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Identification and Modulation of Electrophysiological Markers of Reward Sensitivity, Relevance to Drug Addiction

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Abstract of the Dissertation

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Drug addiction is primarily a disease of the brain's reward system. The resulting compromise in reward sensitivity traces its roots to the striatal "reward circuitry", where excess dopamine is released by the acute administration of the drug of abuse; chronic use is in turn associated with a hypodopaminergic state. In individuals with cocaine use disorder (CUD), these maladaptive changes in striatal dopamine are shown to be predictive of the choice for cocaine over other non-drug rewards. This deficit in reward sensitivity may therefore be bi-pronged, such that CUD manifest hyposensitivity to non-drug-related rewards (e.g. money) as well as hypersensitivity to drug-related rewards, as associated with cue-induced craving.

This thesis aims to study the electrocortical markers of reward sensitivity in healthy controls and compare them to CUD to highlight the electrophysiological manifestations of this dichotomous impairment in reward sensitivity, using electroencephalogram (EEG) and event-related potentials (ERP). Moreover, using multimodal neuroimaging techniques, their underlying neuroanatomical correlates are also explored. Finally, a proof-of-concept study is presented to show that the EEG/ERP markers associated with motivated attention (i.e. drug seeking) can be modulated using cognitive control.

These findings establish the ground work for potential interventional and therapeutic use of EEG/ERP methods to reinforce cognitive control over craving and other drug-seeking behavior in CUD. Instead of using positron emission tomography (PET) or functional magnetic resonance imaging (both modalities are costly and location/facility specific; PET adds the additional cost of subjecting research participants to radiation), we demonstrate the use of non-invasive, portable, substantially less expensive and high temporal resolution EEG and ERP methods to track (and possibly correct) deficits in reward sensitivity in drug addiction.

Dedication Page

This endeavor is dedicated to my family. To my parents, my wife, daughter, sisters and all other family members, who supported me every step of the way.

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List of Abbreviations

- **BCI:** Brain Computer Interface
- **CUD:** Individuals with cocaine use disorder
- **EEG:** Electroencephalography
- **ERD:** Event-related desynchronization
- **ERP:** Event-Related Potential
- **LPP:** Late Positive Potential
- **SPM:** Statistical Parametric Mapping
- **VBM:** Voxel-Based Morphometry

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I would first like to thank Allah (SWT) for enabling me to write this dissertation and defend it. I would not have been able to come this far without the continued support and prayers of my family and friends. This dissertation could not have been written without Dr. Rita Goldstein who not only served as my advisor but also encouraged and challenged me throughout my academic program. She and Dr. Thomas Maloney, guided me through the dissertation process, never accepting less than my best efforts. I thank them all.

Publications

PEER-REVIEWED PUBLICATIONS

1. **Motivated Attention to Cocaine and Emotional Cues in Abstinent and Current Cocaine Users: An ERP Study**
   Dunning JP, **Parvaz MA**, Hajcak G, Maloney T, Alia-Klein A, Woicik PA, Telang F, Wang G-J, Volkow ND, Goldstein RZ. *European Journal of Neuroscience.* 2011. Mar 31 *(in press)*

2. **Gene by disease interaction on Orbitofrontal Gray Matter in Cocaine Addiction**.
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3. **Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour.**
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4. **Enhanced Choice for Viewing Cocaine Pictures in Cocaine Addiction.**
   Moeller SJ, Maloney T, **Parvaz MA**, Dunning JP, Alia-Klein N, Woicik PA, Hajcak G, Telang F, Wang GJ, Volkow ND, Goldstein RZ. *Biological Psychiatry*. 2009 Jul 15:66(2):169-76

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   Dunning JP, Hajcak G, **Parvaz MA**, Maloney T, Alia-Klein A, Woicik PA, Telang F, Wang G-J, Volkow ND, Goldstein RZ. *Psychophysiology.* 2008 45: S53-S53

6. **Compromised sensitivity to monetary reward in current cocaine users: an ERP study.**
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8. **Time course of processes underlying picture and word evaluation: an event-related potential approach.**
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MANUSCRIPTS IN PREPARATION OR SUBMITTED

1. **Structural integrity of prefrontal cortex mediates electrocortical sensitivity of reward.**
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2. **Sensitivity to monetary reward is most severely compromised in recently abstaining cocaine addicted individuals: An ERP study**

Parvaz MA, Maloney T, Moeller SJ, Woicik PA, Alia-Klein N, Telang F, Wang G-J, Squires NK, Volkow ND, Goldstein RZ. (*Submitted to Biological Psychology*)

3. **Event-related potentials in the prediction of choice: relevance to insight.**
   Moeller SJ, Hajcak G, **Parvaz MA**, Dunning JP, Volkow ND, Goldstein RZ. (*Submitted to PNAS.*)

4. **Electrophysiological Correlates of Frontal Activation during Emotion Reappraisal**
   Parvaz MA, Hajcak G, MacNamara A, Goldstein RZ. (*In preparation*)

5. **Processing of monetary reward in addiction: evidence for an aberrant reward circuitry.**
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CHAPTER 1

RATIONALE

Drug addiction is a chronically relapsing disease characterized by repeated periods of drug intoxication, mediteraninan craving, bingeing and withdrawal; multiple attempts by the addicted individual to stop or curtail drug use are unsuccessful. Substance abuse is endemic nationwide: results from the 2009 National Survey on Drug Use and Health[1] showed that 21.9 million persons aged 12 or older were classified as currently (past year) substance dependent and/or abusers. After alcohol and marijuana, cocaine is the drug most frequently associated with treatment for substance abuse problems (787,000 persons received treatment for cocaine use during their most recent treatment). These statistics become all the more alarming considering the associated morbidity and mortality rates. For example, cocaine is one of the substances most frequently associated with drug-abuse-or-misuse deaths: based on the 2009 Drug Abuse Warning Network report, among illicit drugs cocaine was responsible for the most emergency room admissions (137.7 per 100,000; among adults 21 or older: 181.6 per 100,000). In 2009, 23.5 million people needed treatment for an illicit drug or alcohol, of which only 2.6 million received treatment at a specialty facility. Thus, 20.9 million people, who needed treatment, did not receive it. However, of those 20.9 million people, only 1.1 million reported they felt they needed treatment for their illicit drug or alcohol use problem.

Drug addiction is defined by compulsive drug-seeking and drug-taking, with a loss of control over drug use manifesting an uncontrolled motivated behavior towards abused drugs and drug-related cues. In cognitive neuroscience, such behavior is often explained by attraction to external stimuli that have appetitive or rewarding properties. However, in the absence of immediate goals, an animal usually must use past experiences to predict the likelihood of such occurrence. This learning may either involve classically conditioned reflexes or goal-directed behaviors or both. With the latter behaviors, an outcome that increases the occurrence of a preceding behavior is a positive reinforcer or reward. Incentive, on the other hand, generally refers to the attractiveness of a goal, and positive reinforcement strengthens specific responses by presenting stimuli contingent on performance. For example, rats can learn arbitrary instrumental actions, such as a lever press, to gain access to positive reinforcers, such as food or drugs (also known as self-administration behavior), or to stimuli associated with these primary reinforcers.

The complexity of motivated behavior, from selection of voluntary actions based on past experiences to reflexive control of consummatory behavior, involves coordination of several levels of neural control, the hub of which consists of the mesolimbic and mesocortical dopamine (DA) fibers, which originate in the ventral tegmental area and terminate in the ventral striatum [VStr; encompassing the nucleus accumbens (NAcc)], ventral pallidum, amygdala, hippocampus and prefrontal cortex (PFC). Natural reinforcers induce DA increases in this system within the physiological range that habituate with repeated consumption or decrease with satiety [2-5].

Neuroimaging studies have also reported the ability of drugs of abuse to increase DA concentration in these brain regions, which is crucial for their reinforcing effects[6-7]. Animal and human studies show that drugs of abuse exert their reinforcing and addictive effects either by directly triggering supra-physiological DA action that does not habituate[8] or indirectly, by modulating other neurotransmitters (e.g., glutamate, Gamma Aminobutyric Acid, endogenous opioids, acetylcholine, cannabinoids and serotonin) in the brain's reward circuit. With chronic use, DA receptor availability is reduced[9-12], altering functions in dopaminergically innervated corticolimbic areas [encompassing the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)] that mediate processing of reward salience, motivation and inhibitory control[13-14]. The Impaired Response Inhibition and Salience Attribution (I-RISA) model[15] of drug addiction posits increases in the value attributed to the drug of choice occurs with a concomitant decrease in the value attributed to other nondrug reinforcers by drug addicted individuals. The resulting disproportionate attribution of salience to potential drug-related rewards enhances the motivation to procure drugs, but at the expense of the salience of non drug-related goals- producing a concomitant decrease in the ability to self-control.

