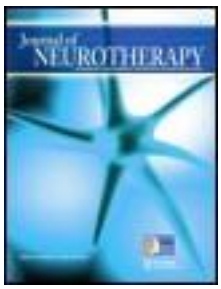

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Integrating Cognitive Neuroscience Research and Cognitive Behavioral Treatment with Neurofeedback Therapy in Drug Addiction Comorbid with Posttraumatic Stress Disorder: A Conceptual Review

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Integrating Cognitive Neuroscience Research and Cognitive Behavioral Treatment with Neurofeedback Therapy in Drug Addiction Comorbid with Posttraumatic Stress Disorder: A Conceptual Review

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ABSTRACT. Persons with co-occurring mental and substance use disorders have a more persistent and refractory illness course than those without dual diagnosis. However, few studies have assessed the effects of cognitive-behavioral and biobehavioral treatments on brain function and behavioral indices in people with comorbid drug abuse and posttraumatic stress disorder (PTSD). In this conceptual review, we propose an integrated approach to assessment and treatment utilizing cognitive neuroscience methods, conventional psychotherapeutic treatment and neurofeedback therapy to assess the recovery of cognitive and emotional functions affected by chronic psychostimulant drug abuse co-occurring with PTSD. We review cognitive and motivational factors (e.g., craving, hypersensitivity to drug- and threat-related cues, deficient executive top-down control etc.) involved in addiction and PTSD, and discuss reasons for their persistence and high vulnerability to relapse in cocaine and methamphetamine users with co-morbid PTSD undergoing behavioral treatment. Incorporating neuroscience assessment methods to assess the effects of psychotherapy and neurofeedback interventions for comorbid disorders may provide significant potential for identifying side-by-side psychophysiological with clinical markers of treatment progress, and may also provide useful information for planning interventions. doi:10.1300/J184v11n02_03

KEYWORDS. Cognitive neuroscience, cognitive-behavioral treatment, neurofeedback, substance use disorder, drug addiction, posttraumatic stress disorder, EEG, ERP

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INTRODUCTION TO NEUROBIOLOGY OF SUBSTANCE USE DISORDER AND PTSD

Addiction as a Mental Disorder with Behavioral, Cognitive and Psychosocial Deficits

The psychoactive substance use disorder commonly referred to as "drug addiction" is characterized by physiological dependence accompanied by the withdrawal syndrome on discontinuance of the drug use, psychological dependence with craving, the pathological motivational state that leads to the active drug-seeking behavior, and tolerance, expressed in the escalation of the dose needed to achieve desired euphoric state. Drug addiction is a chronic, relapsing mental disease that results from the prolonged effects of drugs on the brain (Dackis & O'Brien, 2001; Leshner, 1997; Wexler et al., 2001). Drug addiction can take control of the brain and behavior by activating and reinforcing behavioral patterns that are excessively directed to compulsive drug use (Di Chiara, 1999; Gerdeman et al., 2003). Addiction leads to behavioral, cognitive and social adverse outcomes that incur substantial costs to society. In 2002, it was estimated from the Substance Abuse and Mental Health Service Administration (SAMHSA, 2004) that 22 million Americans have a substance abuse or dependence disorder (9.4% of the U.S. population), and 2 million of them were current cocaine users. Of this group, it was estimated that 3.5 million sought treatment, 796,000 of them with cocaine dependence (Vocci & Ling, 2005). According to the 2004 revised National Survey on Drug Use and Health, nearly 12 million Americans have tried methamphetamine (commonly known as "meth," "speed," or "crystal"), and 583,000 of them are chronic methamphetamine users (SAMHSA, 2004). Results reported at a recent CEWG meeting (2005) indicate that methamphetamine abuse and production continue at West Coast areas, and some southwestern areas of the United States-but methamphetamine abuse also is continuing to spread eastward. Some cocaine users are currently switching to methamphetamine, ignorant of its severe toxicity. Many patients seeking treatment for addiction have multiple drug dependencies and psychiatric comorbidities (Volkow & Li, 2005). Information from epidemiological surveys shows that drug addiction is common and associated with significant morbidity and mortality. Large individual and societal costs of drug abuse make research and treatment of stimulant addiction an imperative problem (French et al., 2000; Mark et al., 2001).

Recognizing psychostimulant substance use disorder (PSUD) as a chronic, relapsing mental disorder, the effective treatment approaches must address its behavioral, cognitive, perceptual, motivational, emotional, and psychosocial domain components. Recently through intensive neuroscience research and clinical psychiatric studies many specific components of cognitive, emotional, and behavioral deficits typical for stimulant substance abuse have been identified and investigated. But the practical values of these cognitive neuroscience and psychotherapeutic findings depends on a further integration of these methodological approaches in a framework which will allow the formulation of new hypotheses and testing them in soundly designed experimental clinical studies.

Substance Use Disorder Comorbidity with PTSD

Co-occurrence of PSUD and other psychiatric diagnoses (e.g., PTSD, antisocial personality disorder, attention deficit hyperactivity disorder [ADHD] etc.) is highly prevalent (Drake & Wallach, 2000; Evans & Sullivan, 1995; Grant et al., 2004; Jacobsen, Southwick, & Kosten, 2001). Persons with co-occurring mental and PSUD have a more persistent illness course and are more refractive to treatment than those without dual diagnosis (Brown, Recupero, & Stout, 1995; O'Brien et al., 2004; Schubiner et al., 2000; Swartz & Lurigio 1999;). Rates of PTSD occurring in persons primarily identified with or in treatment for substance abuse vary from 43% (Breslau et al., 1991) up to 59% (Triffleman, Carroll, & Kellogg, 1999). In epidemiological samples, PTSD is itself a syndrome affecting up to 12.3% of the general community (Clark et al., 2001; Kessler et al., 1997). In a general population study, Cottler et al. (1992) reported that cocaine

abusers were three times more likely to meet diagnostic criteria for PTSD compared to individuals without a PSUD. Kalechstein et al. (2000) found that methamphetamine-dependent individuals are at greater risk to experience particular psychiatric symptoms. There was reported a significant dependence-by-gender effect, with methamphetamine-dependent females reporting significantly more overall posttraumatic stress symptomatology compared to females reporting no dependence, whereas males significantly differed only with respect to depression. This finding is concordant with our own observation of higher rates of this form of dual diagnosis (methamphetamine dependence with PTSD) among female addicts.

There are several pathways which may explain high rate of co-occurrence of PTSD and PSUD (Stewart et al., 1998). According to the "self-medication" hypothesis (Khantzian, 1985, 1997), PTSD might precede and be responsible for the development of drug abuse since persons with PTSD may take drugs in an attempt to reduce their PTSD symptoms. Development of drug dependence and escalation of drug abuse can, on its turn, exacerbate PTSD symptoms and result in a worsening of PTSD severity, in part because drug withdrawal symptoms can mimic PTSD symptoms in dual patients. On the other hand, drug abuse itself may increase the risk and probability of PTSD development because drug habit may render individuals more susceptible to the development of PTSD due to a decreased stress tolerance (Sinha, Catapano, & O'Malley,1999; Stewart, 1996; Stewart et al., 1998), and continuous involvement in dangerous illegal activities associated with obtaining controlled substances.

In dually diagnosed patients, symptoms of both disorders are in complex relationships where one disorder serves to sustain another (Jacobsen, Southwick, & Kosten, 2001; Stewart et al., 1998). Presence of a linkage between comorbid PSUD and PTSD is a very important issue, because in some dual-diagnosis cases stimulant dependence and the comorbid condition may exist independently (Grabowski et al., 2004; Nunes, 1997). More research is needed to understand the synergistic effects of drugs of abuse and PTSD on behavioral, cognitive and physiological variables. Conversely, investigation about how PTSD-related symptoms and accompanying physiological dysfunctions affect drug the dually diagnosed patients is also needed.

Neurobiological Basis of Drug Addiction: Evidence from Neuiroimaging Studies

The reinforcing effects of drugs have been attributed to increased dopamine (DA) concentration in brain regions (Di Chiara, 1999; Everitt, Dickinson, & Robbins, 2001; Volkow et al., 2002). Many of the substances of abuse share the common feature that they can modulate the brain reward system that is fundamental to motivational behaviors important for survival. One part of this system is the medial forebrain bundle (MFB) which connects the ventral tegmental area (VTA) to the nucleus accumbens (NA). Neural pathways projecting from the VTA and the NA innervate limbic (e.g., the amygdala) and frontal areas of the brain. These brain structures are important for the expression of emotions, reactivity to conditioned cues, planning and judgment. Although the MFB consists of neurons that contain DA, noradrenalin and serotonin, it is the dopaminergic projection that has been most closely implicated in reward in cocaine addiction (Goldstein & Volkow, 2002; Lingford-Hughes et al., 2003; Lyvers, 2000).

