pictorial emotional stimuli are expected to show enhanced reactivity to both cocaine-related and traumatic-stress-related cues because of preferential processing of drug and trauma distracters, and are consequently expected to present lowered attentional resources availability for the processing of task-relevant target signals. The specific aim of this study is to examine cue reactivity to drug- and trauma-associated stimuli in a modification of cue reactivity test in three groups: dual diagnosis of cocaine dependence and PTSD (DUAL), cocaine addiction without PTSD (SUD), and controls (CNT). In this experiment we use an oddball task with distracters being either drug related, traumatic stress related, or emotionally neutral pictorial cue. Our aim is to examine as well drug-related and trauma-related cues interference on both behavioral performance and cognitive ERP P300 (P3a, P3b) indices. By using both drug-related and trauma-related cues to create interference we attempt to address the question of how both categories of cues may affect performance on task of the three study groups by assessing behavioral (reaction time, accuracy) and ERP indices (P3a, P3b), We predicted preferential selective attention to drug-related items but not to traumatic stress images in the SUD group, and enhanced processing of both drug- and trauma-related distracters in the DUAL group. Processing of highly salient but task-irrelevant distracters was expected to result in a decreased attentional capacity and a reduced allocation of resources to process task-relevant targets. This effect was predicted to be manifested in a delayed reaction time (RT), lower accuracy, lower magnitude of posterior ERP indices of task-relevant information processing (P3b) in DUAL patients compared to SUD and CNT groups. Thus, the goal of the study was to examine ERP measures of cue reactivity to drug-associated and trauma-associated stimuli and to investigate how heightened orienting to these salient distracters will interfere with cognitive functions during performance on a visual three-category oddball task. We predicted an increased amplitude of the anterior ERP component (e.g., P3a) in response to novel pictorial distracters containing both drug-related and trauma-related cues, and a reduced posterior ERP (e.g., P3b) in response to neutral targets and frequent standards in the DUAL group compared to the other groups. We expected that the patients with cocaine dependence and PTSD diagnoses compared to controls will show enhanced reactivity to the task-irrelevant drug-related and threat-related cues and will present selective attention to these highly motivationally salient signals, which will negatively affect processing of task-relevant stimuli.

METHODS

Participants

Cocaine abusing/dependent participants were referred primarily from the University of Louisville Hospital emergency rooms; drug abuse treatment outpatient services, such as Jefferson County Alcohol and Drug Abuse Center (JADAC); and other psychiatric ambulatory units. There are established collaborations with other facilities and Louisville metro agencies. Dr. Stewart, a co-investigator in this study, is a medical director at JADAC and a clinical consultant at two residential addiction treatment centers (The Healing Place and Volunteers of America) located in Louisville metro area. He provided a substantial number of referrals through these programs. Dr. Hollifield, another co-investigator in the study, is a director of the Anxiety Disorder Program at the University of Louisville and consulted on diagnosis of PTSD in addicted patients from the pool of referred patients with cocaine addiction. Participants were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local Institutional Review Board (IRB). The consent forms were reviewed and explained to all individuals who expressed interest in participating. All questions were answered before consent signature was requested. If the individual agreed to participate, she or he signed and dated the consent form and received a copy countersigned by the investigator who obtained consent.

All procedures were conducted within the facilities of the Department of Psychiatry and Behavioral Science and the University of Louisville Hospital. Initial contact with prospective participant was typically made via the telephone screening. An interviewer queried callers regarding major study criteria. Those meeting criteria received an appointment for consent, typically within 1 to 5 days after their initial call. Control participants in this study were recruited from the Louisville metro community by advertisements approved by the local IRB. Responders were telephone screened to meet initial inclusion criteria. All control participants were free of neurological or significant medical disorders, had normal hearing and vision, and were free of psychiatric disorders. Following telephone screening, the control participants received a psychiatric assessment in the laboratory to verify the telephone screening and rule out Axis I diagnoses using Structured Clinical Interview for DSM–IV (SCID I; First, Spitzer, Gibbon, & Williams, 2001). Control participants were chosen so that the control group was not significantly different from the patient group on age, education level, handedness, sex, and ethnicity. The same consent procedures followed for the patients was applied to the controls. Because these individuals were participating in research, they were paid for their time. Payment methods followed the University of Louisville Health Science Center's Committee for the Protection of Human Subjects' guidelines concerning reimbursement for research time and parking. Participants were paid $20 per hour for completing required research activities (e.g., taking ERP tests, providing urine sample, completing self-report forms) at each visit.

Psychiatric Status Questionnaires, Drug Use, and Psychosocial Functioning Screening

The SCID I (First et al., 2001) was used for Axis I diagnoses. PTSD was assessed using the Post-traumatic Symptom Scale-Self Report (Foa, Cashman, Jaycox, & Perry, 1997; Foa, Steketee, & Rothbaum, 1989) questionnaire. The Hopkins Symptom Checklist-25 (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974) was used to measure symptoms of anxiety and depression. Handedness of patients was assessed using the Edinburgh inventory (Oldfield, 1971). Scores from the Addiction Severity Index were used to measure problem severity in the areas of medical, employment, drug abuse, legal, family, social, and psychiatric difficulties (McLellan, Luborsky, Woody, & O'Brien, 1980). Cocaine Negative Consequences Checklist (Michalec et al., 1996)

was used to assess short-term and long-term adverse effects resulting from cocaine use. Psychosocial adjustment was assessed using the Social Adjustment Scale (Weissman & Bothwell, 1976).

Qualitative urine toxicology screens (DrugCheck 4, NxStep, Amedica Biotech Inc., CA) were conducted on each participant to confirm cocaine abuse. In addition, qualitative urine toxicology screens for amphetamines, opiates, and marijuana were performed to assess presence of additional abused substances. Positive test for marijuana was not considered as exclusion criteria. Qualitative Saliva drug test (ALCO SCREEN, Chematics, Inc., IN) was also used to rule out current alcohol use.