An allostatic hypothesis, regarding the hyposensitivity to non-drug reward in drug addiction posits that the brain reward thresholds become chronically elevated as a result of repeated drug use and do not return to baseline levels with abstinence[16]. Similarly, the Reward Deficiency Syndrome hypothesis[17] posits that individuals prone to addiction have a deficit in recruiting DA motivational circuitry by non-drug rewards, such that abused drugs become uniquely able to normalize DA levels in the VStr (including NAcc) to readily motivate drug-taking behavior[17]. In parallel, the hypersensitivity to drug-reward in addiction highlighted by the Incentive-Sensitization theory[18-19] of addiction which posits that drug cues trigger excessive incentive motivation for drugs, leading to compulsive drug seeking, drug taking, and relapse. The central finding supporting these models is that addictive drugs alter NAcc related brain systems, dysregulating attribution of incentive

salience. This maladaptation results in neural circuits becoming hypersensitive to drugs effects and to drug-associated stimuli, which leads to excessive attribution of incentive salience to drug-related stimuli, causing pathological drug-seeking[19]. In laboratory animals, presentation of cues associated with prior cocaine delivery increases DA levels in the NAcc and the amygdala (the hub of affective appraisal and memory[20]), and, more importantly, increase drug-seeking behavior[21]. In humans, functional neuroimaging studies show that cocaine related cues are associated with increased activity in the basolateral amygdala, the ACC (involved in cognitive control and decision making[22-23]) and the OFC (involved in salience attribution and in conditioned responses[24-25])[26]. Thus, one mechanism by which environmental cues may trigger drug seeking involves projections from limbic cortical structures to subcortical regions including the NAcc.

Another hallmark of chronic drug use is impairment of inhibitory control. Frontal cortical structures known to mediate decision making and inhibitory control include the PFC, OFC, and ACC, which are closely linked with the NAcc, amygdala, and the ventral tegmental area, and also appear to be affected by chronic cocaine exposure[27]. Drug-altered interactions between these regions also affect the outcome behavioral response to the drug. For example, the activation of memory circuits (the hippocampus and amygdala) associated with a drug-related context activates OFC and ACC areas, in expectation of the reinforcer. That expectation, in turn, activates DA cells[28], leading to a further increase in the craving sensation and possibly decreased inhibitory control, culminating in the failure of self-control and consequent drug bingeing[15].

This view of how drugs of abuse affect the brain suggests strategies for intervention, including: (1) decreasing the reward value of the drug, and simultaneously increasing the value of non-drug reinforcers; (2) changing stereotyped conditioned drug-seeking behaviors; and (3) strengthening/training the frontal mechanisms responsible for inhibitory control[29-30]. One could conceive of interventions designed to ‘‘exercise’’ brain circuits using specific cognitive and behavioral tasks to remediate and strengthen circuits affected by chronic drug use. Cognitive and behavioral interventions to activate and strengthen circuits involved in inhibitory control would be expected to support, and should increase successful abstinence from drug taking. In such interventions, the OFC is at center-stage because of its specific involvement in reversal learning and altered emotional responding through correcting updates of stimulus-reinforcer associations that have become inappropriate [31]. A recent neuroimaging study showed that when instructed to volitionally inhibit cue-induced craving in a laboratory environment, some individuals with cocaine use disorder (CUD) reported lower levels of craving and showed decreased OFC activity,

demonstrating retention of a level of control over drug-related cue reactivity[32]. Therefore, an effective model of intervention could employ reinforcement of such cognitive control by training CUD with coping skills and other cognitive and behavioral interventions.

A similar concept has long been used in neurofeedback training protocols. Neurofeedback training usually employs highly salient physical markers as feedback for otherwise imperceptible resting state (i.e., tonic) electroencephalogram (EEG) marker patterns, which can induce a wide variety of physiological and cognitive changes that can influence behavior. For example, volitional control of specific EEG frequency components (e.g., sensorimotor rhythms, slow cortical potentials) have been shown effective for reducing epileptic seizures[33] and alleviating symptoms of attention deficit hyperactivity disorder[34-35]. Of relevance for substance abuse disorders, neurofeedback training using alpha (8 – 13 Hz) and theta (4 – 8 Hz) EEG oscillation thresholds[36] has shown some clinical benefits in the treatment of alcoholism[37] and in mixed substance abusing populations[38]. In contrast to protocols that targeted tonic electrocortical fluctuations (presumedly reflecting stable subject traits) primarily to improve general mental health, it may also be possible to specifically target drug-cue induced electrophysiological markers (i.e., transient phasic responses to specific classes of stimuli) to develop protocols for modulation/training to reduce drug-seeking behavior and enhance self-control. For example, a potential cognitive behavioral intervention may provide drug addicted individuals with the feedback of their impaired salience attribution to drug-cues (instead of alpha/theta neurofeedback training) and they can subsequently be trained to cognitively control such enhanced cue-reactivity.

The first step in developing such cognitive neurorehabilitation protocols must be the identification of suitable targeted EEG markers of impaired reward sensitivity in drug addiction. This thesis used EEG and subsequently extracted event-related potential components (ERPs) to study the electrocortical metrics of reward sensitivity in healthy controls for comparisons with drug addicted individuals- to determine whether neural manifestations available from convenient noninvasive apparatus reflect a dichotomous (drug>non-drug) impairment in reward sensitivity. Moreover, using multimodal neuroimaging techniques, underlying neuroanatomical correlates of these markers were also explored. The association between these electrophysiological markers and drug-seeking behavior is also established to show that these responses predict drug-seeking. Finally, a proof-of-concept is presented to show that the obtained neural markers associated with motivated attention (i.e., drug seeking) can be modulated using cognitive control.

The choice of EEG over more sophisticated neuroimaging techniques [e.g., positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)] had two major justifications. First, EEG recordings offer a level of temporal resolution (~ 1 ms), which exceeds that of other neuroimaging modalities, and reflects the ongoing flow of information on an electrophysiologically appropriate time scale[39]. Other neuroimaging technologies cannot achieve such temporal resolution because blood flow and glucose utilization changes are indirect measures of neural activity, and are also slow to recover. Thus PET and fMRI are less able to identify or track the neural chronometry of a given brain function. Second, EEG technology is robust, well-understood, portable and easy to use. Numerous manufacturers produce small, light-weight and battery-operated multichannel EEG amplification systems which could be mobilized to study patients in treatment facilities, rural settings, and other locked-in or removed residences (such as prisons). This portability and ease of use can lead to rapid translation between laboratory findings and their clinical implementations, particularly for relapse prediction[40-42] or recovery assessments[43].

CHAPTER 2

SPECIFIC AIMS

Specific Aim 1: Identification of electrophysiological markers of hypersensitivity to drug-related, and hyposensitivity to non-drug reward.

A typical pattern of drug addiction in humans is characterized by intermittent periods of abstinence from drug-taking followed by increased craving and relapse[44-45]. These stages in drug addiction are believed to result from persistent drug-induced neuroadaptations within the mesocorticolimbic dopaminergic reward circuitry, although it is possible such neural compromises could predate the onset of drug abuse and predispose to it[15, 30]. Irrespective of the direction of causality, dysregulated reward sensitivity can take the form of enhanced sensitivity to drug reward at the expense of all other non-drug reward. Indeed, animal research has shown that in drug addiction, the value of a drug reward is increased[46] while that of a non-drug reward is decreased[47].

To explore whether sensitivity to non-drug reward in individuals with cocaine use disorders (CUD) is dampened, we chose to study the P300 ERP component. The P300 ERP component is typically elicited by task-relevant odd-ball stimuli, showing maximum amplitude at posterior (parietal) scalp locations[48-49]. The P300 has previously been shown to be sensitive to reward, with greater amplitude to larger compared to smaller (or no) reward[50]. Other studies have also confirmed the role of the P300 in processing the incentive value of reinforcers by systematically varying monetary amounts received for correct performance on tasks[51-53]. It has been emphasized that the P300 uniquely reflects reward magnitude (and motivational relevance) but not reward valence (i.e., gain vs. loss)[54-55]. These results bolster the use of the P300 as an electrophysiological marker for the cognitive processing of salient stimuli[49], such as those with high emotional value, providing informative feedback or tasked for tracking as target stimuli[56-58]. In drug addiction, the role of the P300 as a potential phenotypic marker has long been recognized[59]. Specifically, using the oddball paradigm, which presents a mix of target and non-target stimuli in which the probability target stimuli is reduced, P300 amplitude has been shown to be decreased in cocaine addiction and predictive of relapse[41], and has been variously attributed to the effects of abstinence or withdrawal[60-61], history of conduct disorders[62], or impulsivity[63]. Similarly, the latency of P300 has been reported to be delayed in individuals with cocaine, and cocaine and alcohol, dependence[64].

However, a gap in the literature awaits the evaluation of the P300's sensitivity for studies of the response to reward and non-reward stimuli in drug addiction. Such use is suggested by a study

in which males with a family history of alcoholism did not show the expected greater amplitude and shorter latency of the P300 response to a performance-contingent monetary incentive on a visual discrimination task[50]. Given the paucity of other such studies, our goal was to inspect the P300's modulation by monetary reward in CUD. In the first study (**Appendix A**; *published in Psychophysiology, 2008*), we compared the P300 amplitude in response to a sustained attention Go/No-Go task with three monetary values (45¢, 1¢, and 0¢), and showed that in contrast to healthy control subjects (N=18), CUD (N=18, all current users as documented by the presence of cocaine in urine on the study day) failed to show the expected graded P300 response to the different levels of monetary reward (i.e., 45¢ > 0¢) in the "Go" trials. CUD also showed significantly faster latency of P300 than healthy controls[65] (*Figure 1.1*).