Structural deficiencies within limbic and prefrontal regions may contribute to the typical drug-seeking and drug-taking behaviors observed in cocaine dependent individuals. There is a decrease in gray matter concentration in the ventromedial orbitofrontal, anterior cingulate, anteroventral insular, and temporal cortices of cocaine-dependent patients in comparison to controls (Trantham et al., 2002; Volkow, Fowler, & Wang, 2004). Functional abnormalities in fMRI and PET studies of cocaine-dependent patients vs. controls have been observed in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), the insula, basal ganglia, and limbic regions (Childress et al., 1999; Makris et al., 2004; Volkow, Fowler, & Wang, 2003). The functional abnormalities in drug addicts emerge in prefrontal regions that are importantly involved in behaviors such as decision making (Bechara et al., 1994, 2001; Damasio, 1996; Grant, Contoreggi, & London, 2000; London et al., 2000), behavioral inhibi-

tion (Hester & Garavan, 2004; Hester, Dixon, & Garavan, 2006), and assigning emotional valence. Another major target for drugs of abuse, and specifically cocaine, is the striatum, a subcortical brain region important for the habit formation and storing of fixed behavioral patterns (Gerdeman et al., 2003; Koob & Le Moal, 2001).

Methamphetamine is also classified as a psychostimulant drug. Methamphetamine is structurally similar to amphetamine and the neurotransmitter dopamine, but it is quite different from cocaine. Although both these stimulants have similar behavioral and physiological effects, there are some major differences in neural mechanisms of action on the cellular level. For example, cocaine inhibits reuptake of dopamine (as well as serotonin and norepinephrine), whereas methamphetamine releases these monoamines from storages, also the half-life of methamphetamine metabolism is much longer that cocaine (NIDA, 2002). This results in methamphetamine being present in the brain longer, which ultimately leads to prolonged neurotoxic effects. Active methamphetamine users often exhibit performance deficits on tests of verbal memory, as well as tests of perceptual motor speed and executive functions such as inhibition, problem solving, abstract thinking, and tasks that require mental flexibility (Simon et al., 2000, 2002; Thompson et al., 2004). Abstinent methamphetamine users show impaired response inhibition in neurocognitive tasks (Salo et al., 2002; Kalechstein, Newton, & Green, 2003) and decision-making (Paulus et al., 2002). The structural and functional neural abnormalities within prefrontal and limbic structures contribute to the deficits in executive functions, decision making, behavioral inhibition and assignation of emotional valence to stimuli, which are characteristics of both chronic cocaine and amphetamine users.

Neurobiological Basis of PTSD

Acute and/or chronic exposure to traumatic stress can produce long-term changes in behavior and may result in the development of PTSD. Symptoms of this disorder include altered cognitive, affective and behavioral functioning in the form of intrusive re-experiencing (flashbacks, heightened physiological reactivity to trauma-related cues), behavioral avoidance of trauma-related stimuli, and general hyperarousal such as exaggerated startle response, poor concentration, insomnia, and hypervigilance (DSM-IV, APA, 1994). Individuals with PTSD usually exhibit deficits in information processing including dysfunctions in attention, working memory, encoding information, and in inhibition of task-irrelevant stimuli and responses (Karl, Malta, & Maercker, 2006; Vasterling et al., 2002). Another typical abnormality in PTSD is excessive reactivity to trauma-specific cues, and enhanced processing of stimuli relevant to trauma (Buckley et al., 2000). Functional neuroimaging studies have used traumatic slides and sounds or scripts to probe the neural circuits of PTSD (Bremner, 2005; Bremner et al., 2004). Findings in these studies included decreased function in the medial prefrontal cortex (PFC) and ACC, dorsolateral PFC, inferior parietal lobule, hippocampus, and temporal cortex, and increased function in the posterior cingulate cortex (reviewed in Bremner, 2005). The brain regions implicated in these studies are involved in emotional reactivity to affective stimuli and threat (Rauch et al., 1996). Disruption in neural circuits connecting dorsal prefrontal and posterior cingulate and parietal areas involved in processing of threat with the para-limbic and limbic regions (OFC, hippocampus, and amygdala) may lead to impairments in stress coping ability which is typical for PTSD.

Executive Dysfunctions: Disinhibition and Decision Making Deficits in Drug Addiction

Neurological and neuropsychological evidence indicates that the prefrontal cortex mediates complex "executive" top-down control functions including behavioral self-control (Fuster, 2001; Miller & Cohen, 2001). The term "executive functions" refers to a range of cognitive processes involved in coordination of information processing and action control (Elliott, 2003). Neuroanatomical substrates of executive processing are believed to be served by neural circuits connecting the PFC with subcortical structures (Faw, 2003; Heyder, Suchan, & Daum, 2004). The frontal cortex is also involved in the suppression of limbic im-

pulses and this inhibitory dysfunction may underlie the difficulty of addicted individuals to resist drug use urges (Dackis & O'Brien, 2001). Impaired inhibitory functions may result in a loss of control over behavioral impulses leading to drug-seeking and self-administration (Filmore & Rush, 2002). Considering that impairments of self-control are characteristic of addictions (Wexler et al., 2001), and specifically psychostimulant abuse, frontal lobe dysfunction may play a significant role in disinhibited compulsive drug-seeking and drug-taking behaviors, which are so common in cocaine and methamphetamine addicts.

Drug-dependent persons often exhibit deficiencies in behaviors usually observed in patients with OFC or insular damage. Both groups choose immediate gratification over long-term rewards in decision-making tasks (Bechara et al., 1994, 2001; Grant, Cantoreggi, & London, 2000). This tendency to make poor decisions may underlie the propensity of cocaine-dependent individuals to engage in risky behaviors, particularly when attempting to obtain cocaine. OFC dysfunction has also been linked to behavioral disinhibition, perseveration, and the inability to modulate reward behavior. The functional deficits in OFC may result in an overwhelming desire to seek and use drugs while ignoring the future negative consequences (Bechara et al., 2001).

The Iowa gambling task (IGT) was designed to examine decision-making deficits exhibited by people with frontal damage (Bechara et al., 1994, 2001; Bechara & Damasio, 2002). In this task, subjects choose cards from several decks, with each choice resulting in monetary wins along with occasional monetary losses. Advantageous decks have small wins, but smaller losses, resulting in an overall gain. Disadvantageous decks have larger wins, but larger penalties, resulting in an overall loss. This task is thought to simulate decision-making process involving balancing rewards and punishments. Patients with damage to PFC and amygdala, as well as abusers of alcohol, cocaine, and heroin, all show impairments on the performance of this task (Bechara & Damasio 2002; Grant, Cantoreggi, & London, 2000; Rogers et al., 1999). In these laboratory gambling tests, drug abusers compared to normal controls select more risky decision making (Bartzokis et al., 2000; Bolla et al., 2003; Fishbein et al., 2005). One of the motivational models explaining these results of the gambling tests in addicts is focusing on over-sensitivity to positive reward and under-reactivity to punishment in patients with PSUD. In this model, in drug addiction an approach tendency behavior dominates compared to a withdrawal-avoidance type of behaviors (Davidson, 1998). Personality-trait centered models are suggesting explanation of risky behaviors as a dominance of such traits such as impulsivity, extraversion, sensation-seeking in individual predisposed to risky decisions, which are resulting in drug abuse and addiction (Corr, 2002; Francis, 1996; Gray, 1987; Knyazev, 2004; Zuckerman, 1993). These models, nevertheless, do not exclude that chronic drug abuse will consequently aggravate pre-existing genetically determined deficits in the ability to execute less risky judgments.

Attentional Processing Deficits: Stroop Task in Drug Abuse and PTSD

The Stroop color naming task is used to measure attentional bias by testing whether stimuli are differentially attended. Stroop tasks are used to determine the level of attention provided by the word component of the stimulus, whereby increased activation makes the suppression of its meaning more difficult (MacLeod, 1991). Research with the classic color and emotional Stroop tasks have demonstrated an attentional bias for drug-related stimuli in drug abusers (Duka & Townshend, 2004; Franken et al., 1999; Franken, 2003; Hester & Garavan, 2004; Hester, Dixon, & Garavan, 2006). The results of the Stroop tests have been interpreted as reflecting a preoccupation with drug-related items caused by PSUD. For example, when participants are pre-occupied with alcohol they take significantly longer to respond to the color of a word such as "beer", than a neutral word such as "chair" (Lusher, Chandler, & Ball, 2004). These studies provide support for the hypothesis that part of the addiction process is an alteration in attentional processing (Lyvers, 2000; Robinson & Berridge, 1993), whereby substance-related cues attain greater salience, particularly during craving for the drug.

Patients with PTSD have been found relative to controls slower to color-name emotional words in Stroop task than other types of words (McNally, Amir, & Lipke, 1996). Stroop interference has also been shown in patients with PTSD related to the trauma of rape (Foa et al., 1991), motor vehicle accidents (Beck et al., 2001), mixed-trauma groups (McNeil et al 1999), and in children with PTSD (Moradi et al., 1999). Increased anterior cingulate activation has been consistently shown during the Stroop interference condition (Pardo et al., 1990; West, 2003). A study of combat-related PTSD utilizing the counting Stroop found a failure in ACC activation during counting of emotional words (Shin et al., 2001). Bremner et al. (2004) showed that women with PTSD had a relative decrease in ACC blood flow during exposure to the emotional Stroop task. The Stroop task is thus shown to differentiate between groups of individuals with and without psychopathology (e.g., PSUD, PTSD), providing a reliable instrument for assessing attentional bias and ability to suppress task-irrelevant lexical component. Therefore, it is feasible to use either classic color word or emotional Stroop task to assess interference and inhibition deficits, and to probe ACC function in patients with dual diagnosis.