Participants in the Study

Twenty five cocaine abusing/dependent participants (9 female, 16 male; *M* age = 41.3 ± 6.1, range = 32–52 years, 64% Afro Americans) participated in the study. Fourteen were cocaine-abusing participants without PTSD, and they were assigned to the SUD group (42.2 ± 6.6 years old; 6 female, 8 male), whereas 11 cocaine addicts were diagnosed with PTSD (diagnosis was confirmed by consensus of Drs. Stewart and Hollifield) and composed dually (SUD–PTSD) diagnosed group (DUAL). Six had been diagnosed earlier with PTSD and had record of PTSD in their history at the intake stage. The DUAL group consisted of 3 female and 8 male participants (38.8 ± 6.3 years). Nine non-drug-using control participants (4 female, *M* age = 36.7 ± 5.3, range = 29–45 years, 44% Afro Americans)—the CNT group—also participated in this study.

Twelve participants in SUD group tested positive for cocaine, 7 of whom tested positive for marijuana use as well. Two participants in the SUD group who did not tested positive were recovering addicts enrolled in this study after the inpatient JADAC rehabilitation course with abstinence period of less than 60 days. Nine participants in the DUAL group tested positive for cocaine use, and 5 of them also tested positive for marijuana use. Therefore the majority of our outpatient population consisted of current cocaine users, with almost half using marijuana as a drug of second choice. The most preferred form of administration of the drug was smoking crack cocaine. Only 1 cocaine addict participant in this study used cocaine intravenously. The majority of addicted participants reported regular use of nicotine/smoking. None of the participants in the SUD group was in any treatment program other than participating in Narcotics Anonymous or Alcoholic Anonymous meetings. All of the participants except 2 patients from the SUD group, 1 from the DUAL group, and 1 from the CNT group were right-handed. All control participants reported no current or past history of neurological or psychiatric disorders or dependence on any substances other than nicotine or caffeine. Participants were fully informed about the nature of this research and signed informed consent form approved by the IRB of the University of Louisville (Protocol IRB #240.06, pt. 2). For the specimen collection (urine drug screen) participants signed a separate consent form also approved by the IRB within the same study protocol.

Stimulus Presentation, EEG/ERP Data Acquisition, and Signal Processing

All stimulus presentation, behavioral, and subjective response collection was controlled by a computer running E-prime software (Psychology Software Tools, PA). Visual stimuli were presented on a 15-in. flat-panel display. Manual responses were collected with a five-button keypad. Participants were instructed to press key number 1 when they saw a picture of target category and not to press the key to nontarget category images. In all experiments participants were seated in a chair with their chin in a chinrest. The chinrest was placed so that participant's eyes were 50 cm from the center of the flat panel screen. Breaks were provided every 10 min. All EEG data were acquired with a 128-channel Electrical Geodesics system (Net Station 200, v. 4.0; Electrical Geodesics Inc., OR) running on a Macintosh G4 computer. EEG data are sampled at

500 Hz, 0.1–100 Hz analog filtered, referenced to the vertex. The Geodesic Sensor Net is a lightweight elastic thread structure containing Ag/AgCl electrodes housed in a synthetic sponge on a pedestal. The sponges are soaked in a KCl solution to render them conductive. Stimulus-locked EEG data are segmented off-line into 1000-msec epochs spanning 200-msec prestimulus to 800-msec poststimulus around the critical stimulus events. For example in our task the events were (a) neutral target, (b) neutral nontarget, (c) traumatic stress target, (d) traumatic stress nontarget, (e) drug target, and (f) drug nontarget. Frequency of targets for each emotional category was 20%. Data were digitally screened for artifact (eye blinks, movement, etc.), and bad trials were removed using built-in artifact rejection tools. The remaining data were sorted by condition and averaged to create the ERPs. Averaged ERP data were digitally filtered at 30 Hz lowpass to remove residual high-frequency noise before averaging. After averaging the baseline was corrected over a 200-msec baseline period relative to segment start, and data were rereferenced into an average reference frame. The participant ERPs were averaged together to produce the mean grandaverage across participants.

Pictorial stimuli. The emotional pictorial material were taken from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2001). Cocaine images were selected and validated by the first author during his postdoctoral fellowship at Rice University. In that prior study (Potts, Martin, Stotts, George, & Sokhadze, 2003, Validation study of drug-related images, unpublished report, Rice University, Houston, TX), 25 cocaine abusing patients rated 115 cocaine-related images on a 5-point scale (5 being high) as to how evocative each drug image was. The mean rating for the entire set was 2.66 ($SD = 0.48$). The 30 images with the highest rating (all 30 with mean rating above 3.0) were selected for use in this study. Valence, arousal, and dominance rates were matched within each set of images in neutral and traumatic stress categories using ratings from the International Affective Picture System database (Lang et al., 2001). The experiment used pictures from three categories: neutral (household items, animals, nature), traumatic stress (violence, accidents, victims of attack, etc.), and drugs (cocaine and drug paraphernalia). Participants were instructed to respond to stimulus items from one of the categories, ignoring the others within each block (e.g., targets are household items in a "neutral" block). The order of blocks (with 240 trials per block) was counterbalanced. In the task a stimulus was presented on a screen for 200 msec, whereas recording of EEG data occurred for 1000 msec. Intertrial interval varied in 1500∼2000 msec range to avoid anticipation effects. Each of three blocks of trials was followed by a short break. The task took approximately 30 min to complete.

Dependent Variables

Behavioral variables were mean RT and response accuracy (in percentage) to target stimuli, whereas *electrophysiological variables* were adaptive mean amplitude and latency of the frontal P3a and the centro-parietal P3b. Statistical analyses were performed on the participant-averaged data with the participant averages being the observations. The primary analysis model was the repeated measures analysis of variance (ANOVA), with physiological dependent variables being those just described. Therefore, each ERP component's amplitude and latency were analyzed for preselected regions-of-interest (ROI) and time window. Time window was in the 300 to 590 msec range for both P300 measures. The ROI for the frontal P3a included AFz, AF3, AF4, Fz, F1, F2, F3, F4, and four neighboring EEG sites (EGI channels 10, 19, 5, 12). Frontal EEG channels AF3, F1, F3, EGI-19, and EGI-12 were used as the left frontal ROI, and channels AF4, F2, F4, EGI-5, and EGI-10 were used for the right frontal ROI. Analysis was performed as well for the midline frontal EEG sites (AFz, Fz). ROI for the centro-parietal P3b included Cz, CPz, Pz, CP1, CP2, CP3, CP4, and four neighboring EGI channels, and they were calculated separately for left, right, and midline ROIs.