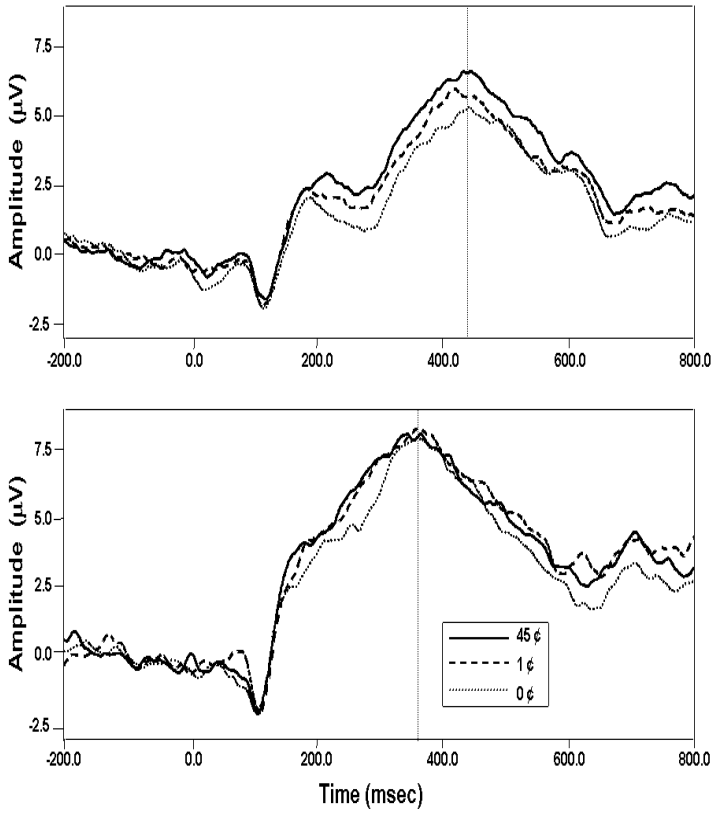

Figure 0.1. Grand averaged waveforms for controls (top) and CUD (bottom) reflecting 200 msec before to 800 msec after the target stimulus for each reward condition (45¢, 1¢, 0¢) at PZ electrode site. Of note is the lack of P300 difference between the monetary conditions (denoted by the vertical line) in CUD, and an earlier P300 latency in CUD compared to healthy controls.

In the follow-up study (**Appendix B**; *Submitted to Biological Psychology*), we asked whether these deficits in sensitivity to non-drug reward are associated with the recency of drug use.

For this purpose, we included a new group of CUD (N=14) with short-term abstinence (3 – 30 days). Thus, that study included both those who tested positive (CUD+, confirming to drug use within the prior 72 hrs) versus negative (CUD-) for recent cocaine use. The results demonstrated for the first time that the more severe impairment in reward sensitivity characterized ***CUD-*** (i.e., CUD with *less* recent cocaine use and therefore *longer* short-term abstinence), while corroborating our previous results showing deficits in sensitivity to monetary reward in all CUD, compared to healthy controls (*Figure 1.2*).

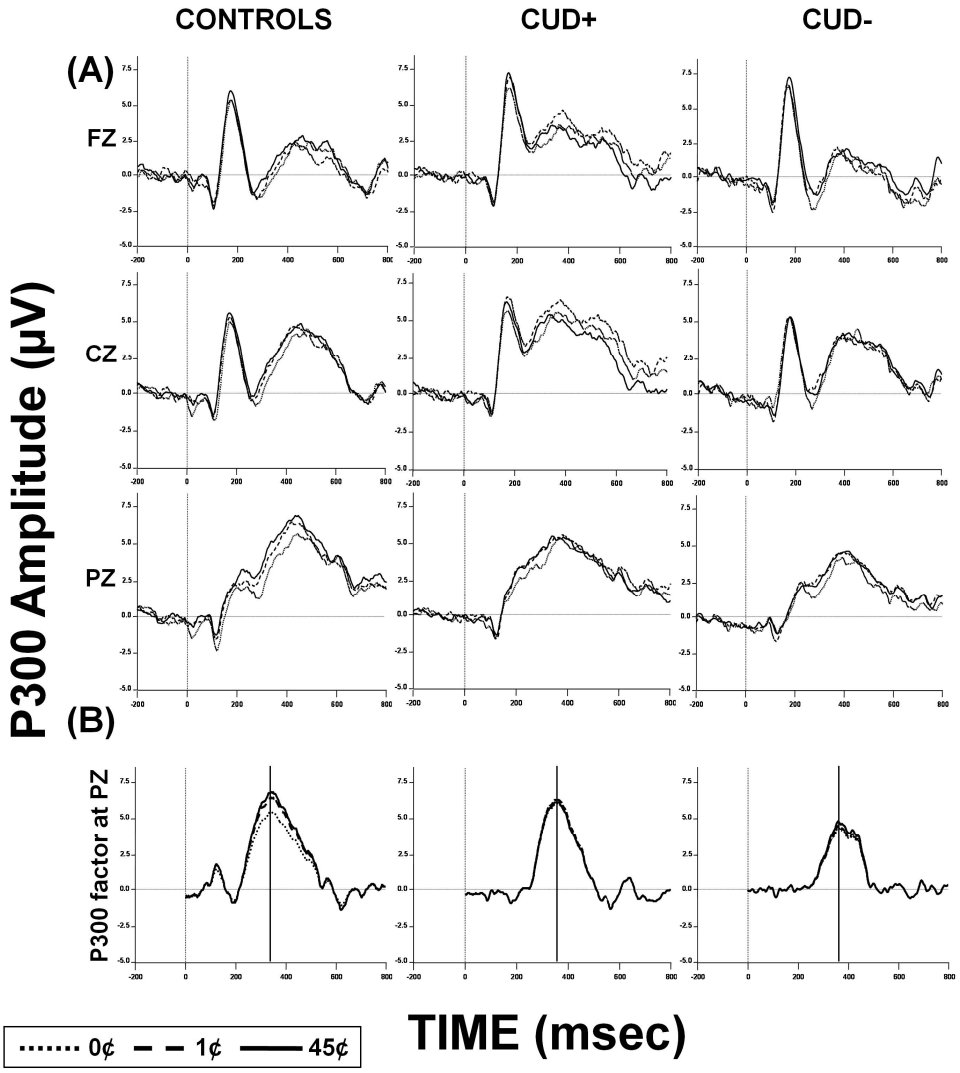

Figure 0.2. (A) Grand averaged ERP waveforms for controls (left; N=23), CUD+ (center; N=21) and CUD- (right; N=14) for each monetary reward condition (45¢, 1¢, 0¢) at midline (Fz, Cz, and Pz) electrode sites. (B) PCA components of the P300 at PZ. Of note is the lack of P300 amplitude difference between the monetary conditions (denoted by the solid vertical line on the PCA factor) in both CUD subgroups (CUD+ and CUD-) and the reduced overall P300 amplitude in the CUD-.

Taken together, these studies demonstrated compromised sensitivity to monetary reward (as compared to non-reward) in CUD (irrespective of the recency of cocaine use). This compromise was also evident despite faster P300 latency (only in the study reported in Appendix A) and enhanced self-reported interest in the task by the CUD as compared to the control subjects. Because we further controlled for all other stimulus properties (the 0¢ condition was identical to the 45¢ condition in all properties but the amount of expected reward), we cannot attribute this specific compromise to a generalized impairment in information processing. Instead, we attribute this compromise to specific deficits in the neural network that underlies reinforcement learning (i.e., sensitivity to changing reinforcement contingencies required to effectively control goal-directed behavior). A potential candidate for the affected neural substrate encompasses the anterior prefrontal cortex, which showed a similar compromise in cocaine addicted individuals who were expecting monetary reward in our previous fMRI study[66]. Our results also, for the first time, demonstrate that the more severe impairment in reward sensitivity characterizes CUD with *less* recent cocaine use/*longer* short-term abstinence, while corroborating our previous results showing decreased neural sensitivity to sustained monetary reward in a larger group of CUD (CUD+ and CUD- combined) compared to healthy controls. Collectively, these results support a self-medication hypothesis where CUD may be acutely using cocaine to temporarily normalize underlying cognitive and emotional disruptions, albeit at the expense of longer-term detrimental impact on their sensitivity to non-drug rewards. These results highlight the importance of developing treatment modalities, including pharmacological interventions, to target improvements in neuropsychological function without reducing sensitivity to non-drug reward.

Despite the specific compromise in responding to reward vs. non-reward documented in these studies, contingency management (through the use of reinforcers) has been shown to improve retention and associated abstinence outcomes in cocaine and methamphetamine abusers[67]. This indicates that abstinent drug abusers are able to respond to reinforcers in well-structured and constrained environments that also incorporate treatment programs. However, these behaviors may not generalize beyond the outpatient milieu to the everyday environments of drug addicted individuals- where dependable external reinforcements for advantageous behaviors are not readily available. It is therefore possible that alternative treatment modalities such as targeting improvements in reinforcement learning, inhibitory control or advantageous decision-making in the absence of overt reward could further reduce longer-term relapses in drug addiction.

The next question that we asked was whether the observable deficits in monetary reward sensitivity in CUD generalized and were similar for other non-drug reinforcers, and how neural responses of those reinforcers compares with the heightened neural processing of (and motivated attention to) drug-related stimuli? Therefore, to study enhanced salience attribution to drug-related reward in CUD, we studied the late positive potential (LPP), an ERP component shown to be larger for both pleasant and unpleasant compared to neutral visual stimuli, and interpreted as reflecting increased attention to motivationally relevant stimuli[68-72].