Cue Reactivity and Craving: Subjective and Psychophysiological Responses

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., 1994; Drummond et al., 1995; Franken, 2003; Johnson et al., 1998; Robbins et al., 1997,1999, 2000; Robbins & Ehrman, 2004). Craving is described as a strong subjective urge to take drugs and is considered to be an important factor for subsequent engagement in drug-seeking behaviors and relapse in abstained addicts (Bauer & Kranzler, 1994; Childress et al., 1999; Franken, Kroon, & Hendriks, 2000; Grant et al., 1996; McKay et al., 1995; Robinson & Berridge, 1993). One of the cognitive components of cue reactivity is the preferential allocation of attentional resources to items related to substance abuse (Franken, 2003; Weiss et al., 2001). It has been proposed that conditioned sensitization in neural pathways associating incentives with stimulus items may be responsible for cue reactivity (Lubman et al., 2000; Stormark et al., 2000). In laboratory conditions drug-related cues are used to elicit craving and to examine neurophysiological substrates of cue-elicited craving (Bonson et al., 2002; Ehrman et al., 1992,1998; Franken, 2003; Robbins et al., 1997). Studies are reported on neuroimaging (Childress et al., 1999, Garavan, Ross, & Stein, 1999; Kilts et al., 2004), EEG (Bauer & Kranzler, 1994; Liu et al., 1998; Reid et al., 2003) and autonomic (Robbins et al., 1999; Ingjaldsson et al., 2003) effects associated with drug cue-related responses and craving.

PTSD may modulate the expression of PSUD. Of special importance is whether PTSD in persons with SUD renders these individuals vulnerable to a more severe drug-related behavioral disorder. The question of similar nature is whether PSUD, on its turn, can aggravate PTSD (Brown, Recupero, & Stout, 1995; Dansky, Brady, & Saladin, 1998; Najavits et al., 1998; Ouimette et al., 1997). Only few studies have examined mechanisms by which PTSD might exert the adverse effects on addiction. One possible mechanism is that the negative emotional states associated with PTSD augment motivational state of craving (Childress et al., 1994, 1999; Coffey et al., 2002; Robbins et al., 2000). Emotional dysfunctions may play an important modulatory role in PSUD. The persons with a PSUD and a co-occurring mental disorder with strong emotional features (i.e., PTSD) may be particularly reactive both to traumatic stress and drug-related cues. Emotional component of PTSD may happen to be uniquely deleterious to addiction treatment outcome (Back et al., 2001; Brown, Recupero, & Stout, 1995; Ouimette et al., 1997). One explanation for the high prevalence of PTSD within substance abusers and their poorer treatment outcome is the presence of PTSD-related negative affect and high arousal. Therefore, for individuals diagnosed with PSUD and PTSD, negative emotional states, resulting from PTSD cluster symptoms, are relatively common and may adversely affect their PSUD treatment. Withdrawal from drugs of abuse,

such as cocaine, can produce high levels of anxiety (Brady et al., 2001; Dansky, Brady, & Saladin, 1998). Abstinent individuals experiencing distress and craving may relapse in drug seeking and drug taking behavior to dampen their negative emotions and exacerbated PTSD symptoms.

Psychophysiological Reactivity to Emotional Stimuli in PSUD and PTSD

It has been shown that emotional abnormalities are typical for addicts (Fukunishi, 1996; Wexler et al., 2001). Alexithymia is highly prevalent among substance abusers (Brady, 1997; Bremner et al.,1996; Fukunishi, 1996; Ouimette, Finney, & Moos, 1999), and in turn, is highly prevalent in individuals with PTSD (Sifneos, 1996; Handelsman et al., 2000). Addicted individuals could be affected by a dysfunction associated with changes in emotional reactivity to natural positive reinforcers (Gerra et al., 2003). Sensitization to drugs and counter-adaptation are hypothesized to contribute to dysregulation of hedonic homeostasis and to observed brain reward system abnormalities according to the "allostasis" theory (Koob, 1999; Koob & Le Moal, 2001). 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 (DSM-IV, PTSD Criterion B.5). Research findings consistently demonstrated that individuals with PTSD produce heightened physiological responses (e.g., startle, heart rate [HR], skin conductance response [SCR]) to stimuli related to traumatic events (Blanchard, 1990; Buckley et al., 2000; Orr et al., 1998; Orr & Roth, 2000; Prins, Kaloupek, & Keane, 1995; Shalev, Orr, & Pitman, 1993). This heightened reactivity has been found across a variety of psychophysiological measures during presentations of trauma-related auditory or visual cues, and during personal imagery of traumatic events (Grillon et al., 1998; McNally, Amir, & Lipke, 1996; Sahar, Shalev, & Porges, 2001). An abnormal state of autonomic balance, assessed by the heart rate variability (HRV), which is observed in response to traumatic cues, has been considered to be one more characteristic feature of the PTSD syndrome (Cohen et al., 1998, 2000). Physiological reactivity on exposure to cues related to traumatic events is common for PTSD. Psychophysiological assessments of emotional reactivity in PTSD co-occurring with PSUD can provide valuable practical and theoretical insight.

ELECTROENCEPHALOGRAPHIC STUDIES ON STIMULANT DRUG ABUSE AND PTSD

EEG in Cocaine Addiction

Qualitative and quantitative electroencephalographic (qEEG) measures are highly sensitive to the acute and chronic effects of neurointoxication produced by drugs, tolerance, withdrawal and long-term abstinence (Ehlers, Wall, & Schucit, 1989; Pollock et al., 1992). Some EEG characteristics observed in drug addicts are considered to be due to the toxic effects of drugs on the brain, whereas some EEG characteristics in individuals with addictive disorders may indicate a predisposition toward the development of SUD (Porjesz et al., 2005). Several recent studies employing qEEG techniques have already demonstrated an association between the amount of beta activity in the spontaneous EEG and relapse in cocaine abuse (Bauer, 2001). Prichep et al. (1999, 2002) extended the idea of relating baseline EEG activity to outcome in cocaine-dependent patients in treatment programs. QEEG studies in the cocaine-dependent population have reported excess alpha activity (Herning et al., 1994b; Lukas, 1993; Prichep et al., 1996; Roemer et al., 1995) and decreased delta and theta (Noldy et al., 1994; Prichep et al., 1996; Roemer et al., 1995), while several studies have reported increased beta power (Bauer, 2001; Costa & Bauer, 1997; Herning et al., 1994b; Noldy et al., 1994). Subjects with cocaine dependence have persistent changes in brain function assessed with qEEG methods, present when evaluated at baseline, 5-14 days after last reported crack cocaine use, and persistent at one and six month follow-up evaluations (Alper, 1999; Alper et al., 1990,1998; Prichep et al., 1996, 2002). Decrease in the delta and theta bands of the EEG can be regarded as a specific sign of brain dysfunction. However, this sign, as well as other qEEG abnormal patterns,

can be found in many different psychiatric disorders and none of them can be considered as pathognomonic of any specific mental or neurological disorder.

EEG in Methamphetamine Addiction

Several studies have examined the neurobiological consequences of methamphetamine dependence using qEEG methods (e.g., Newton et al., 2003, 2004). It was found that patients with methamphetamine dependence had significantly increased power in delta and theta bands compared to non-drug-using controls (Newton et al., 2003). These results are in accordance with other neurocognitive studies (Kalechstein, Newton, & Green, 2003) suggesting that methamphetamine abuse is associated with psychomotor slowing and frontal executive deficits. Within the methamphetamine-dependent subjects increased theta qEEG power was found to correlate with response time and was accompanied with reduced accuracy (Newton et al., 2004). To our knowledge, qEEG patterns associated with acute withdrawal and recent abstinence in methamphetamine dependence have not yet been described.

EEG in PTSD

There are only a few EEG studies of PTSD patients. Wolf, Alavi, and Mosnaim (1988) examined the EEG activity in sleep and waking states of PTSD patients to find that all EEG parameters (in sleep and awake) were within normal limits. Begic, Hotujac, and Jokic-Begic (2001) using conventional spectral methods found that PTSD patients had increased theta activity over central regions and increased beta activity over frontal, central and left occipital regions. The recent study of Chae et al. (2004) using non-linear dynamical analysis of the EEG found that PTSD patients exhibit disturbed cortical information processing. PTSD patients had increased theta activity over central regions, and increased beta activity. Slow beta (13.5-18 Hz) activity was found increased over frontal, central and left occipital regions; whereas fast beta (18.5-30 Hz) activity increased over frontal regions. No significant differences were noted between the PTSD and control group in delta and alpha activity. These results point to the role of theta and beta rhythms as the potential markers in PTSD.