Figure 1 illustrates the layout of Electrical Geodesics Sensor Net and ROIs.

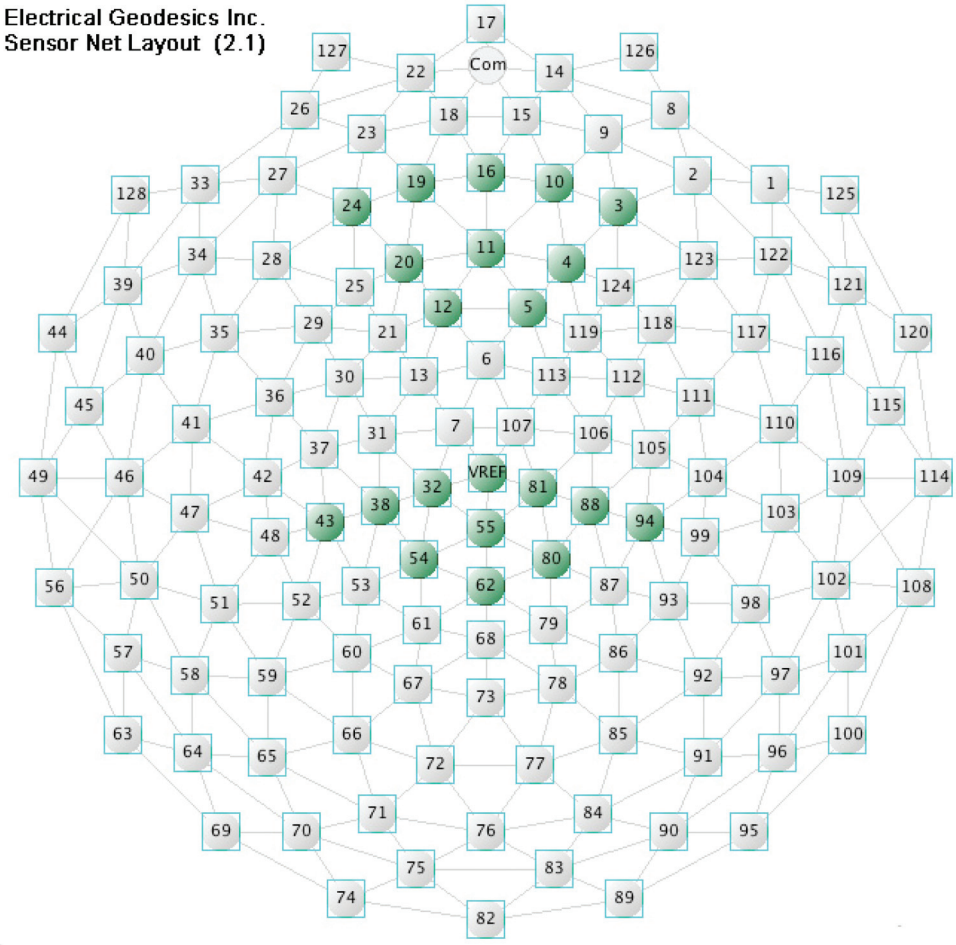
Initially all dependent variables were analyzed using one-way ANOVA to find group differences (CNT vs. SUD, CNT vs. DUAL, SUD vs. DUAL, CNT vs. SUD+DUAL). Then data for selected dependent ERP variable were analyzed using a repeated measures ANOVA with the following factors (all within-participants): Stimulus Type X (target, nontarget) × Cue Category (neutral, drug, trauma) × Hemisphere (left vs. right). Between-subject factors in the tasks were Group (DUAL, SUD, CNT) and the following variations of grouping (CNT vs. DUAL, CNT vs. SUD, DUAL vs. SUD). Post hoc analysis was conducted using Tukey test for groups with unequal sample size. A priori hypotheses were tested with two-tailed Student's *t* tests for groups with unequal variance. In all ANOVAs, Greenhouse-Geisser (GG) corrected *p* values were employed where appropriate. SPSS (v.14) and Sigma Stat 3.1 packages were used for statistical analysis. Topographic maps were created using spherical spine interpolation available in the EGI Net Station work-tools (v. 4.01).

RESULTS

Behavioral Responses

RT was globally slower in both SUD and DUAL groups compared to controls;

FIGURE 1. Electrical Geodesics Inc. Sensor net layout (2.1 version) for 128-channel EEG sites with channel numeration. Frontal (for P3a component) and centro-parietal (for P3b component) regions-of-interest are highlighted.



however, the one-way ANOVA showed significance of RT differences between controls and addicts (both SUD and DUAL groups, SUD + DUAL) only for trauma targets (529.6 ± 55.9 msec CNT vs. 642.6 ± 121.9 all addicts), $F\,(1, 33) = 6.25$, $p = .018$. These differences were very well expressed when the CNT group was compared with DUAL group on targets of neutral and trauma (stress) categories. Stressful targets had main effect on RT across all participants (517 msec neutral vs. 581 msec traumatic target), $F\,(2, 27) = 15.18$, $p = .001$. There was also a trend to between-group difference on trauma targets (CNT vs. DUAL), $F\,(2, 27) = 4.63$, $p = .046$, and a marginally significant Category (neutral, trauma) × Group (CNT, DUAL) interaction, $F\,(4, 36) = 4.66$, $p = .046$, with RT to neutral targets being similar, whereas RT to trauma cues being slower in the DUAL group. Target Category (neutral, trauma, drug) had main effect (shortest RT to neutral, longest to trauma), $F\,(2, 36) = 4.89$, $p = .016$, showing that this manipulation of stimulus emotional category was affecting RT in all participants. There were not any significant differences in RT between SUD and DUAL groups.

Accuracy. Comparison across all three groups did not yield any differences in error rate. However, when controls and addicts were compared separately, Cue Category (neutral, trauma, drug) × Group (CNT, SUD) interaction tendency was found, $F\,(2, 27) = 3.98$, $p = .043$, which can be described as a tendency to lower error rate 5.89% (SUD) vs. 9.25% (CNT) on drug targets and a higher rate of errors on neutral targets (11.5% vs. 6.6%) in addicts. Comparisons of CNT and DUAL groups on the same accuracy measure also showed a trend toward Category × Group interaction, $F\,(2, 18) = 3.86$, $p = .049$, with DUAL patients compared to controls committing more errors to trauma targets but not to drug or neutral targets.