Several drug cue reactivity paradigms have reported that larger LPPs are elicited by drug-related, compared to neutral, pictures in individuals addicted to either alcohol[73], heroin[74], or cocaine[75-76]. The extant LPP data have been interpreted in terms of increased allocations of neural resources to addiction-related stimuli by addicts. However, more nuanced interpretations of these findings have been complicated by the inconsistent use of control groups, comparison stimuli, and variability in the recency of drug use by the addicted participants. Only a few ERP studies have directly compared drug-related to other emotionally salient stimuli in both drug addicted and control individuals[77-78]. That is a crucial comparison, considering that, in general, more emotion-related abnormalities have been implicated among substance dependent individuals[79-80]. In addition, the recency of drug use could also influence aberrant neural reactivity to drug cues among addicted individuals[81]. Therefore, we conducted a study in which the CUD sample included both those who tested positive (CUD+; recent cocaine use) versus negative (CUD-; longer abstinent users) for recent cocaine use.

In this study (**Appendix C**; *accepted in the European Journal of Neuroscience, 2011*), we measured ERP responses while subjects viewed drug-related, pleasant, unpleasant and neutral pictures. We hypothesized that unlike healthy controls, CUD would manifest enhanced processing of drug-related cues, similar to processing for other emotional pictures. Indeed, results showed that cocaine pictures elicited an increased LPP component in ways similar to affectively pleasant and unpleasant pictures, in all CUD. However, CUD+ also exhibited deficient processing of all emotional stimuli in a later LPP time window (1000 – 2000 ms) (*Figure 1.3*). Whereas all CUD rated cocaine pictures as pleasant, controls rated them as unpleasant; within the CUD group, CUD+ rated cocaine pictures as more pleasant and arousing than CUD-. Taken together, results suggest that recent cocaine use impairs sustained processing of emotional stimuli among CUD, an effect not captured by self-report.

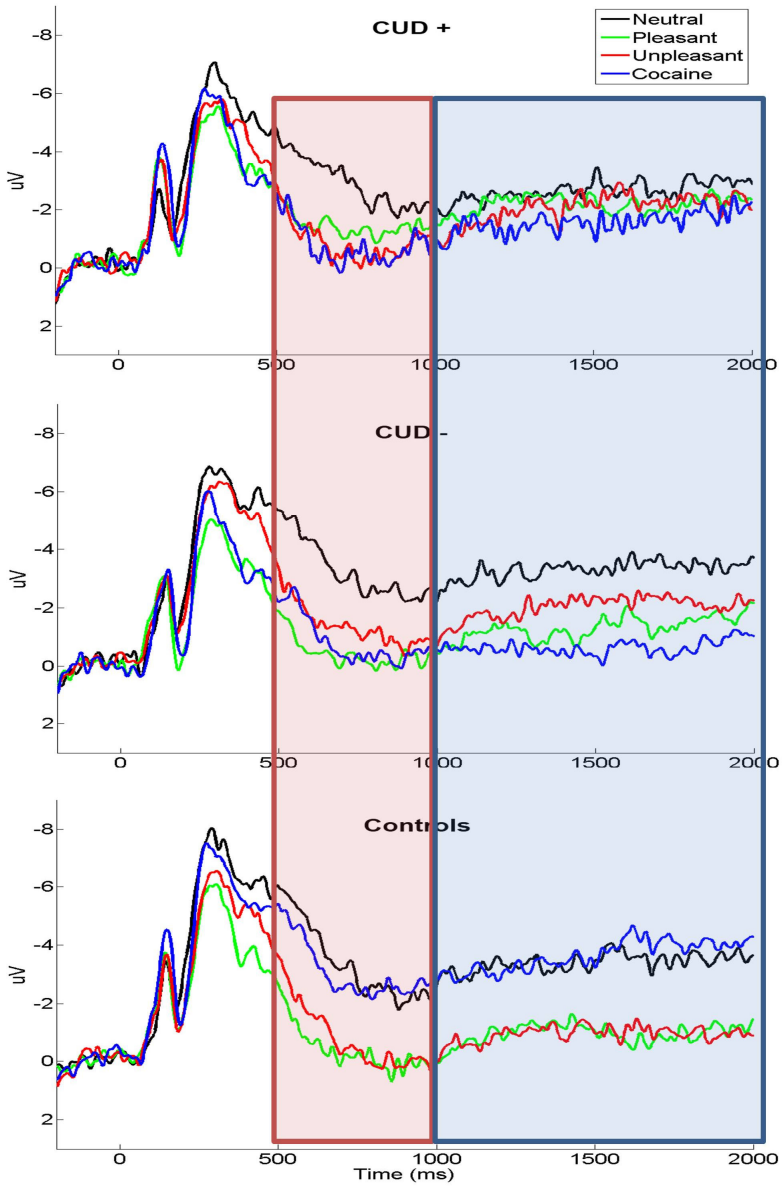

Figure 0.3. Grand averaged late positive potentials (at the average of sites Cz, FCz, FC1, FC2, and Fz) elicited by neutral, pleasant, unpleasant, and cocaine-related pictures for CUD+ (top), CUD- (middle), and control subjects (bottom). Of note are the LPP amplitude differences between picture types in the early (500 – 1000 ms; brown) and late (1000 – 2000 ms; blue) LPP windows.

Therefore, in this specific aim, we identified P300 and LPP ERP components as functional electrocortical markers of reward sensitivity. Hyposensitivity to non-drug reward was highlighted in CUD by the lack of P300 amplitude difference between high- and non-monetary reward conditions, and the lack of P300 amplitude difference was not driven by recency of drug use. The decreased P300 amplitude in CUD-, compared to CUD+, and the correlation between P300 amplitude and

recency of cocaine use (Appendix B) point to the validation of a self-medication hypothesis, according to which drug abusers use their preferred drug for the relief of negative symptoms such as anhedonia, boredom susceptibility, low self-esteem[82], avoidance of withdrawal symptoms[83], or underlying cognitive deficits[84]. By contrast, hypersensitivity to drug reward in CUD was highlighted by increased LPP amplitude in response to drug-cues compared to the response to neutral pictures. We have also shown that, unlike in the late LPP window, differences within the early LPP window do not depend on the recency of drug use. Unlike the P300 study, the LPP study identified CUD+ with more severe cognitive deficits, which seems to suggest that current cocaine use might be uniquely associated with deficits in *sustained* attention to emotional stimuli. Taken together, prior ERP work has demonstrated clear distinctions (and by inference, underlying neurocognitive deficits) in the reward sensitivity of CUD, with the ERP components P300 and LPP reflecting unique aspects of altered salience attribution in drug addiction.

Specific Aim 2: Identification of neuroanatomical correlates of electrophysiological markers of reward sensitivity.

Magnetic resonance imaging (MRI) techniques [both structural (sMRI) and functional (fMRI)] have played a vital role in *in vivo* neuroscience examinations of brain conditions related to normal and abnormal brain morphology and functions. While analyses of regions of interest generally require substantial *a priori* hypotheses to formulate the problem under study, whole brain analysis methods have increasingly been utilized to explore the morphological and functional brain changes rendered by neurological factors[85-86].

A major advance in neuroimaging research has been the demonstration that the brains of many patients suffering from select psychopathologies (such as schizophrenia) appear structurally abnormal[87-92]. Such abnormalities have recently been also reported in drug addiction[91-92], a disorder previously attributed to 'moral weakness.' To investigate regionally specific differences in neuroanatomical structures, voxel based morphometry (VBM) is most commonly used. VBM is a fully automated, unbiased, and operator-independent MRI analysis technique using a voxel-wise comparison across subjects (once gross anatomical differences have been accounted for by linear and non-linear registration[85]). The technique typically uses T1-weighted volumetric MRI scans and performs statistical tests across all voxels in the image to identify regional volume differences between groups. For example, to identify differences in patterns of regional anatomy between groups of subjects, a series of t-tests can be performed at every voxel in the image. Regression analyses can also be performed across voxels to assess neuroanatomical correlates of cognitive or behavioral deficits. The technique has been applied to a number of different disorders, including neurodegenerative diseases[93], movement disorders [94], epilepsy [95], multiple sclerosis [96], schizophrenia [97], and drug addiction [92], contributing to the understanding of how the brain changes in these disorders and how these changes relate to characteristic clinical features. Although results from VBM studies are generally difficult to validate, studies have compared them to manual measurements of particular structures and have shown relatively good correspondence between the techniques [98-100], providing confidence in the biological validity of VBM.

It remains unclear, however, how structural abnormalities in different psychopathologies relate to the pathophysiological, attentional, cognitive or emotional deficits in these disorders. While functional and structural neuroimaging techniques may have separately identified neural structures affected in a given psychopathology, there is a lack of evidence that each of these individual techniques infer any information about the processing integrity of brain's structure and

function, respectively. For example, fMRI studies have accumulated much information about the functional neuroanatomy related to substance abuse[15]. Nevertheless, these studies still fail to establish that functional changes in affected regions actually manifest a change in the structural integrity of these brain regions. Therefore, it is imperative that multimodal techniques be used and the results subjected to comprehensive interpretation of all perspectives. One approach to understanding such relationships is to look for correlations among the different structural, functional and behavioral variables[101-107].

One such functional variable is EEG data, which can be correlated with structural measures and might indicate when both reflect common processes and could suggest how they relate to clinical features. In addition, such correlations could also yield insights into which neural systems may affect or contribute to abnormal evoked potentials and provide information about neuroanatomical substrates of scalp recorded ERPs. Therefore, we conducted a study to establish structural neural underpinnings of the functional markers of impaired reward sensitivity. To do so, we used an SPM regression method to correlate functional (ERP) data with brain structural information (using VBM). The goal of this specific aim was to establish that the ERP markers of reward sensitivity are not an epi-phenomenon detected on the scalp and indeed are representative of the neural integrity of brain regions implicated in reward processing using the regression method.