Event-Related Potential (ERP): P300

The most widely used in psychiatry and other clinical applications is the P300 component of the ERP (300 to 600 ms post-stimulus) (Polich, Pollock, & Bloom, 1994; Polich & Herbst, 2000; Pritchard, 1981, 1986; Pritchard, Sokhadze, & Houlihan, 2004). The amplitude of P300 reflects the allocation of attentional resources, while the latency is considered to reflect stimulus evaluation and classification time (Katayama & Polich, 1998; Polich & Herbst, 2000). 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 frontocentral P300, so called P3a, whereas the rare targets elicit a parietal P300, so called P3b (Katayama & Polich, 1996, 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). Though P300 in general is thought to represent "context updating/closure," in a three-stimuli oddball task the P3a is interpreted as "orienting," and the P3b as an index of the ability to maintain sustained attention to target (Näätänen, 1990). 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 oddball paradigm provides possibilities for delineating the cognitive processes engaged in this task when motivational salience and novelty of distracter stimuli are manipulated.

P300 Abnormalities in Cocaine Addiction, Methamphetamine Addiction and PTSD

Acute and chronic use of cocaine exerts neuropharmacological effects on amplitude and latency of ERP components (Biggins et al.,

1997; Fein, Biggins, & McKay, 1996; Herning et al., 1994a; Kouiri, Lukas, & Mendelson, 1996; Polich,1990). Longer P300 latency without abnormalities in amplitude was reported in several studies on cocaine withdrawal (Herning et al., 1994a; Lukas, 1993). Noldy and Carlen (1997) demonstrated effects of cocaine withdrawal on the latency of the P300 in an auditory oddball task. In cocaine-dependent patients, P300 amplitude decrements over frontal areas are persistent even after long periods of abstinence (Bauer, 1997). The latency of the P3a was delayed and amplitude reduced to novel non-targets in cocaine and alcohol-dependent subjects compared to controls (Biggins et al. 1997; Hada et al., 2001) in auditory and visual three-stimuli oddball tasks. 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 the frontal ERP components is important considering increased evidence of frontal dysfunctions in substance use disorders.

Several studies have investigated ERP changes associated with methamphetamine abuse and dependence. The P300 component of the auditory ERP was reported to show prolonged latency in the oddball task in methamphetamine dependent subjects with a history of psychosis, compared to normal controls (Iwanami et al., 1994,1998). In particular, the patients with methamphetamine dependence showed reduced P3a amplitude in the reading task and delayed P3b latency with normal P3b amplitude in the auditory oddball task. This was interpreted as indicating prolonged central noradrenergic dysfunction due to earlier methamphetamine use. Acute methylphenidate treatment decreased the P300 latency (Halliday et al., 1994; Sunohara et al., 1999), while acute amphetamine administration was found to block P50 suppression in normal volunteers (Light et al., 1999).

Meta-analysis on ERPs in PTSD can be found in a recent review by Karl, Malta, and Maercker (2006). Most of the studies on PTSD report abnormalities in P300, thus providing evidence for impaired cognitive processing in this disorder (Attias et al., 1996; Blomhoff, Reinvang, & Malt, 1998; Charles et al., 1995; Felmingham et al., 2002; Kimble et al., 2000; Kounios et al., 1997; McFarlane, Weber, & Clark, 1993; Metzger et al., 1997ab; Neylan et al., 2003; Noldy & Carlen, 1997; Stanford et al., 2001). Studies finding attenuated P300 and delayed N200 attributed their results to concentration impairment (McFarlane, Weber, & Clark, 1993) or attention deficits (Charles et al., 1995; Metzger et al., 1997ab). Increased P300 amplitude in PTSD was explained as due to altered selective attention (Attias et al., 1996) or heightened orienting to threatening or trauma-specific stimuli (Kimble et al., 2000). Several studies emphasized that P3a enhancement in PTSD is expressed when distracters are either trauma-related or novel stimuli in oddball tasks (Bleich, Attias, & Furnam, 1996; Felmingham et al., 2002; Kimble et al., 2000; Stanford et al., 2001; Neylan et al., 2003; Weinstein, 1995). In general, increased P300 amplitude in PTSD is thought to reflect attentional bias towards threat stimuli and reduced P300 amplitude is thought to reflect a consequent reduction in attentional resources to process non-threatening stimuli.

ERP Components Other Than P300 (N2b, P2a, N450)

It should be stated that most of ERP studies on PTSD and PSUD have limited their analysis to P300 (P3a, P3b), thus potentially ignoring more earlier cognitive ERP potentials. There is a family of negative ERP components (N200, N2b, etc.), occurring between about 180 and 300 ms post-stimulus, that index various aspects of the processing of task relevant stimuli (Wijers et al., 1996). The N2b components are enhanced if the presented stimulus contains a perceptual feature defining the target in the current task (Näätänen, 1990; Wijers et al., 1996). In a study of Felmingham et al. (2002) the group of PTSD patients showed increased N200 amplitude and latency to target stimuli. The authors associated disturbance of N200 with impairments in stimulus discrimination and attention. A frontal positive component (P200, P2a, etc.) in the same latency range as the posterior N2b was reported in oddball tasks (Potts et al., 1998; Potts, Patel, & Azam, 2004; Wijers et al., 1996). In a visual oddball study, Potts et al. (1996) showed that the frontal P2a was present only to the task-relevant targets,

consistent with an index of motivational relevance evaluation. The timing, topography, and psychological responsiveness of the P2a was consistent with activity in the orbitofrontal cortex(Potts et al., 1996, 1998, Potts, Patel, & Azam, 2004). The ERP studies of the neural correlates of conflict processing using interference tasks have reveal the frontal N450 (400-500 ms) negative wave that was associated with conflict detection and thought to originate from the activity in the anterior cingulate cortex (ACC) (Liotti et al., 2000; Liu et al., 1998; West, 2003; West & Alain, 2000). The generators of the N450 reflect activity of the ACC and serve as neural correlates of conflict and interference processing. Analysis of endogenous ERP components other than P300 (e.g., P2a, N2b, N450 etc.) may provide with more specific data about functional abnormalities on the different stages of salient information processing in PSUD and PTSD.

Measuring Prefrontal Inhibition Deficits in Addiction Employing a "Go-NoGo" Task

Cortical inhibitory state can be assessed experimentally by use of a continuous performance test in which a motor response is required to one situation ("Go" condition) but must be suppressed to others ("No-Go"). The frontal activation is larger in the No-Go than in the Go condition and is presumed to reflect the inhibition that is required for response suppression. In substance dependent persons the frontal activation during No-Go task is lower than in normal individuals, an indication that frontal lobe control of response inhibition is reduced (Strik et al., 1998; Taber et al., 2000). However, the deficits in inhibitory control have been reported in a variety of behavioral disorders, which share disinhibitory psychopathology in common (Bauer & Hesselbrock, 1999; Brandeis et al., 2002; Johannes et al., 2003; Kouiri, Lukas, & Mendelson, 1996; Smith, Johnstone, & Barry, 2004; Weisbrod et al., 2000). Two major ERP components have been identified as the markers for response inhibition: first, the "No-Go-N2," a negative deflection with a frontocentral maximum around 200-300 ms, and second, referred to as "No-Go-P3," an augmented positive-going wave usually peaking between 300 and 600 ms (Falkenstein, Hoorman, & Hohnsbein, 1999, 2002; Fallgatter & Strik, 1999; Kaiser et al., 2003; Kiefer et al., 1998; Kopp, Rist, & Mattler, 1996; Nieuwehuis et al., 2003; Salisbury et al., 2004). The ERP markers of response inhibition (NoGo-N2 and NoGo-P3) represent different time points of response inhibition process and can be used in addiction research as functional outcome measures.

ERP and QEEG Abnormalities in Addiction: Pharmacological Effect or Trait Markers?

Whether P300 decrements are only a coincident "marker" of vulnerability or make a direct etiologic contribution to risk for substance dependence is still unknown (Bauer & Hesselbrok, 2001; Carlson, Iacono, & McGue, 2002; O'Connor et al., 1994; Polich, Pollock, & Bloom, 1994; Porjesz & Begleiter, 1998). The P300 reduction is seen in mental disorders that often are comorbid with substance abuse, such as conduct disorder (Bauer & Hesselbrock, 1999, 2001), ADHD (Bauer, 1997; O'Connor et al., 1994), bipolar or major affective disorder (Friedman & Squires-Wheeler, 1994). Reduced P300 amplitude related to prefrontal brain dysfunction may tap that a deficit in inhibitory control is an underlying mechanism shared by different psychopathologies (Bauer & Hesselbrock, 1999; Clark, Parker, & Lynch, 1999; Tarter et al., 2003). According to Bauer (2002), certain ERP and qEEG abnormalities and impaired functioning on complex cognitive tests in patients formerly dependent on cocaine might be not proximately caused by drug use per se but be more related to comorbid alcohol use or other psychiatric condition. Taken together, the findings converge on the conclusion that there exists an inherited predisposition for an externalizing psychopathology that includes ADHD, conduct disorder, and substance abuse. PTSD seems to heighten the risk for addiction as well. Thus, the reviewed findings support the hypothesis that addicted subjects may manifest a P300 amplitude reduction and qEEG abnormalities as a trait reflecting the central nervous system disinhibition, which may be a predisposing factor for addiction liability, resistance to drug habit extinction, and relapse vulnerability.