ERPs

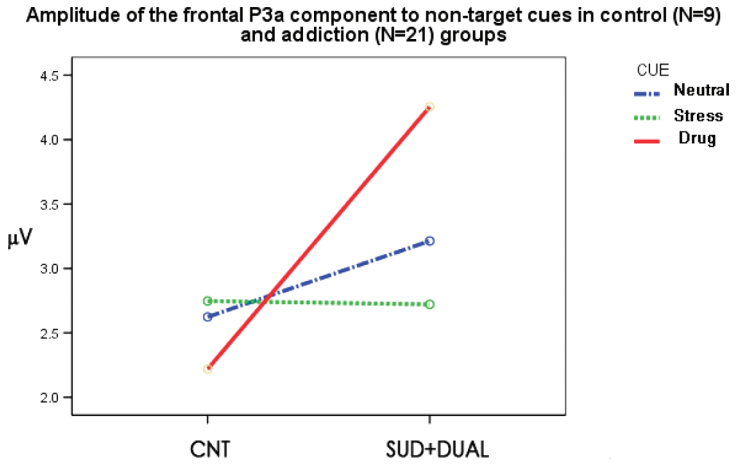
Data from 1 participant from DUAL and 2 participants from the SUD-only group were not included in the ERP analysis because of an excessive number of artifacts caused by movement, eye blinks, and so on. Therefore we report data on 9 controls (CNT group), 12 participants with SUD without PTSD (SUD group), and 10 participants with SUD-PTSD comorbidity (DUAL group). For certain controls versus addiction group comparisons we included for analysis as well a combined addiction group (SUD+DUAL group).

Frontal P300 (P3a)

Amplitude of P3a. Cue Category (neutral, trauma, drug) had a main effect on P3a amplitude, $F\,(2, 28) = 15.6$, $p = .006$, with the highest amplitude of P3a component in trauma, whereas the lowest in drug cues, Stimulus (target, nontarget) type, also had a main effect, $F\,(1, 28) = 7.33$, $p = .011$, with amplitude being higher to targets than to nontargets. Comparison of controls ($N = 9$) with all addicts (both SUD and DUAL groups, $N = 21$) showed a significant cue Category (neutral, trauma, drug) × Hemisphere (left, right) × Group interaction, $F\,(2, 27) = 9.42$, $p = .001$, where addicts showed larger P3a to drug cues, but not to neutral cues, and manifested less hemispheric differences. Figures 2 and 3 illustrate higher amplitude of P3a to nontarget drug-related cues in cocaine addicts. Effect of enhanced P3a was better expressed at the left rather then at the right frontal site. The same effect was observed when controls (CNT, $N = 9$) were compared with addicts without PTSD (SUD, $N = 12$): $F\,(2, 18) = 4.12$, $p = .03$.

Comparisons of control and dual diagnosis groups showed a cue Category (neutral, trauma, drug) × Stimulus (target, nontarget) × Group (CNT, DUAL) interaction effect, $F\,(2, 38) = 4.52$, $p = .038$ (GG corrected $df = 1.19$), and a well-manifested Category × Hemisphere × Group effect, $F\,(2, 38) = 8.14$, $p = .005$. The effect can be described as a larger P3a to trauma targets than nontargets at the right frontal sites, and lower amplitude to neutral and drug nontargets than targets. Figure 4 shows this cue Category × Group interaction for target cues in control and dual participants.

FIGURE 2. Amplitude of the frontal P3a component to nontarget neutral, stress, and drug cues in control ($N = 9$) and combined addiction ($N = 21$) groups. *Note.* Addicted participants show excessive reactivity to nontarget drug cues.



Latency of P3a. A one-way ANOVA showed significant differences between three groups (CNT, SUD, DUAL) in the latency of P3a to neutral targets, F (2, 29) = 4.32, $p = .022$; traumatic targets, F (2, 29) = 3.71, $p = .036$; nontargets, F (2, 29) = 7.65, $p = .002$; drug targets, F (2, 29) = 4.55, $p = .019$; and drug nontargets (at the right side only), F (2, 29) = 4.74, $p = .016$. Dual patients showed a longer P3a latency to neutral targets and nontargets, whereas both SUD and DUAL groups had longer latencies to drug targets and nontargets than controls. The most interesting differences were revealed during comparison of addiction-only versus dual patient groups. Stimulus type (target, nontarget) had a main effect, F (1, 20) = 5.52, $p = .03$, but cue Category (neutral, trauma, cue) had no main effect on latency in these groups. Stimulus × Category × Group (SUD, DUAL) yielded significant interaction, F (2, 38) = 5.56, $p = .014$. In particular, P3a latency was globally delayed both to target and nontarget cues in DUAL patients compared to SUD patients and was longer to nontarget trauma and to target trauma cues (Figure 5).

Centro-Parietal P300 (P3b)

Amplitude of P3b. Both cue Category, F(2, 28) = 56.01, $p = .006$, and Stimulus type (target, nontarget), F (1, 29) = 7.32, $p = .011$, exerted main effect on the amplitude of P3b. Comparison of P3b between controls and addicts revealed Stimulus (target, nontarget) × Hemisphere (left, right) × Group (CNT, all SUD) interaction, F (2, 58) = 4.21, $p = .03$. Patient group had a lower P3b to neutral, but not to drug cues, and less differentiated hemispheric differences compared to controls. The P3b amplitude in addicts was higher in response to drug category cues at the left hemisphere. A Stimulus × Hemisphere × Group interaction was found as well when CNT and DUAL groups were compared, F (2, 38) = 3.86, $p = .031$ (GG corrected, $df = 1.59$, $p = .042$). See Figures 6, 7, and 8.

Latency of P3b. This measure showed a Hemisphere × Group interaction, F (1, 28) = 4.84, $p = .036$ (CNT vs. all SUD). The lower left–right hemispheric differences were better visible when CNT and SUD-only group where compared, F (1, 28) = 5.40, $p = .028$. The same effect was marginally close but did not reach significance level when CNT and DUAL groups were compared.