In this study (**Appendix D**; *submitted to the Journal of Cognitive Neuroscience*), we showed a robust positive correlation between P300 differential amplitude (high- minus non-reward conditions, from the sustained attention monetary task) response to the expectation of monetary reward, and gray matter volume in brain regions functionally involved in reward sensitivity and salience attribution, namely the dorso- and ventro-lateral prefrontal, anterior cingulate, and lateral orbitofrontal cortices in healthy controls (*Figure 1.4*). In contrast, CUD demonstrated – in addition to the expected compromised psychophysiological sensitivity to money and reduced prefrontal gray matter volume – lack of interdependence between these two measures. Taken together, although correlation analyses are inconclusive about direction, causality or predisposition, results suggest that structural integrity of the prefrontal cortical regions mediates electrocortical sensitivity to monetary reward (positive in controls, null in CUD). These findings extend the study of reward processing, commonly accomplished with a single modality to a multimodal functional-structural investigation.

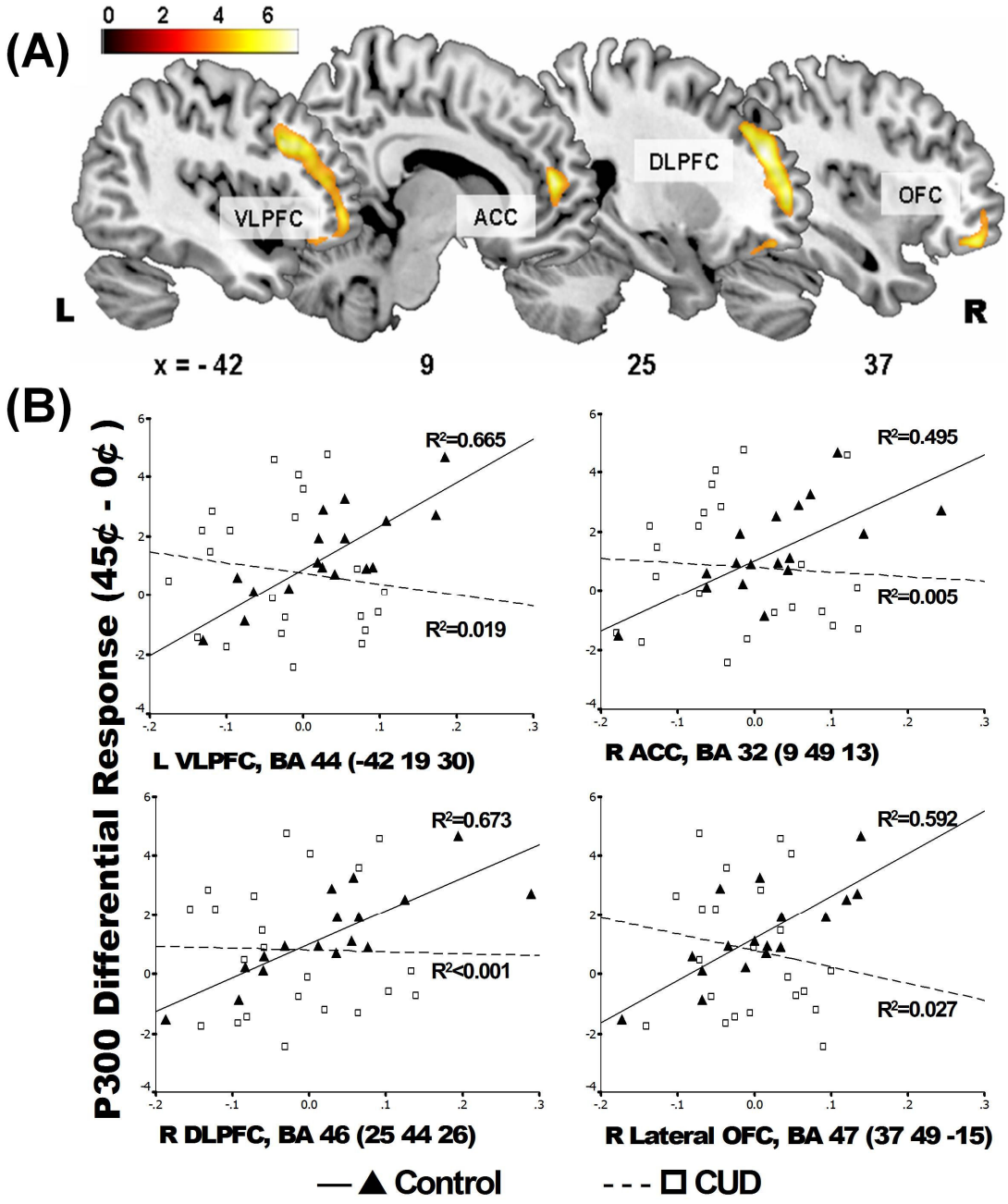

Figure 0.4. Neuroanatomical correlates of reward-modulated P300 amplitudes. (A) Whole brain correlations between differential P300 response (45¢ minus 0¢) and gray matter volume. (B) Scatter plots for each correlated brain region. Of note are the differences in regression coefficients between healthy controls (all significant, $p < 0.05$) and CUD (all non-significant, $p > 0.1$), for each brain region.

Given that EEG is a substantially less expensive alternative to other imaging techniques, establishing the P300 response to reward as an indirect biomarker of prefrontal cortical integrity would be beneficial for numerous future studies, from noninvasive monitoring of healthy

development to monitoring disease course or impact of treatment in clinical settings- specifically, in psychopathologies affecting the prefrontal cortex. It must also be noted that neuroanatomical correlates of the LPP component were not analyzed as part of the current thesis. The reason such analyses were not undertaken is because, unlike P300- for which there exists a significant amount of *a priori* knowledge and a clear sensitivity to the magnitude of the monetary reward (Appendix A & B), LPP did not distinguish emotional valence (pleasant versus unpleasant emotion) and was instead found to be a metric of emotional arousal (Appendix C). Therefore, the current regression method applied to P300 would not have been valid for the LPP-VBM analysis. Since LPP research is still is in its infancy, isolating neuroantomical structures underlying LPP modulation as a function of motivated attention can be another doctoral thesis.

Specific Aim 3: Assessment of the association of these electrophysiological markers with drug-seeking and cognitive control.

Recently, neuroimaging studies have shown that neural responses to active evaluation of stimuli predict subsequent choice behavior[108]. In parallel, some evidence suggests that automatic neural processes may guide choice behavior, even in the absence of explicit deliberation and attention to the choice task. For example, neural responses were shown to engage automatically in assessing facial attractiveness and preferences even when such judgments were not part of the designated task[109-110]. Moreover, a recent study has demonstrated that LPP amplitude predicts subsequent behavioral (reaction time) and ERP (P300 amplitude) interference with target processing[111]. Specific Aim 1 relies on the finding that in CUD, LPP amplitude tracks increased motivated attention attributed to drug-cues compared to neutral images, while in healthy controls no such LPP differences were found [112]. In parallel, we have also previously shown that given a choice between pleasant, unpleasant, neutral and drug related pictures, CUD chose to look at drug-related pictures more often, compared to healthy controls, who preferred looking at pleasant images[113]. Therefore, in the context of the current thesis, we inquire whether LPP amplitude can predict enhanced drug-seeking in CUD.

To investigate the relationship between LPP amplitude in response to emotionally salient stimuli (including drug-cues) and choice behavior, we conducted a study (**Appendix E**; *submitted to Proceedings of the National Academy of Science*) in which 32 healthy controls and 59 CUD first underwent ERP recordings while passively viewing pleasant, unpleasant, neutral, and cocaine images, and then provided self-report ratings of each picture's arousal and completed a previously validated choice task to assess objective preferences for viewing these same images, in that order. Results showed that LPPs elicited by pleasant relative to neutral images predicted subsequent choices in all subjects. By contrast, and only in a subgroup of CUD, LPPs to cocaine relative to pleasant images predicted respective choice. Also in that CUD subgroup, choice behavior was associated with increased disease severity. This CUD subgroup suffered from impaired insight, measured by previously validated procedures[114]. Thus, LPPs elicited by salient stimuli (pleasant images in all subjects; cocaine images in some CUD) have utility for predicting subsequent objective choices to view the same stimuli. Thus, relatively inexpensive and portable ERPs could therefore provide a diagnostic tool to predict disadvantageous behaviors in select psychopathologies (e.g., drug seeking in CUD), with the goal of improving prevention and intervention efforts.

For LPP to be the candidate ERP component for feedback training to bolster inhibitory control and devalue drug reward, important for a potentially successful behavioral intervention in drug addiction[29-30], it is imperative to investigate whether LPP amplitudes (a marker of hypersensitivity to drug reward in CUD) can volitionally be modulated under cognitive control. A recent PET study showed that when asked to volitionally control their drug craving, some cocaine addicted individuals showed decreased cue-induced craving and decreased activity in brain regions that process the motivational value of rewards (such as the OFC), thereby retaining some cognitive control over their drug craving[32]. Prior studies on LPP have shown that LPP amplitudes are sensitive to emotional reappraisal instructions[115-117]. For example, Hajcak and Nieuwenhuis[115] found that when participants were asked to reappraise unpleasant pictures, the LPP was reduced relative to the control condition. However, unlike neuroimaging reports of lateral prefrontal cortical (PFC) activation, a region that supports top-down stimulus appraisals and regulate cognitive control during emotional reappraisal[118-121], LPP findings seem to only suggest suppression of emotional arousal, and have not shed light on the cognitive control mechanisms attributed to the PFC during reappraisal.