NEUROCOGNITIVE MODEL OF BEHAVIORAL IMPAIRMENTS IN COMORBID PSUD-PTSD

Attentional Bias to Drug Cues in Addiction

The experience of emotions by psychostimulant substance abusers is distorted as a result of dysfunctions of the cerebral mechanisms involved in the motivational and emotional processes (Goldstein & Volkow, 2002; Volkow, Fowler, & Wang, 2003,2004). Individuals with PSUD 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; Gerra et al., 2003). 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 (Lubman et al., 2000; Robbins & Ehrman, 2004). In drug addicted individuals, a set of drug-related perceptual representations is tagged as highly salient and is repeatedly selected for processing. Attentional bias toward processing of salient stimuli is hypothesized to be an implicit cognitive process which 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 (Franken et al., 1999; Johnson et al., 1998; Lubman et al., 2000). Drug abuse-related after-effects 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 et al., 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.

Attentional Bias to Threat/Fear In PTSD

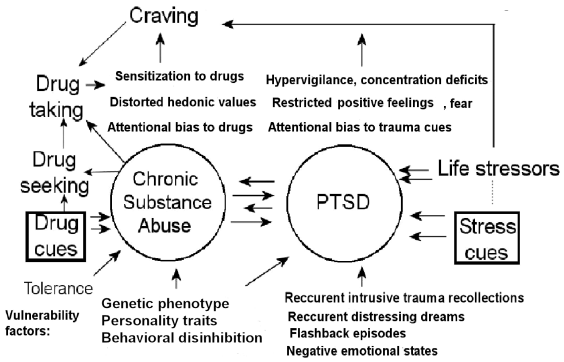
There is converging evidence that implicit automatic processes are also involved in the fear processing (Mogg & Bradley, 1998). Neuroimaging studies showed that medial prefrontal cortical areas modulate fear responding through inhibitory connections with the amygdala (Davidson, 2002; Devinsky, Morrell, & Vogt, 1995). It was hypothesized that dysfunction of the interaction of prefrontal and limbic structures plays a role in failure of extinction to fear in PTSD (Bremner et al., 1996, 2004; Cohen et al., 2000). 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 ACC over the amygdala (Charney et al., 1993; Gilboa et al., 2004; Rauch et al., 1996). These PFC deficits may further enhance the effects of the amygdala, thereby increasing the frequency and intensity of PTSD symptoms (Bremner et al., 1996; Elzinga & Bremner, 2002).

Relationships Between Emotions, Craving, and Cognition in dual Diagnosis

High rates of comorbidity of PTSD and PSUD suggest that these disorders might be functionally related to one another (Jacobsen et al., 2001). Relationship between emotional (e.g., fear), motivational (e.g., craving), and cognitive (e.g., attentional bias) processes in the dual diagnosis is complex and requires specific approaches to reveal casual relations. Possible functional relationships of substance abuse and PTSD are presented on Figure 1.

Since the medial PFC is involved in inhibition of amygdala function, it is reasonable to suggest that the PFC functional over-activation after drug intake may result in a reduction of subjective fear. Therefore, if we consider a self-medication theory of drug use in PTSD, the potential mechanism mediating reinforcing effects of drugs is a decreased fear responsiveness, which may at a certain degree relieve PTSD symptoms in dually diagnosed subjects. With the escalation of drug use due to the development of tolerance, however, according to the opponent-process theory (Koob, 1999; Koob &

FIGURE 1. Model of possible functional relationships of chronic drug abuse and PTSD.



Le Moal, 2001), occurs a spiraling cycle of progressive dysregulation of brain reward systems. Compulsive consumption of drugs further distorts emotional regulation and results in an affective lability. This may lead to a rebound in fear-associated affect and negative moods, and further aggravate PTSD symptoms. Negative emotions typical for PTSD and decreased stress coping capacity may augment craving and promote drug-seeking and relapse behaviors (Goeders, 2003; Koob, 1999; Sinha, Catapano, & O'Malley, 1999). In dually diagnosed individuals, an enhanced reactivity to both traumatic and drug cues may represent a combined conditioned and unconditioned response which increases vulnerability for further progression of drug use.

Role of Frontal Inhibition Deficit

Functional abnormalities of cocaine-dependent patients vs. controls have been observed in the OFC, insula, ACC, basal ganglia, and limbic-related regions (Volkow, Fowler, & Wang, 2003, 2004). Another major target for drugs of abuse is the striatum, a subcortical brain region important for the habit formation and storing of fixed behavioral patterns (Koob & Le Moal, 2001). The neural structural deficits within prefrontal and limbic structures contribute to the deficits in behavioral inhibition which are the characteristics of chronic cocaine users (Kaufman et al., 2003). The PFC might be a necessary, but not sufficient component of inhibition, since the interaction between the PFC and basal ganglia, motor cortex, and memory-related parietal and temporal lobe, seem to be also engaged in implementing inhibition (Aron, Robbins, & Poldrack, 2004). 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 and pathological craving to drive behavior. Individuals predisposed to behavioral disinhibition and externalized psychopathologies 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 (Goeders, 2003; Koob, 1999; Sinha, Catapano, & O'Malley, 1999). Therefore, addictive behavior leads to functional abnormalities resulting in: (1) an imbalance in reward values due to hyper-sensitization to drug-stimuli and drug-associated motivation at the expense of a natural reinforcement, (2) impaired ability to suppress overlearned habitual drug-seeking and drug-taking behaviors; (3) fluctuations in cognitive and affective functional capacities (lability) that are dependent on the drug-dependence stage (occasional use, chronic dependence, withdrawal, protracted abstinence [Koob & Le Moal, 2001]). PTSD is further contributing to the severity of drug dependence through: (1) negative emotional states and distress in response to external and internal cues, (2) further diminishing reward values of natural reward due to affective "numbing," (3) conditioned sensitization to general threatening and specific trauma-related cues.

COGNITIVE AND BEHAVIORAL TREATMENT IN COMORBIDITY OF COCAINE ABUSE WITH PTSD

General Cognitive-Behavioral Treatment Strategy for Drug Addiction Treatment

Because of its chronic nature, long-term treatment for psychostimulant drug addiction is usually necessary (Crits-Christoph et al., 1997, 1999). Effective agonist and antagonist pharmacotherapies as well as symptomatic treatments exist for opioid dependence, but neither

agonists nor antagonists have been approved as uniquely effective for treatment of stimulant abuse or dependence (Grabowski et al., 2004). Currently, no proven effective pharmacological interventions are available for cocaine addiction or for methamphetamine addiction, and treatment has to rely on existing cognitive-behavioral therapies, or CBT combined with other biobehavioral approaches (Van den Brink & van Ree, 2003). According to Volkow, Fowler, and Wang (2004) successful strategies for behavioral treatment in psychostimulant addiction may include (1) interventions aimed to decrease the reward value of the drug and simultaneously increase values of natural reinforcement; (2) approaches aimed to change stereotype conditioned drug-seeking behaviors; and (3) methods to train and strengthen frontal inhibitory control. Since stressful events can result in relapse to drug taking behavior (Koob & Le Moal, 2001), an adjunct treatment strategy is to interfere with the neurobiological responses to stress (Goeders, 2003; Koob, 1999). Stress reduction therapies may offer a potential behavioral intervention for prevention of relapse in addiction co-occurring with PTSD. Treatment of comorbid mental condition may also require the concurrent treatment of drug addiction. In some cases, however, comorbid drug addiction may result from attempts to alleviate the psychiatric disorder through self-medication (i.e., co-occurring cocaine use and ADHD and/or heroin addiction co-occurring with PTSD). In other cases, severity of a psychiatric disorder symptom may increase as a result of drug abuse (Volkow, Fowler, & Wang, 2004).

In patients with drug abuse arising from an attempt to self-medicate (Khantzian, 1985, 1997), treatment of the comorbid mental disorder may prevent abuse. For instance, treatment of the preexisting condition of ADHD may prevent cocaine abuse (Biederman et al., 1995, 1997). Although in some cases the persistent qEEG abnormalities associated with chronic PSUD may happened to be independent from ADHD clinical status (Trudeau, Thuras, & Stockley, 1999). The co-occurrence of ADHD and PSUD has received considerable attention in recent clinical and scientific literature (Davids et al., 2005). These two disorders are often linked to one another, and since the core symptoms of ADHD may be mimicked by the effects of psychoactive drugs it is difficult to diagnose one disorder in the presence of the other (Davids et al., 2005). ADHD has been found to be associated with an earlier onset of PSUD (Horner & Scheibe, 1997). It is generally assumed that untreated ADHD is a risk factor for PSUD development (Biederman et al., 1998; Manuzza et al., 1998; Trudeau, 2005b).