DISCUSSION

Our experiment tested the hypothesis that the stimulus evaluation cortical circuits have been conditioned to drug cues in addiction

FIGURE 3. Frontal event-related potential to target and nontarget drug cues in three groups of participants. *Note*. CNT = control; SUD = substance use disorder; DUAL = dual diagnosis of cocaine dependence and PTSD.

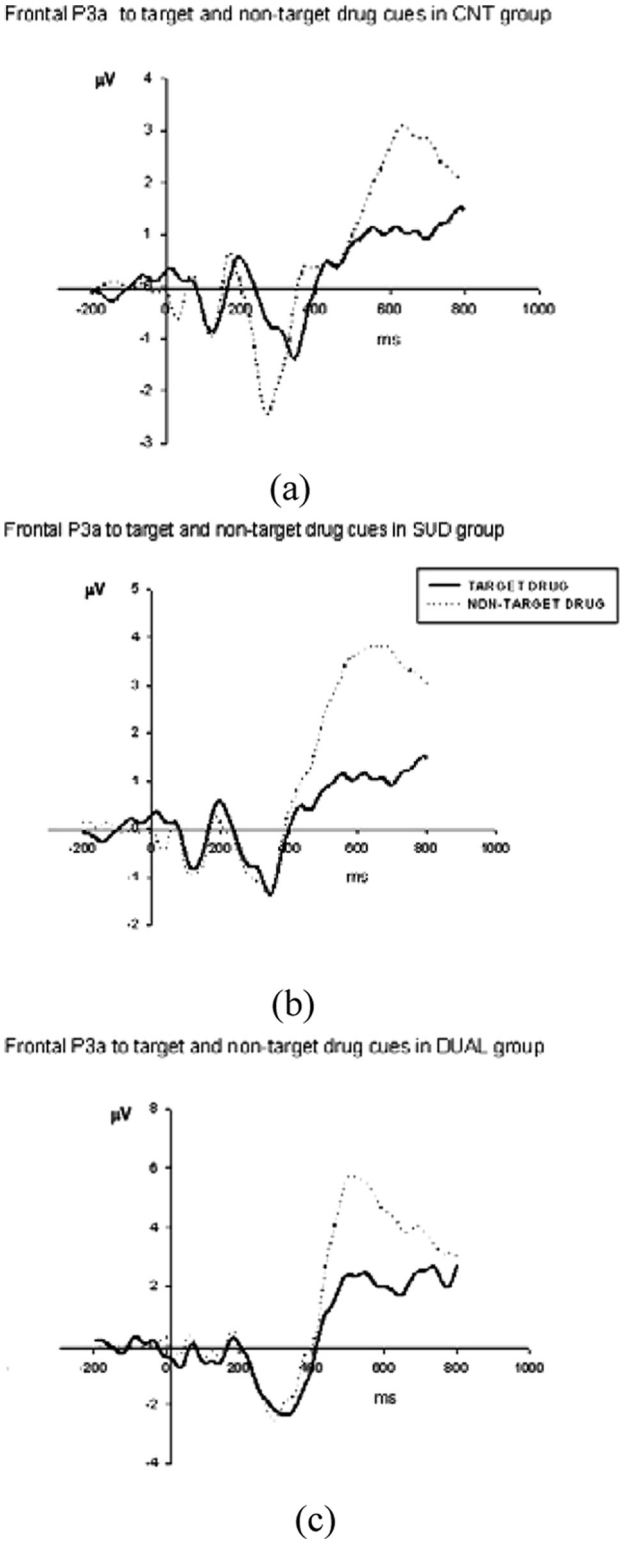
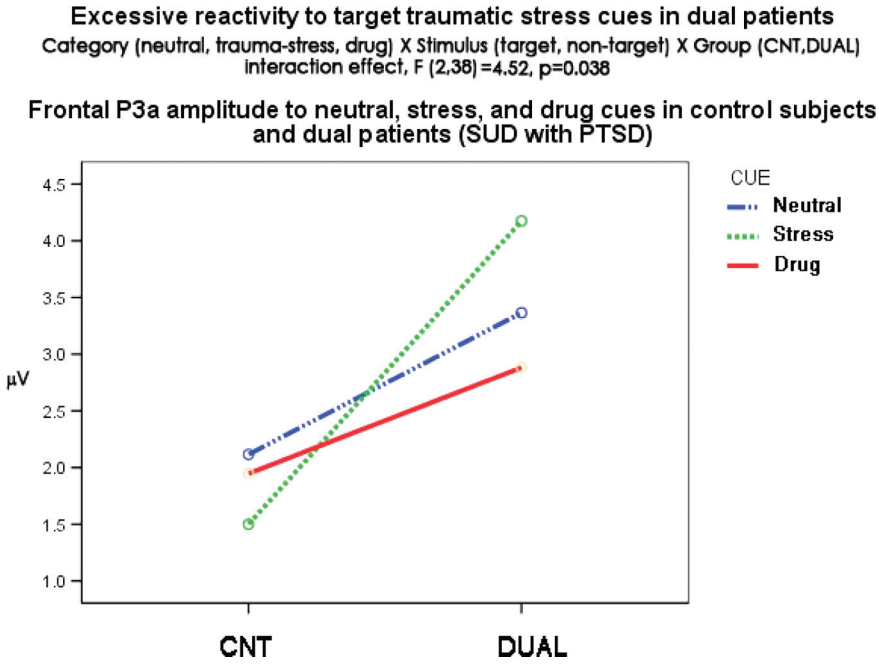