Therefore, as the final part of the current thesis, we carried out a study (**Appendix F**; *manuscript in preparation*), in collaboration with Dr. Greg Hajcak, Ph.D., in the Psychology department at Stony Brook University, to show that (1) LPP amplitude can be modulated using cognitive control; and (2) frontal alpha rhythm, whose desynchronization (reduction in power) is a marker of prefrontal cortical activation[122-123], can also be modulated as a function of cognitive control. Therefore, in this study we used time- and time-frequency domain analysis of electrophysiological data during an emotion regulation picture-viewing task. In this study, healthy undergraduate students viewed neutral and unpleasant pictures. Shortly after the picture onset, subjects were instructed by auditory cue either to ATTEND or REAPPRAISE the currently presented image. On ATTEND trials, participants were instructed to focus on any feelings elicited by the picture. On REAPPRAISE trials, participants were instructed to reinterpret the picture so that it no longer seemed negative. As expected, there was a significant difference between attended and reappraised LPP amplitudes (REAPPRAISE > ATTEND; inverted because of averaged referencing of EEG/ERP data) for unpleasant pictures at frontal electrode sites ($p < 0.001$) (*Figure 1.5A*). Furthermore, analysis of the induced spectral activity showed significant alpha desynchronization in the reappraised compared to the attended trials at left frontal electrode sites ($p < 0.001$) (*Figure 1.5B*). There was also a positive correlation between the differentials (ATTEND minus

REAPPRAISE) of these two responses (r = 0.32, p = 0.03) (*Figure 1.5C*), indicating that these two neural indices covary as a function of emotion regulation. These results suggest that neural responses to affective stimuli (including LPP and induced alpha activity) can be successfully modulated through willed cognitive control in healthy individuals. Therefore, a future study should replicate these results in CUD with an emotion regulation task with drug-related pictures to investigate CUD's ability to cognitively control their drug-cue reactivity. We hypothesize that CUD will be able to modulate these electrocortical responses to cognitive reappraisal of drug-cues.

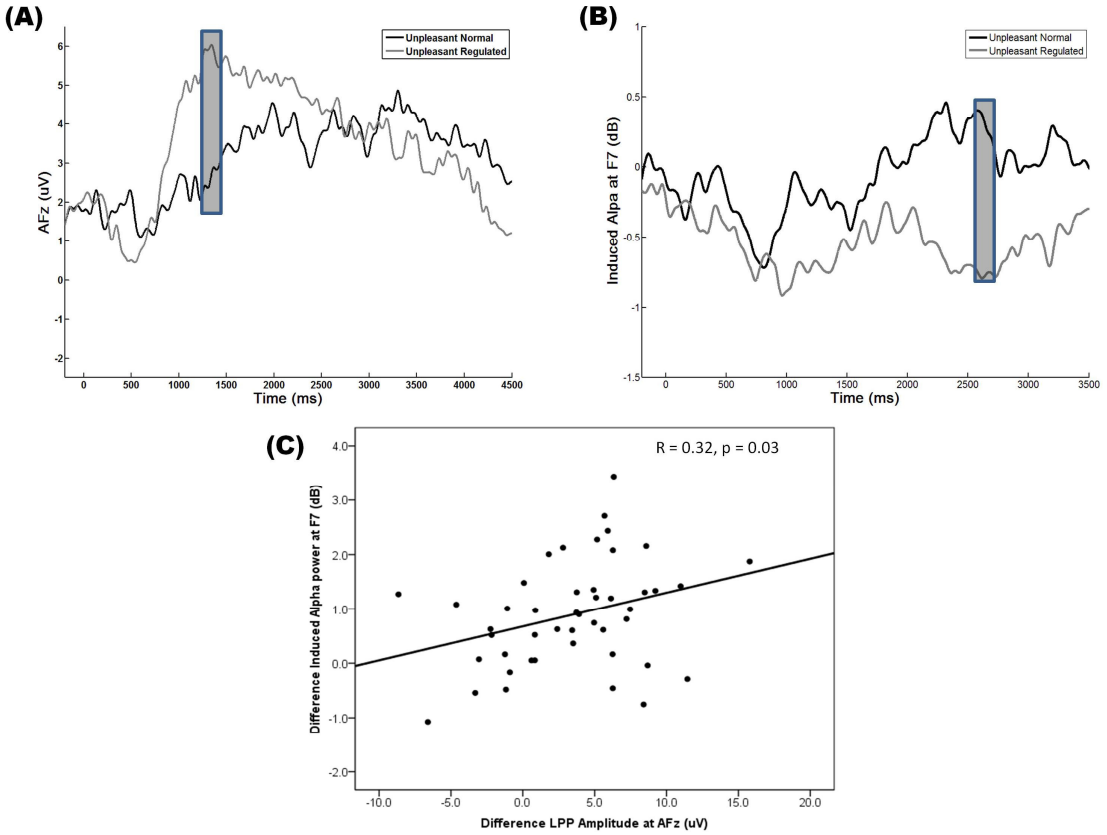

Figure 0.5. Grand averaged ERP waveform at AFz electrode (A), and induced alpha band oscillation at F7 electrode (B), for attended (black) and reappraised (gray) unpleasant pictures. Highlighted regions in (A) and (B) show significantly different temporal regions between the two conditions. (C) Positive correlation between the differential (attended minus reappraised) LPP amplitude (inverted due to averaged referencing) and corresponding alpha power desynchronization in response to emotional reappraisal.

In sum, in the current thesis, we showed that P300 and LPP are markers of hyposensitivity to non-drug reward and hypersensitivity to drug-related reward, respectively, in CUD. Further, it was shown that these electrocortical functional markers (in this case, the P300) have specific

neuroanatomical correlates to show that they are not just a scalp-recorded epi-phenomenon, but are reflective of neural functional and structural integrity. Moreover, we showed that LPP amplitude could predict drug-seeking in some CUD, and finally we showed that, LPP and induced frontal alpha rhythm can be modulated under cognitive control. Thus, LPP and alpha band are ideal electrophysiological candidates for a targeted interventional training for behavioral modification in drug addiction; such lab training could be clinically meaningful (e.g., reducing drug-seeking and relapse).

FUTURE DIRECTIONS

Brain Computer Interface (BCI)

The advent of the study of the brain's oscillatory activity with respect to practical applications has paved the way for Brain Computer Interface (BCI) research. The BCI technology allows the communication between people and mechanical devices and translates human mental activity into device commands. The BCI paradigm bypasses the normal biological pathways (e.g., muscle contraction) mediating volitional movements and employs upstream neural activity that may have a complex relationship to motor or cognitive behavior[124]. The transform between this neural activity and the required BCI control parameters can be facilitated by sampling relevant activity in appropriate brain regions. For example, electrocortical data from neurons in the motor cortex can be sampled to assist limb movement[125]. Neurons in the sensory association areas are volitionally activated in conjunction with *cognitive imagery*. In the temporal lobe many single neurons that respond selectively to a particular visual stimulus are in addition specifically activated during imaginative recall of the same effective stimulus[126]. Beyond representations of sensory and motor events, internal higher-order cognitive activities like 'thinking' also have neural correlates and these also represent volitionally controllable processes[127]. These neural activities are independent of sensory input or motor output, and indeed operate autonomously because they are effectively buffered from peripheral activity [124].

These advances have been made possible due to rapid development in methods of EEG analysis and in information technology, associated with a better understanding of the functional significance of certain EEG parameters. By means of a BCI, either the ongoing EEG signal, or other evoked neural activities [ERPs and event-related oscillations (EROs)] are used to operate computer-controlled devices (Figure 1.6)[128]. The kernel of this technology is an algorithm that takes samples, extracts features, and classifies the EEG signal in real time.

There are 3 essential elements to the practical functioning of a BCI system: (1) signal acquisition: recorded brain signal or information input; (2) signal processing: the conversion of raw information (e.g., ERO signal of intent) into a useful device command (algorithm); (3) device output: the overt command or control functions administered by the BCI system (e.g., computer cursor movement). Conversion of the neural signals to generate the requisite control parameters can be aided by appropriate transform algorithms[129]. But even with the best matches and the optimal algorithms, accurate device control under diverse behavioral conditions depends significantly on the

degree to which the neural activity can be volitionally modulated[129]. Thus, a BCI system utilizes control signals to allow the user to make a selection. This selection capacity is often realized using a computer cursor[130-131], controlling an arrow on a dial[132], a moving robot[133], or controlling other external devices[134-135]. Within this context, key performance characteristics of BCI systems are speed (i.e., how long does it take to make a selection) and precision (i.e., how often the executed selection is the one the user intended).