In a case of comorbidity in which the use of drugs antecedes mental disease (e.g., substance-induced anxiety disorder, DSM-IV, APA, 1994) or is not driven by self-medication strategies, the simultaneous treatment of both psychiatric conditions may be required. There could be proposed following approach concepts: (1) Behavioral interventions to activate and strengthen circuits involved in inhibitory control, such as biobehavioral self-regulation training, may increase successful abstinence from drug taking; (2) Considering the important role of cognitive and emotional processes involved in the predisposition for drug abuse, the development of non-pharmacological interventions (e.g., cognitive behavioral therapy, stress management, neurofeedback) is a feasible strategy. We believe that understanding of the interactions between stress, affect, and drug dependence may help develop behavioral interventions to counteract deleterious effects of traumatic stress on the brain that in turn facilitates drug abuse and chronic addiction in dual diagnosis.

Cognitive-Behavioral Therapy for Comorbid Addiction and PTSD

While substance abuse and PTSD are known to frequently co-occur (Breslau et al., 1991; Clark et al., 2001), there have been few published clinical trials evaluating integrated treatment approaches for this form of dual diagnosis (Crits-Christoph et al., 1997, 1999). Various kinds of cognitive behavioral therapy (CBT) for PTSD have been described and proven effective (reviewed in Ehlers et al., 2005; Evans & Sullivan, 1995; Foa et al., 1991). Effective treatments for PTSD includes different forms of CBT (Ehlers et al., 2005), eye movement desensitization and reprocessing (EMDR) (Bradley et al., 2005), imagery rehearsal therapy (Krakow et al., 2001) and various pharmacological therapies (Albucher & Liberzon,

2002), sometimes in combination with CBT (Ballenger, 2004). Trauma-focused CBT, such as exposure and desensitization, uniformly report large treatment effects and are thought to be superior to therapies that do not focus on trauma content (Ehlers et al., 2005; Foa et al., 1999; Resick et al., 2002). However, trauma-focused CBT has its limitations, such as treatment non-engagement and withdrawal rates of approximately 15% to 25% (Resick et al, 2002). Furthermore, more people who become worse with psychotherapy have received exposure therapy (Tarrier et al., 1999), and a large percentage of people with PTSD may prefer not to engage in trauma-focused therapy in clinical practice (Scott & Stradling, 1997). Interventions that minimize exposure to trauma content such as imagery rehearsal therapy and stress management have also been shown to be efficacious for chronic nightmares and PTSD symptoms (Foa et al., 1999; Krakow et al., 2001).

In a psychosocial treatment study (Najavits et al., 1998), significant decreases in PTSD and addiction symptoms were reported among treatment completers in a pilot trial of a group therapy for women with addictions and PTSD. Abueg and Fairbank (1992) developed a 1- to 2-year, phased-treatment approach for male Vietnam veterans. Following detoxification and initial stabilization, a brief period of psychoeducation was followed by direct therapeutic exposure for PTSD, cue exposure, self-control training for addiction, and relapse prevention for both substance abuse and PTSD. Triffleman, Carroll, and Kellogg (1999) described an outpatient CBT and controlled clinical trials of patients with PTSD and heroin or cocaine dependence. Back et al. (2001) described a CBT developed specifically for individuals with PTSD and cocaine dependence. Treatment completers in the outpatient study based on this exposure therapy demonstrated reductions in all PTSD symptoms and cocaine use (Brady et al., 2001). Although the dropout rate was high in this study, treatment completers demonstrated significant reductions in all PTSD symptom clusters and cocaine use from baseline to end of treatment. Comorbid PTSD not only affects clinical presentation but also exerts substantial influence on outcome and leads to higher risk of relapse (Brady, 1997; Brown, Recupero, & Stout, 1995; Najavits et al., 1998; Ouimette et al., 1997; Ouimette, Finney, & Moos, 1999). In spite of these issues, systematic development and study of treatment for comorbid substance use disorder-PTSD population has been largely neglected.

Biobehavioral Treatment in Addiction: Neurofeedback Methods

Neurofeedback uses real-time EEG technology to measure electrical activity of the brain. The information is presented in a form that enables the individual to visualize changes in the state of the brain. By learning to modify abnormal EEG patterns through the use of neurofeedback (NFB) technology, the patient is trained to overcome its abnormalities. Neurofeedback can be considered as a form of operant conditioning (Vernon et al., 2003). There have been an increasing number of neurofeedback protocols that report success in treating a variety of disorders such as addictive behaviors and PTSD among others. Detailed review and historical perspectives of neurofeedback application for addictive disorders treatment in adolescents and adults can be found in Trudeau (2000, 2005ab).

Clinical EEG biofeedback training for alcohol and drug addiction suggested by Peniston and Kulkosky (1989) has renewed interest in so-called "alpha training," and has actually revived the very technique that already once passed through the stages of especial popularity (Nowlis & Kamiya, 1970) followed by criticism (Plotkin, 1976) and years of oblivion. The second "advent of alpha training" was not smooth either, despite the expectancies and special interest to this method expressed by biofeedback professional community.

The training for drug abuse treatment used by Peniston and Kulkosky was called "alpha-theta" training or Brain-Wave Training (BWT) protocol (Peniston & Kulkosky, 1989, 1990, 1991; Peniston et al., 1993). BWT protocol represents a modification based on the "alpha-theta training" protocol developed earlier for PSUD treatment (Goslinga, 1975, Green, Green, & Walters,1974; Twemlow & Bowen, 1976, 1977). The rationale to use slow wave enhancement training was based on the observation that many alcoholics are deficient in alpha

and theta activity. The BWT protocol for alcoholism is a self-regulation procedure, when after initial temperature feedback sessions, patient are trained first to increase the amount of alpha activity, and then to increase theta at the occipital scalp areas. The person progresses into a relaxed "theta" state. While in the relaxed, hypnogogic "theta" state the patient is asked to do visualizations picturing abstinence and refusal to drugs. In many patients with PTSD conditions this state facilitates the re-experiencing of traumatic memories in a setting that allows them finally to be processed and remembered in normal ways. Following the session, in BWT protocol a therapy was conducted where imagery contents were discussed and subjective experiences explored. Peniston and Kulkosky (1989, 1990, 1991) did their first study with a group of VA alcoholics. Initial research using the BWT protocol has demonstrated increased power of alpha and theta rhythms, decreases in depression and anxiety rating scores, lower relapse rates, and positive changes in personality. A subsequent study (Saxby & Peniston, 1995) reported similar results.

Though Peniston's study was seriously criticized by reviewers (e.g., Graap et al., 1997; Graap & Friedes, 1998; Lowe, 1999; Taub & Rosenfeld, 1994; Trudeau, 2000) for certain methodological issues, it still has served important role by stimulating further attempts on application of neurofeedback in addictive disorders. Several other studies using the BWT protocol and its modifications reported cases with positive clinical effects (DeBeus et al., 2002; Burkett et al., 2005; Fahrion et al., 1992; Fahrion, 2002; Finkelberg et al., 1996; Kelley, 1997; Skok et al., 1997). These studies indicate that applied psychophysiological approach is a valuable alternative to substance abuse treatment (Walters, 1998). Nevertheless, only few of these studies were published in mainstream peer-reviewed journals. There still exists the possibility that effects of Peniston's alpha-theta BWT for addiction were non-specific, and that positive results might due to intensive accompanying therapy rather than neurofeedback itself. Comorbidity (and specifically PTSD) issues in Peniston's studies were not sufficiently addressed and explored (Graap & Friedes, 1998), and that fact was actually acknowledged by Peniston (1998) in his response to this criticism. More controlled studies of neurofeedback effects on addictive disorders and PTSD are needed.

Cocaine-dependent persons are cortically under-aroused during protracted abstinence (Roemer et al., 1995). QEEG changes, such as decrease in high beta (18-26 Hz) power are typical for withdrawal from cocaine (Noldy et al., 1994). Cocaine abusers who are still taking drug often show low amounts of delta and excess amount of alpha and beta activity (Alper, 1999; Prichep et al., 1999), whereas chronic methamphetamine abusers usually exhibit excessive delta and theta activity. Thus cocaine and methamphetamine users may need a different EEG biofeedback protocol, at least at the beginning stages of neurofeedback therapy. In such cases protocol aims on increasing brain rhythms called "SMR" (12-15 Hz) (Sterman, 1996) and/or "low beta" (14-18 Hz) that characterize focus and concentration, and is commonly used in the treatment of ADHD (Lubar, 1995; Monastra et al., 2005). Protocols similar to those in ADHD treatment, sometimes combined with the Peniston's BWT, were successfully used in cocaine and other stimulant abuse treatment studies (Burkett et al., 2003, 2005; Scott et al., 2002; Scott & Kaiser, 1998).