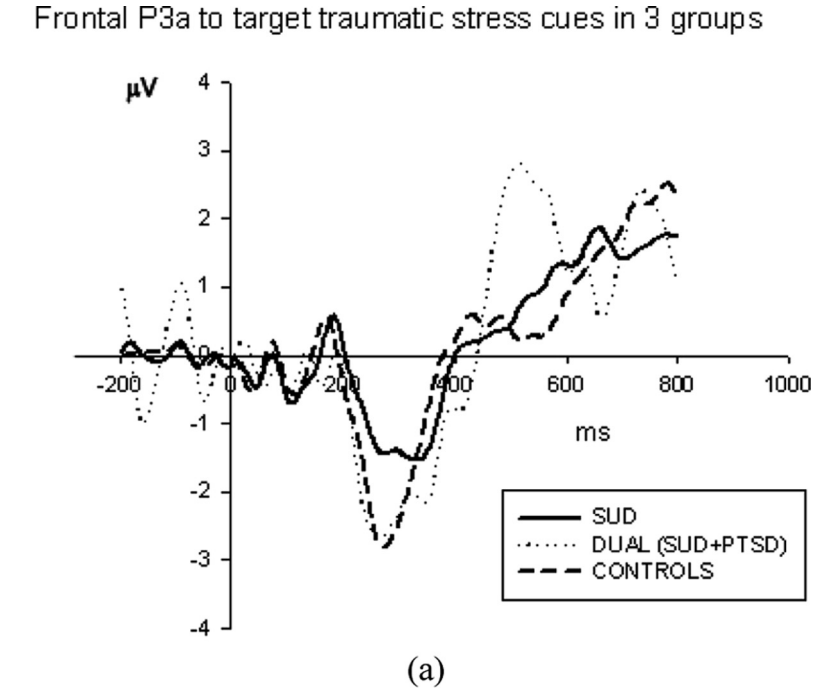
FIGURE 4. Amplitude of the frontal P3a component to neutral, stress, and drug targets in control participants and dual patients (SUD with PTSD). *Note*. The dual patients show excessive reactivity to traumatic stress-related cues. CNT = control; DUAL = dual diagnosis of cocaine dependence and PTSD; SUD = substance use disorder; PTSD = posttraumatic stress disorder.



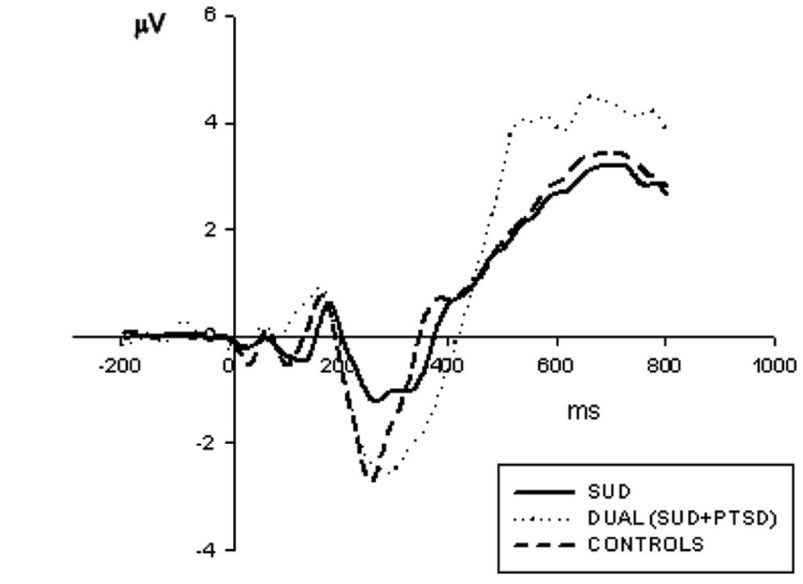
group (drug cue reactivity) and conditioned to both drug-related and stress-related cues in group of patients with cocaine addiction and PTSD comorbidity (drug-cue and stress-cue reactivity). The frontal P3a and centro-parietal P3b components were predicted to be larger to targets than nontargets in each category of images in all groups of participants (CNT, SUD, DUAL), but P3a and P3b were predicted to be larger to drug-related (both targets and nontargets) cues in SUD-only group compared to controls, whereas larger to both drug-related and stress-related categories in dually diagnosed participants compared to controls and cocaine addicts without PTSD. Specifically such predictions assumed presence of a main effect for stimulus type (target, nontarget), larger P300 to targets, but no Stimulus × Group interaction. At the same time our hypothesis predicted a main effect of Category (neutral, stress, drug), and a Category × Group interaction, namely, larger ERPs to drug images in both groups of cocaine addicts (SUD, DUAL) and larger ERPs of interest to traumatic stress images in the DUAL group compared both to CNT and SUD groups.

Our predictions were partially confirmed by the obtained results. Our data showed the predicted larger P3a and P3b components to target stimuli (main effect for Stimulus), regardless of stimulus category (neutral, stress, drug), in both the addicts and the controls, even though reactivity to nontarget trauma and drug cues was globally higher in addiction groups compared to controls. Several higher order interactions (Stimulus × Category × Group; Category × Hemisphere × Group) were obtained for the amplitude and latency of P3a when addict groups were compared with the CNT group. The DUAL patients showed the predicted enhancement of P3a to traumatic stress cues (differentially to targets and nontargets) that reached significance, thus supporting the enhanced

FIGURE 5. Frontal ERP to target and nontarget traumatic stress-related cues in three groups of participants (CNT, SUD, DUAL). *Note*. The DUAL group shows higher and delayed P3a to both target and nontarget stress-related pictures. CNT = control; SUD = substance use disorder; DUAL = dual diagnosis of cocaine dependence and PTSD; PTSD = posttraumatic stress disorder.

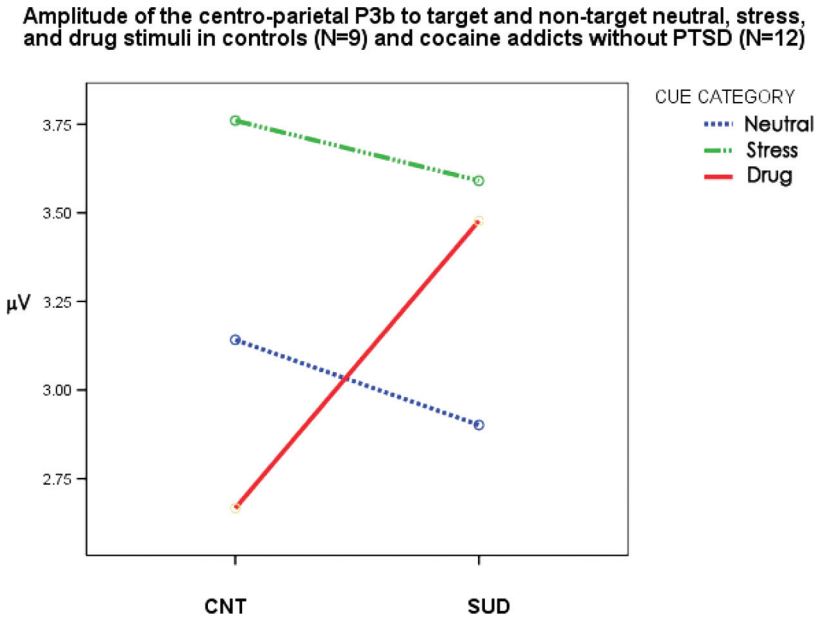


(a)