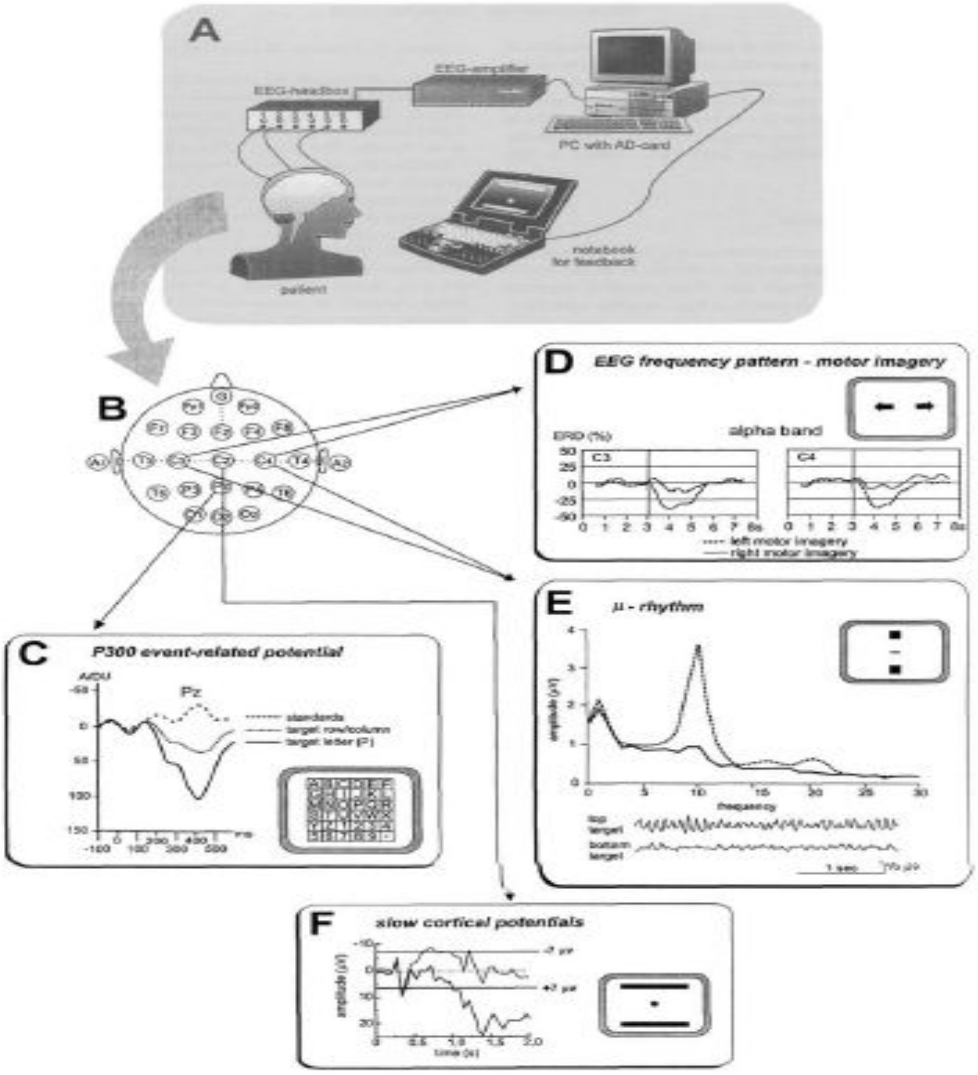

Figure 0.6. (A) A typical EEG-based BCI system. (B) The electrodes are placed on the scalp according to the international 10-20 system. (C) The P300 based BCI used to spell words [136]. (D) Alpha based BCI used to move cursor using motor imagery [135]. (E) Sensorimotor (SMR) mu rhythm based BCI [129]. (F) Slow cortical potentials (SCP) based BCI system [128].

BCI and Neural Rehabilitation

A major use of BCI is its implementation for neural rehabilitation. This has been extensively studied in patients suffering from amyotrophic lateral sclerosis (ALS), a progressive motor disease that results in a complete destruction of the peripheral and central motor system affecting sensory or cognitive functions to minor degree. Various BCI systems have been developed for ALS patients, based on modulation and self-regulation of different EEG responses by the patient, such as their P300, SCPs, and sensorimotor (SMR) potentials[129, 137-140] (*Figure 1.6*). This strategy is straightforward and has already been the focus of a considerable body of research. BCI systems can substitute for the loss of normal neuromuscular outputs by enabling people to interact with their environment through brain signals rather than through muscles [129]. Thus, for example, a person can use EEG activity to indicate "yes" or "no" to control a cursor on a computer screen or to control a neuroprosthetic arm[135, 141-142].

The Proposed BCI-Based Neurofeedback in Drug Addiction

As a potential application of the current thesis, we propose to develop and evaluate an automatic BCI-based neurofeedback system that will use currently identified EEG and ERP markers of heightened drug-cue neural reactivity in individuals with cocaine use disorders; using a portable device, that will integrate real-time event-related EEG feedback training, this BCI will then be used outside the lab to facilitate volitional cognitive modulation of drug-cue reactivity. We hypothesize that such a device, by enhancing volitional decrease of the drug-cue reactivity EEG/ERP features, will decrease craving and drug-seeking in addicted individuals.

Currently, there are no effective treatments that enhance self-control in addiction or other related psychiatric disorders. Medications exist for some addiction disorders (e.g., nicotine, alcohol, opiate) but not other (cocaine, methamphetamine, marijuana) and, unfortunately, relapse into drug use after any addiction treatment is the rule rather than the exception. We postulate that the proposed system will improve abstinence rates over current state-of-the-art interventions in drug addiction given its **(1)** sensitivity to the users' own neural signature of drug-cue reactivity; **(2)** ability to provide event-related feedback in real-time (applicable outside of controlled environments); and **(3)** ease of use. This project will thus allow researchers and health professionals to individually tailor treatment on the basis of one's own brain signature of illness, a more reliable and valid measure of the neural dysfunction than the measures used to date (self-reported craving, behavioral and relaxation neurofeedback training).

The proposed system will change the practice of medicine by allowing individuals access to their automatic neural processes, which begin outside of one's awareness, providing better control over one's own internal states (craving as generalized to other negative emotions and cognitive functions including self-monitoring) and behavior. Scientifically, this project will greatly advance the field as, to date, BCI has not been used for the purpose of increasing self-control, and reducing relapse, in addiction or related disorders. Given the numerous day to day instances where self-monitoring is threatened (e.g., overeating when exposed to food and food related cues, distraction during work or the preparation of homework assignments, or shouting/door slamming during an argument), a portable device that can enhance self-control would have enormous commercial appeal even in healthy individuals.

An NIH National Research Service Award (NRSA) post-doctoral fellowship grant (F32) proposal has recently been submitted by the student for the proposed BCI-based feedback system based on results from the current thesis.

CHAPTER 3

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Title: Compromised sensitivity to monetary reward in current cocaine users: an ERP study

Abbreviated title: P300 in cocaine addiction

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ABSTRACT

We studied modulation of the P300 by monetary reward expected to be received on a sustained attention task in 18 individuals with current cocaine use disorders (CUD) and 18 control subjects. Results in the controls revealed sensitivity to money as measured with P300 amplitude and speed of behavioral response and their intercorrelations. In contrast, despite generally faster P300 waveforms and higher self-reported interest in the task, CUD did not display these responses to money vs. non-reward; at the behavioral level, this impairment correlated with frequency of recent cocaine use. These preliminary results suggest a compromised sensitivity to a secondary reinforcer in CUD. This deficit, that needs to be replicated in larger samples of currently active vs. abstaining CUD, may underlie the compromised ability to advantageously modify behavior in response to changing inner motivations and environmental contingencies.

INTRODUCTION

(Removed to reduce redundancy)

METHODS

Participants

Thirty-six medically healthy right-handed subjects participated in this study, 18 individuals with current CUD and 18 healthy control subjects. There were no statistically significant differences between the two study groups in distributions of sex and race or in age, education, and socio-economic status (Table 3.1). Although we excluded subjects with severe levels of self-reported state depression [143] (scores: >29, N=2), this variable and history of cigarette smoking differed between the CUD and healthy controls (Table 3.1); their possible confounding effects on results were examined as described under Analyses and Results.

Subjects were recruited using advertisements in local newspapers and by word-of mouth. A full physical and neurological examination ensured the following inclusion criteria were met for all subjects: absence of 1) head trauma with loss of consciousness; 2) current neurological or any medical disease that required hospitalization or regular monitoring (note that subjects were not tested for HIV); and 3) except for psychostimulants (cocaine or amphetamine / methamphetamine) in the CUD subjects, urine screens for other drugs or their metabolites (phencyclidine, benzodiazepines, cannabis, opiates, and barbiturates) had to be negative. All CUD had a history of using cocaine for at least 3.5 days a week, for at least six months (the smoked route was used by 17 subjects; one subject used the intranasal administration instead). All healthy control subjects denied regular drug use.

In addition, a licensed clinical psychologist conducted an in-depth, 1-3 hour, psychiatric (diagnostic) interview in all subjects. This interview included the: (1) Structured Clinical Interview for DSM-IV Axis I Disorders [144-145] - Nonpatient Edition or Patient Edition for control or CUD subjects, respectively; (2) Addiction Severity Index [146], a semistructured interview that collects data in seven problem areas (medical, employment, legal, alcohol, other drug use, family–social functioning, and psychological status) to provide an estimate of the severity of the drug abuse problems and a detailed assessment for recent and lifetime history of use of various drugs including alcohol; (3) 18-item Cocaine Selective Severity Assessment Scale [147] conducted to evaluate cocaine abstinence/withdrawal signs and symptoms (i.e., sleep impairment, anxiety, energy levels, craving,

and depressive symptoms) 24 hours within time of interview; and (4) 5-item Cocaine Craving Questionnaire [148] and the 3-item Severity of Dependence Scale [149].