Treatment of patients with psychoactive substance abuse disorder using neurofeedback may become more complicated when patients present various psychiatric conditions. When addiction is comorbid with ADHD it is suggested that SMR (or beta increase, theta decrease) training should be conducted to address ADHD disorder-related first (Biederman et al., 1997). After completing the SMR training, alpha-theta training is done to treat addiction. Applicability of neurofeedback methods to treat anxiety and affective disorders is reviewed by Hammond (2005). There are only few case studies on efficacy of neurofeedback in generalized anxiety disorder (Rice, Blanchard & Purcell, 1993; Vanathy, Sharma, & Kumar, 1998). We are not aware of any systematized studies of neurotherapy treatment effects in PTSD. More research needs to be done to determine the clinical outcome and efficacy of biobehavioral treatment based on brain wave self-regulation in addiction commorbidity with anxiety disorders, and first of all PTSD. We

propose that most effective approach in cocaine addiction co-occurring with PTSD is to use both SMR (at initial stages) and alpha-theta (at later stages) protocols of neurofeedback training.

How ADHD Neurofeedback Studies May Enrich Addiction Treatment Programs

Neurofeedback is becoming more commonly accepted as a non-pharmacological treatment alternative in individuals with ADHD (Butnik, 2005). Comprehensive reviews by Lubar (2003), Monastra (2003), Fox, Tharp, and Fox (2005), and Monastra et al. (2005) describe numerous case studies showing clinical benefits of neurofeedback-based therapy in ADHD (Kaiser & Othmer, 2000; Lubar & Lubar, 1984; Lubar, 1995; Thompson & Thompson, 1998). Recently several controlled-group studies have been published on clinical and neurocognitive outcomes of neurofeedback in ADHD treatment (Carmody et al., 2001; Fuchs et al., 2003; Kropotov et al., 2005; Levesque, Beauregard, & Mensour, 2006; Linden, Habib, & Radojevic, 1996; Monastra, Monastra, & George, 2002; Rossiter & La Vaque, 1995). Monastra et al. (2005) in their critical review examined the empirical evidence, applying the efficacy guidelines established by the AAPB and the ISNR (Moss & Gunkelman, 2002), and concluded that according to these principles of efficacy neurofeedback can be determined to be "probably efficacious" for the treatment of ADHD. It is very important to apply the efficacy guidelines to treatment of addictive disorders as well. Another strong side of neurofeedback developments in ADHD area is that research in ADHD area heavily relies on quantitative EEG data to determine appropriate protocol for neurotherapy (Monastra, Lubar, & Linden, 2001; Sterman, 1996).

There are several very important applications of the neurofeedback protocols typically used for ADHD treatment for the purposes of enhancement of cognitive performance in healthy subjects (reviewed in Vernon, 2005). This very promising new line of neurofeedback-based cognitive neuroscience research (Barnea, Rassis, & Zaidel, 2005; Egner & Gruzelier, 2001, 2003, 2004ab; Egner, Zech, & Gruzelier, 2004; Vernon et al., 2003) has significant potential to elucidate neurobiological mechanisms explaining how neurofeedback training may alter and enhance cognition and behavioral performance.

DUAL DIAGNOSIS TREATMENT PROJECT AT THE UNIVERSITY OF LOUISVILLE

Overview of the ULHSC Dual Diagnosis Treatment Project

The study underway at the University of Louisville Health Science Center is aimed to provide a new insight into the neurobiological effects of stimulant drug abuse and PTSD on both emotional reactivity and cognitive functions. This study will also pursue the novel hypotheses posed to explain why presence of PTSD exerts adverse effects on psychostimulant addiction treatment outcome. This study will assess relative efficacy of treatments of cocaine- or amphetamine abusing or dependent patients with comorbid PTSD with: (a) Cognitive-Behavioral Therapy (CBT) for PTSD followed by CBT for addiction, (b) CBT with adjunct neurofeedback, (c) 12-step based residential programs over a 12-week period, (d) 12-step based residential program with adjunct 12-week neurofeedback course. We will measure behavioral performance, ERP, EEG, and autonomic nervous system (ANS) activity (e.g., heart rate [HR], HRV, and skin conductance response [SCR]) in cognitive tasks at baseline, then immediately after 12-week-long treatment, and in post-treatment 12-week follow-up.

Understanding the cognitive and emotional factors that impact drug abuse treatment in dual diagnosis patients is important for the scientifically sound model of treatment strategies in stimulant addiction co-occurring with anxiety disorders, and in particular in a case of concurrent PTSD which is so common for drug abusers. The long-term objectives of our project are to better characterize brain and psychological mechanisms mediating effects of behavioral treatments, and to use obtained results for the model of intervention intended to develop more effective behavioral drug-dependence treatment arms in dual diagnosis patients based on

integration of cognitive-behavioral (CBT) and neurotherapy (neurofeedback) arms.

An important goal of the project is to evaluate recovery of cognitive functions, emotional- and cue-reactivity as indexed by EEG, ERP and ANS parameters following four behavioral treatment approaches for drug-dependent patients with co-occurring PTSD. Although many of behavioral interventions have been found effective with alcohol and drug addiction, few studies specifically used qEEG, ERP and ANS measures of cognitive performance, and, therefore, the changes in functioning of the neurobiological substrates of cognitive functions in addiction and PTSD were not compared and analyzed across employed behavioral treatments.

The study will evaluate outcome of four types of intervention using a between groups design that randomly assigns cocaine and methamphetamine abusing patients with dual diagnosis (substance use and posttraumatic stress disorders) into treatment conditions (CBT, CBT with neurofeedback, 12-step residential, 12-step program with neurofeedback). This design will permit us to test the efficacy of these behavioral interventions and compare with a long-term residential conventional 12-step based program. We will recruit healthy subjects of matched age and ethnicity in a control group, and subjects with cocaine or methamphetamine dependence without PTSD diagnosis as an addiction control group to establish (1) non-PTSD pathological comparative neurobiology, (2) simple time effects for neurobiological change with repeated tests both in healthy subjects and in addicts. Primary efficacy variables of treatment will include measures of substance abuse (urine and saliva toxicology screens for 6 most common drugs of abuse), retention (number of sessions attended, rate of drop-out), addiction severity, PTSD, anxiety and depression measures. Significant relations between behavioral, ERP, qEEG, and ANS measures and treatment outcomes will be explored.

Several decisions have been made regarding the design and methodology of this study. The following decisions are sufficiently important to be outlined: (a) decision to target cocaine and methamphetamine abusing individuals (as more prevalent PSUD in our pool of patients) with dual diagnosis; (b) decision to include PTSD as a comorbid psychiatric disorder; (c) decision to use Cognitive-Behavioral Therapy for behavioral treatment in PTSD and PSUD; (d) decision to use neurofeedback treatment as adjunct therapy, and in particular the SMR (ADHD protocol) on the early stages of treatment and the alpha-theta brainwave training (Peniston's BWT protocol) on the later stages of intervention.

Testing Hypotheses About Neurobiology of Dual Diagnosis Using Cognitive Neuroscience

Executive Prefrontal Top-Down Control Deficiency in Dual Patients

Our hypothesis (1) is that patients with dual diagnosis (co-occurring cocaine or methamphetamine use and post-traumatic disorders), compared to healthy controls, at the intake stage will show impairments in frontal executive functions; and specifically: (1) deficits in cortical inhibition of motor responses during performance on continuous performance task (Go-NoGo), (2) deficits in inhibition of automatic processes (e.g., semantic vs. task-relevant color processing) in color Stroop task, (3) deficits in correct balance of advantageous vs. disadvantageous decisions in the Iowa gambling task. Disrupted executive functions in our model contribute to the perseveration of compulsive drug-taking behavior in addicts with PTSD.

The study will investigate chronic psychostimulant drug abuse effect on cognitive functions assessed during performance on behavioral tests in PSUD comorbid with PTSD in pre-, post-treatment, and follow-up conditions. We plan to run three different cognitive tasks (Go-NoGo, color word Stroop, and Iowa Gambling) to test executive functions. In particular, we will examine behavioral responses and cognitive ERPs indicative of executive function of response inhibition in "Go-NoGo" and color word Stroop tests. These tasks will investigate processing conflicts on response (e.g., ability to inhibit response to "NoGo" signal), and semantic-lexical (color naming conflict in Stroop) levels as indexed by fronto-central N450 ERP component (indicative of response conflict

processing in the ACC), and different stages of response inhibition indexed by anterior-frontal NoGo-N2 and NoGo-P3 (indicative of prefrontal inhibitory processes). We will examine performance of dual patients on the Iowa Gambling Task (IGT) to assess decision-making deficits and accompanied psychophysiological responses (ERP, EEG, HR and SCR).

By examining inhibitory control in pre- and post-treatment conditions in our treatment groups and no-treatment controls we will be able to answer the questions: (a) whether successful treatment, maintaining abstinence and decreased severity of PTSD symptoms will result in an increased prefrontal' "top-down" executive control functions, and (b) specifically, whether deficient inhibitory functions showed any post-treatment improvement. In the IGT test will address questions: (c) whether impaired decision making will be improved in patients with dual diagnosis following treatment, and (d) how physiological variables indicative of response selection (N200 and N450 components of the frontal ERP) and reward anticipation and delivery (SCR and HR before and after monetary feedback presentation) are affected by the treatment and abstinence.