(b)

FIGURE 6. Amplitude of the centro-parietal P3b to all neutral, stress, and drug stimuli in controls and cocaine addicts without posttraumatic stress disorder (PTSD). *Note.* CNT = control; SUD=substance use disorder.

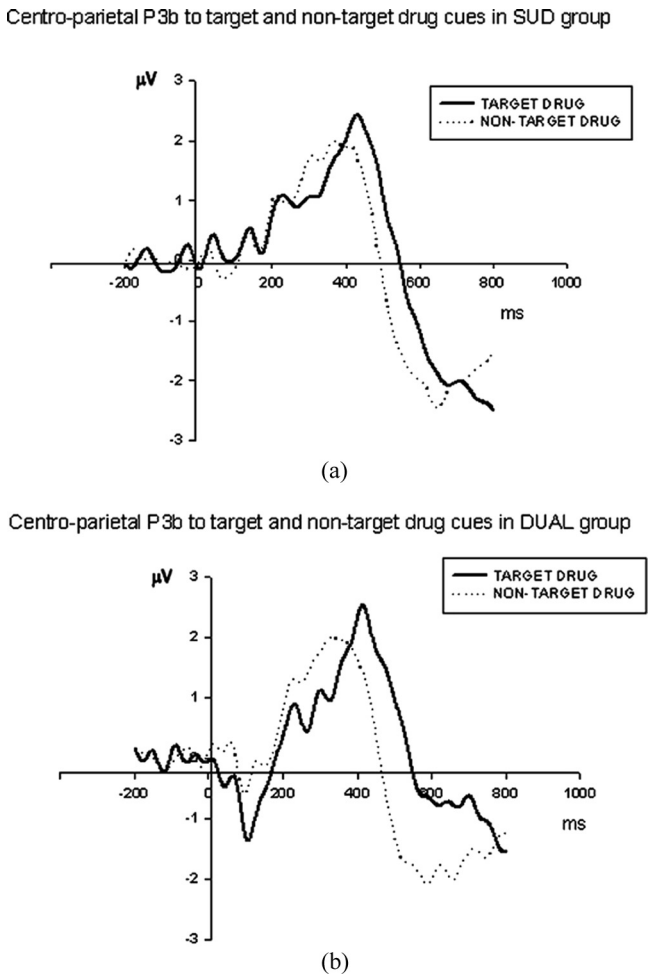


responsiveness and orienting to traumatic stress stimuli in the dually diagnosed patients. The group of addicted patients without PTSD showed the predicted larger frontal P3a to drug cue category, with P3a being larger at the left hemisphere, which is known to be involved in the processing of approach (appetitive) motivation tendencies (Davidson, 2002). It is worth noting that the centro-parietal P3b showed in our study similar but less pronounced Category × Group effects than the frontal P3a, suggesting that the P3a may be a more sensitive index of cue drug-related and stress-related stimuli in cocaine addicts with comorbid PTSD.

Although studies with active cocaine users have indicated a strong physical reaction to drug-related stimuli (Carter & Tiffany, 1999, Childress et al., 1999; Grant et al., 1996; London et al., 2000), research examining an attentional bias for cocaine-related stimuli has been limited (Franken et al., 2000). Our study extended the scope by using both drug- and stress-related cues in dually diagnosed patient group. Obtained data showed reduced reactivity to emotionally neutral and stressful images in cocaine addicts without PTSD. It has been shown that the experience of the emotions by psychostimulant substance abusers is distorted as a result of the dysregulation of the cerebral mechanisms involved in the motivational and emotional processes (Goldstein & Volkow, 2002; Volkow, Fowler, & Wang, 2004). The results are in accord with the reports from other studies that individuals with cocaine addiction produce low activation to natural affective stimuli but present high activation in these brain structures in response to drug-related items (Garavan et al., 2000; Garavan, Ross, & Stein, 1999; Grant et al., 1996; Hester et al., 2006).

It has been proposed that a sensitization of the motivational circuits toward stimuli associated with drugs could be associated with the motivational response of craving (Bonson et al., 2002; Robinson & Berridge, 1993), which could also provoke an inhibition of the emotional response to other natural reinforcement not related to drug use. One of the core features of addictive behavior is the preoccupation of drug-dependent persons with drugs and drug paraphernalia that can be conceptualized according to Franken (2003) as an attentional bias. In cocaine addiction, items related to cocaine and drug paraphernalia

FIGURE 7. Centro-parietal ERP to target and non-target drug cues in two groups of subjects. *Note*. Cocaine addicts from both SUD and DUAL groups show higher reactivity to non-target drug cues. SUD = substance abuse disorder; DUAL = dual diagnosis of cocaine dependence and PTSD.

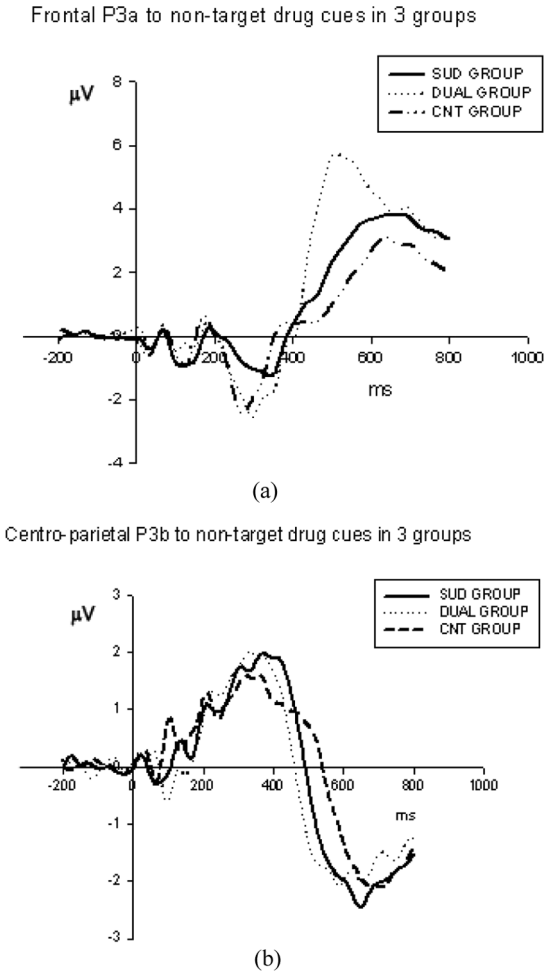


are repeatedly selected by attention for conscious processing, and drug-related representations are disproportionately tagged as relevant.

Attentional bias toward processing of salient stimuli is hypothesized to be an implicit cognitive process that is poorly controlled. Such automatic processing is similar to the orienting reflex to novel signal. The automatic nature of addictive behaviors was outlined as well by other studies (Hester et al., 2006; Lubman et al., 2000). Drug-abuse-related aftereffects in the medial prefrontal cortex (PFC) could be accompanied by impairments in emotional regulation, and specifically in inhibition of all motivations and emotions other than craving (London, Ernst, Grant, Bonson, & Weinstein, 2000; Shalev, Grimm, & Shaham, 2002). Diminished PFC control of the fronto-striatal circuits allows more habitual responses mediated by the posterior and subcortical (e.g., basal ganglia, striatum) structures to take over regulation of behavior.

There is a converging evidence that implicit automatic processes are also involved in the fear processing (Mogg & Bradley, 1998). Neuroimaging studies showed that medial prefrontal cortical areas modulate fear responding through inhibitory connections with the amygdala (Davidson, 2002; Devinsky, Morrell, & Vogt, 1995). It was hypothesized

FIGURE 8. Event-related potentials at the frontal and parietal regions-of-interest (ROI) in response to non-target drug cues. Cocaine addicts from SUD and DUAL groups have higher cue reactivity at the frontal ROI. SUD = substance use disorder; DUAL = dual diagnosis of cocaine dependence and PTSD; CNT = control.



that dysfunction of the interaction of prefrontal and limbic structures plays a role in failure of extinction to fear in PTSD (Bremner, Southwick, Darnell, & Charney, 1996; Bremner et al., 1999; Bremner et al., 2004). PTSD is often conceptualized in terms of conditioned fear with enhanced emotional memory acquisition mediated by a hyperresponsive amygdala and delayed extinction due to failure of inhibitory control of the medial PFC and anterior cingulate cortex over the amygdala (Charney, Deutch, Krystal, Southwick, & Davis, 1993; Gilboa et al., 2004; Grillon, Morgan, Davis, & Southwick, 1998; Li & Sinha, 2008; Rauch et al., 1996). These PFC deficits may further enhance the effects of the amygdala hyperactivation, thereby increasing the frequency and intensity of PTSD symptoms (Bremner et al., 1999). Negative emotions typical for PTSD and decreased stress coping capacity may augment craving and promote drug-seeking and relapse behaviors (Goeders, 2003; Koob, 1999). In dually diagnosed individuals, reactivity to both traumatic and drug cues may represent a combined conditioned and unconditioned response that increases vulnerability for further progression of drug use.

Drug addiction leads to frontal top-down control deficits. Deficient inhibitory control results in an inability to override strong habitual drug-seeking behaviors, thus allowing external salient cues (drug-related cues and both drug-related and stress-related in a case of comorbid PTSD), and pathological craving (and fear in PTSD) drive behavior. Individuals genetically predisposed to behavioral disinhibition are more vulnerable to impulsive drug abuse (Bauer, 1997). Reduced prefrontal inhibitory control results as well in a diminished capacity to override stress responses and generally poor stress coping skills (Koob & Le Moal, 2001; Li & Sinha, 2008; Sinha, Catapano, & O'Malley, 1999). Therefore, addictive behavior leads to functional abnormalities resulting in an imbalance in reward values because of hypersensitization to drug-stimuli and drug-associated motivation at the expense of a natural reinforcement. PTSD is further contributing to the severity of drug dependence through enhanced reactivity to traumatic stress-related external stimuli and negative emotional states in response to external internal cues (e.g., flashbacks, stress-related memories and ruminations, etc.).

Active cocaine use and cocaine withdrawal-related alterations in neural structures involved in stress response are well known (Koob et al., 2004), and these neuroadaptave changes in stress circuits, according to Li and Sinha (2008), may contribute to the increased salience of drug and drug-related stimuli in a variety of challenge or "stress"

contexts (Robinson & Berridge, 1993; Singha, Catapano, & O'Malley, 1999). Furthermore, they have also proposed that addiction-related alterations in cortico-striatal–limbic circuits may contribute to reduced coping ability, poor behavioral flexibility, and deficient problem solving capacity during increasing levels of stress or emotional challenges in psychoactive stimulant users (Li & Sinha, 2008; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006).

This project studies specific components of ERPs and behavioral (RT and accuracy) measures to investigate reactivity to drug-related and stress-related cues in individuals with cocaine use disorder with comorbid PTSD. It shows that cognitive task employing emotionally challenging cues could be used as a potentially useful diagnostic tool to assess cognitive and emotional functioning in cocaine abuse and PTSD. These ERP and behavioral parameters probably could be used as useful measures that can be employed to assess clinical and research outcomes in both pharmacologic and behavioral and neurofeedback interventions. These psychiatric and ERP-based cognitive functioning assessments were important part of our outpatient participants' clinical evaluations at the intake stage, as most of cocaine addicts expressed willingness to enroll in an integrated behavioral treatment trial based on neurofeedback and motivational interviewing. These results contribute to a better understanding of the neurobiologic interaction between these mental disorders and offer a basis for a model explaining the high prevalence of this particular form of dual diagnosis by using cognitive neuroscience methods and theories.

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