Though cortical inhibitory functional deficits may recover at certain extent in the patients who maintain abstinence following treatment, specific ERP parameters related to predisposition to behavioral disinhibition can be considered as trait markers are not predicted to significantly improve with treatment. We predict, nevertheless, that the relatively higher success rate of improvement in inhibitory control will be more likely in the group of patients following CBT with adjunct neurofeedback therapy which is aimed to train self-regulation skills.

Emotional Dysfunctions Are Typical for Both Substance Abuse and PTSD

Our hypothesis (2) posits that patients with dual diagnosis will show under-reactivity to visual affective stimuli of both negative and positive emotional valence as indexed by the CNS (qEEG/ERP) and autonomic measures. The second aim of our project is to investigate specificity of psychophysiological patterns of emotional reactivity in drug users with comorbid PTSD in an emotional category judgment task using affective pictures and images of facial emotional expressions as probes. We will examine psychophysiological manifestations of anhedonia, dysphoria and alexithymia, which are predicted to be expressed in an under-reactivity to both emotionally positive and negative visual affective stimuli, and in an affective "numbing" typical for PTSD patients (Felmingham et al., 2002). We will collect as well subjective reports (arousal and valence dimensions of emotional response) to compare with normative values available for the International Affective Pictures System (IAPS) stimulus material (Lang, Bradley, & Cuthbert, 2001) and data from control subjects. The method for the differentiation of emotional responses by accompanying psychophysiological patterns (Sokhadze et al., 2000) will be used to reveal potential role of autonomic regulation dysfunctions in the symptoms observed in dual patients and answer the question (e) why profile of physiological reactivity in affect is lower in the dual diagnosis group. We predict as well an abnormality in the autonomic balance in dual patients, and first of all decreased HRV indicative of low cardiac parasympathetic tonus and high sympathetic tonic activity characteristic for chronic accumulated stress state (Cohen et al., 2000; Thayer & Friedman, 2002). We will specifically examine differences in physiological profiles sensitive to modulations in arousal and valence dimensions of presented stimuli (e.g., HR sensitive to valence, whereas SCR to arousal). We predict that following combined CBT and biobehavioral treatment, and probably CBT alone for PTSD, the patients will show lower level of emotional interference in cognitive tasks (as indexed by behavioral, ERP and ANS measures), though subjective measures of craving and subjective under-rating of affect may persist even with successful clinical outcome.

Over-Reactivity to Both Drug- and Trauma-Related Cues and Sensitization to These Cues Are Important Components of Abnormal Drug-Seeking Behavior in Dual Diagnosis

Our hypothesis (3) is that patients with addiction co-occurring with PTSD have en-

hanced reactivity to both drug- and traumatic stress related cues and have higher interference effects on tasks due to preferential processing of task-irrelevant drug- and trauma distracters, and consequently lowered resources availability for the processing of task-relevant target signals.

Another aim of our project is to specifically examine cue reactivity to drug-related and trauma-associated stimuli, and its interference with cognitive functions during performance on a behavioral task (three-stimuli oddball with emotional context). For this aim we will run a session with two modifications of cue reactivity test. In tasks we will use three-condition oddball task with novel distracters being either a drug cue or a traumatic cue (verbal and pictorial). We will examine as well drug/trauma cues interference on behavioral (reaction time [RT]) and cognitive ERP (N2b, P3a, P3b) indices. Therefore, using drug- and traumatic cues as interference we will address questions: (f) how both categories of cues may affect behavior of dual patients judging by the ERP indices, and (g) whether there are identifiable ERP similarities or topographic differences in emotional-cognitive interferences in these two types of distracters (verbal vs. pictorial). We propose that cognitive performance impairments will correlate with the dysfunction of neural systems indexed by the frontal ERP measures (e.g., P3a) and can be used as psychophysiological markers. Therefore, if we will observe improved performance post-treatment, then decrease of emotional interference on cognitive tasks (RT, ERP indices such as N2b,P3b) following successful treatment can be considered as a lowered sensitization to drug and trauma cues and serve as a state marker. On the other hand, persistence of interference (as indicated by behavioral and ERP measures) will point to possibility of a trait-like character of impairments. Thus, negative dynamics of recovery of certain ERP parameters following behavioral treatment in substance abuse and post-traumatic stress disorders can be predictive of vulnerability to relapse and poor recovery of cognitive functions.

Behavioral Intervention: Cognitive and Bio-Behavioral Self-Regulation Skills as Moderators of Clinical, Cognitive, and Psychophysiological Outcomes

We propose in our hypothesis (4) that both the CBT alone and CBT combined with neurofeedback therapies will be comparable by post-treatment clinical, cognitive and psychophysiological outcomes with more traditional behavioral intervention such as 12-step residential program. We predict that application of neurofeedback training course as an adjunct therapy in a residential program setting will result in more positive clinical outcome that standard 12-step residential program alone. One more aim of our project is to determine presence of the cognitive and affective impairments on the same battery of cognitive and affective tasks after four types of 12-week long behavioral treatments (peer-mentored 12-step facilitation residential program, 12-step program with adjunct neurotherapy course, cognitive-behavioral therapy, and cognitive-behavioral therapy combined with neurofeedback), and follow-up (12 weeks). Since one of the main objectives of our project is to elucidate potential neurocognitive mechanisms involved in the moderation of behavioral intervention effects in dual diagnosis patients to find better ways of intervention, we will assess treatment outcome using cocaine, methamphetamine and other drug (opiates, marijuana, etc.) use rate (including both saliva analysis and urinalysis), maintaining treatment retention rate, psychiatric status (including PTSD symptoms), cocaine abuse-specific psychosocial (Michalec et al., 1996; Weissman & Bothwell, 1976) and craving (Tiffany et al., 1993) questionnaires, behavioral and cognitive performance indices, and pattern of physiological measures (e.g., qEEG, ERP, and ANS profiles). By assessing both cognitive and affective responses we should be able to draw stronger conclusions about central and peripheral mechanisms underlying adverse effects on emotional reactivity and cognitive functions in population with comorbid stimulant substance use disorder and PTSD and reveal moderators in successful treatment outcomes. Regardless efficiency of the clinical outcome in this hard-to-treat population, we believe that the combination of ERP, qEEG, and

ANS and a battery of cognitive functional testing methods will provide opportunity to analyze brain activity in relationship to observed performance in cognitive tasks to evaluate cognitive deficits at baseline and during drug withdrawal, and assess extent of their functional recovery with the progress of treatment and abstinence from drugs.

CONCLUSIONS

Comorbid psychoactive substance use disorders with PTSD is associated with poorer treatment outcomes, theoretically due to shared synergistic neurobiology. Nevertheless, there is no standard treatment for this comorbidity, nor are there neurocognitive assessments for treatment outcomes. We propose to employ dense-array cognitive ERP, qEEG and autonomic nervous system (ANS) measures to assess the affective and cognitive neurobiology of dually diagnosed cocaine or amphetamine abuse/dependence and PTSD patients. Furthermore, repeated cognitive tests will allow serial evaluation of behavioral treatment and of residual cognitive and affective components in PSUD-PTSD patients. Pre- post-treatment testing of cognitive and affective neurobiology will provide sensitive functional measures to determine what central and autonomic nervous system pathology is reversible with successful treatment, and if there is differential success, both in terms of clinical nd neurobiological outcome between groups undergoing cognitive-behavioral therapy (CBT), and combined CBT and neurofeedback-based treatment courses.

Drugs of abuse can impair cognitive processes, affective responses, and behavior. More basic research is needed to characterize the chronic and residual effects of drugs on attention, emotion, memory, judgment, and overall behavioral performance. Cognitive neuroscience research has the potential to identify neurobiological mechanisms that underlie the cognitive antecedents of drug abuse, and to investigate the ways how acute or chronic stress exerts its adverse effects on drug addiction treatment course.

Demonstration of the reliability and validity of cognitive neuroscience techniques (e.g., executive function tests [Stroop, Go-NoGo, Iowa gambling], cue reactivity, attentional and emotional biases to drug and trauma cues) are needed to foster progress in the integration of these psychophysiological measures as indicators of substance abuse and PTSD treatment outcomes. More research is needed to examine consistency of the functional measures of cognition and affect within dual patients over time. More research is needed also to relate cognitive functionality measures to clinical outcome (e.g., relapse rate, saliva and urine screens, PTSD cluster symptoms, psychiatric status, etc.). Such research may facilitate the translation of basic cognitive neuroscience research data into clinical tools for assessment of functional recovery both in addiction and anxiety disorders treatment clinics. We believe that some of above described cognitive tests at the pre-treatment baseline might be useful as predictors of clinical outcome and/or severity of co-occurring PSUD-PTSD. On the other hand, demonstration of improvement in the cognitive tests (e.g., reduction of emotional and attentional interferences to drug and trauma-related cues) might be related to demonstrated clinical improvement following CBT and combined CBT and neurofeedback treatments. Incorporation of cognitive testing measures into cognitive, behavioral and neurofeedback based interventions may have significant potential for identification whether such cognitive neuroscience measures can be used as psychophysiological markers of treatment progress, and also may provide useful information in planning cognitive-behavioral and neurotherapy treatment in substance abuse comorbid with posttraumatic stress disorder

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