Based on this extended interview, all CUD subjects met DSM-IV criteria for current Cocaine Dependence (N=15) or Abuse (N=2). One cocaine abuser, who admitted to weekly use of cocaine, did not meet current abuse or dependence criteria, but met DSM-IV criteria for past polysubstance abuse (with cocaine as the primary drug). All CUD subjects self-reported using cocaine within 96 hours of the study (Table 3.1). Recent cocaine use was indeed confirmed by the urine screen results (urine was positive for cocaine on study day in all CUD subjects. These results indicate cocaine use within 72 hours of testing, which is the maximum resolution provided by the urine screen; results for the CUD subjects whose urine was negative for cocaine on study day will be reported separately). Current abuse of alcohol or cannabis was reported in two CUD subjects; urine was negative for cannabis in all subjects. Current abuse or dependence on other drugs was denied and corroborated by the pre-scan urine tests in all but one subject (urine was positive for both cocaine and amphetamine/methamphetamine) (see Table 3.1 for drug use variables in all CUD subjects). Despite of their current use status, none of the study participants was intoxicated on study day (as determined by this extended clinical interview). Other current or past psychiatric co-morbidities were identified in seven CUD subjects and included major depression disorder (N=5), post-traumatic stress disorder (N=2), antisocial personality disorder (N=1), and pathological gambling (N=1) (2 CUD subjects met criteria for more than one of these disorders). Subjects did not require medications for these conditions as ascertained by the above-described interviews. Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board.

Task

In the current study, we used a monetary reward paradigm that has been previously described [66, 150]. In brief, there were six sequences/blocks each consisting of all three blocked monetary reward conditions: 45¢, 1¢, 0¢ (that is, each monetary condition appeared for a total of six times). These 63 sec monetary conditions were pseudo-randomized and separated by a 35 sec fixation cross to preclude carry over effects. During each of these monetary conditions, there were 9 "Go" and 9 "No-go" trials, which were pseudo-randomized across all trials (no more than three of same type). Two distinct abstract (fractal) images [151] served as the "Go" and "No-go" warning stimuli [S1: this expectation stimulus elicited the P300, see Figure 2 top in [152]]. Trial sequence was as follows:

fixation screen (1000 msec) followed by one of the two fractal images (visual angle = 4.5°, 500 msec) followed by another fixation screen (1000 msec), and terminating in a target stimulus (S2) in the form of a red square (visual angle = 4.5°, 500 msec) [see Figure 3.1]. A response window overlapped with the full presentation of S2. A fixation point remained in the center of the screen for the duration of each 3500 msec trial. All text was in a ROM 2 font.

The subjects were instructed to press a button (using the thumb of the right hand) on a response pad with speed and accuracy upon seeing S2 after a "Go" S1 stimulus and to not press the button upon seeing S2 after a "No-go" S1 stimulus. Incorrect responses were trials where subjects pressed the button instead of refraining from responding (errors of commission) or did not press the button instead of pressing it (errors of omission) [subjects in our prior fMRI study committed on average less than one error of commission for each of these three monetary conditions [66]; therefore, these two error types were combined in all current analyses]. Feedback was presented (visual angle = 2.25°, 500 msec) immediately after the offset of S2; here the amount of money earned for correct responses/non-responses was: $0.45, $0.01, or $0.00. For incorrect responses/non-responses, which happened in less than 8% of trials across all subjects as further described in Results, subjects saw an "X" and did not receive remuneration. Feedback was thus contingent on behavior (i.e., it was not a priori determined). Together with a screen that displayed the monetary reward contingency at each experimental condition onset (visual angle=1.5°, 5000 msec), subjects were aware of the reward contingencies throughout the task.

Choice of these three monetary conditions was based on our previous fMRI study [66] where we selected these specific levels of reinforcement based on our goal to examine expectation of *real* money (calculations were therefore based on the monetary amount available to pay each study volunteer and the number of trials required for fMRI). Within these constraints, we further aimed to inspect differences between the highest and lowest rewards possible and also to incorporate a baseline non-reward condition (0¢). Similarly to the previous study, subjects were paid up to $50 for completion of this task (Table 3.1).

Procedure

Participants were fitted with electrodes and positioned in a cushioned chair. An LCD panel was placed 115 centimeters from the subject's face. Instructions were provided and followed by a short training session, where no money could be earned (stimuli presented during this training session were the same as those presented during the experimental conditions). At the end of the experiment,

subjects were informed of their monetary gain and were given that exact amount at the completion of the study day (note that there was no difference between the groups in total monetary gain on this task, Table 3.1).

Psychophysiological Recording and Data Reduction

Continuous recordings of the electroencephalogram (EEG, Neuroscan Inc., Sterling USA) and electro-oculogram (EOG) were obtained in all experimental conditions using a 64 silver-silver chloride electrodes cap positioned according to the International 10/20 System [153]. All recordings were performed using a fronto-central electrode as ground, and electronically linked mastoid electrodes as reference. Electrodes were placed above and below the left eye to record vertical eye movements. The EEG was digitized at a rate of 1000 Hz and amplified with a gain of 250, and a band pass filter of 0 to 70 Hz. The amplifiers were calibrated prior to each recording. Electrode impedances were at or below 10 kilo-ohms for all electrodes used in the analysis.

Behavioral Measures and Self-Reported Scales.

Reaction time (RT) and performance accuracy were recorded during all task trials and conditions. Further, upon task completion, participants were asked to rate their interest (Scale 1, ranged from 0-7: boring to interesting, respectively), excitement (Scale 2, 0-7: dull to exciting) and frustration (Scale 3, 0-7: extremely frustrating to not at all frustrating) for all three monetary conditions.

Analyses

Event-Related Potentials. The digitized, continuous EEG was transformed using a DC offset algorithm and was divided into epochs extending from 200 msec before the onset of S1 to 1800 msec after. A linear detrend algorithm was applied to the epoched EEG and after baseline correction (using the 200 msec before S1 onset), epochs were inspected and those containing amplitudes greater than 75 μV or less than –75 μV were rejected to eliminate EOG and movement artifacts. After rejections, there was a minimum of 16 epochs per averaged waveform. Separate averages were composed (across sequences/blocks) for "Go" and "No-go" stimuli (S1) separately for the three money conditions (45¢, 1¢ and 0¢) for a total of six waveforms per subject. Grand average waveforms (across all study subjects) were also created for each monetary condition and on these averaged waveforms a P300 component was defined as the largest positive peak (relative to the pre-S1 baseline) in a latency window occurring 280-600 msec after S1. The P300 component for each individual subject was then defined as the largest positive peak ±75 msec of the grand averaged

P300 peak; the time point at which the P300 reached its maximal amplitude was selected as the P300 latency. We focus on the estimations conducted for the midline parietal electrode, Pz, which showed the most pronounced P300 response to money in previous studies [55, 152]. Nevertheless, before conducting the planned 2 × 3 × 2 *mixed* ANOVA [Trial ("Go", "No-go"), Money (45¢, 1¢, 0¢) and Group (CUD, Control)] on the Pz amplitude and latency data, we also report a similar analysis with Site as an additional factor (frontal: Fz; central: Cz; parietal: Pz).

Behavior: Reaction Time, Accuracy, and Post Task Rating Scales. Reaction time (msec) and percent of correct responses were averaged across all trials for each monetary condition. Percent accuracy was analyzed with a 2 × 3 × 2 (Trial by Money by Group) mixed ANOVA. Reaction time and the three post-task rating scales (interest, excitement and frustration) were analyzed using a 3 × 2 (Money by Group) ANOVA.

In all these analyses (behavior and P300), in cases where the assumption of Sphericity was not met (as tested by Mauchly's Test of Sphericity), the Greenhouse-Geisser correction was used. Significant effects were followed with paired (within group) or independent (between group) t-tests; for performance accuracy and all rating scales (which were not normally distributed), the equivalent non-parametric tests were used (paired: Wilcoxon; or independent: Mann-Whitney U). Planned comparisons were conducted across all dependent variables to test our main hypothesis (45¢ does not equal to 0¢ in the control but not CUD subjects).

Correlations. The ERP variables were correlated with all behavioral variables separately across all monetary conditions or for their respective differential scores (e.g., 45¢ minus 0¢). Pearson correlations were performed for RT while Spearman correlations were performed for all other behavioral variables (the parametric correlations were performed for normally distributed variables, while the nonparametric correlations were performed for skewed variables). We also performed correlations (parametric or non-parametric as appropriate) between the main ERP and behavioral dependent variables with depression, which significantly differed between the groups (Table 3.1). If significant, depression was used as a covariate in the appropriate ANOVA [154]. The dichotomous smoking status, which also differed between the groups, was inspected with t-tests. Moreover, for all current smokers (14 CUD and three controls), we also inspected potential impact on results of current cigarette smoking frequency (number of cigarettes a day: mean±SEM, 11.1±1.7) and time since last use (seven subjects smoked a cigarette ≤4 hours before the study and 10 subjects smoked >4 hours before the study). Finally, we conducted correlations between the selected ERP and

behavioral variables with the drug use measures listed in Table 3.1. To protect against Type I error, a significance level of 0.01 was used for all correlations. Otherwise, $p<0.05$ was considered significant.

RESULTS

P300 at the three midline electrodes

Results of the 2 × 3 × 3 × 2 *mixed* ANOVA [Trial ("Go", "No-go"), Money (45¢, 1¢, 0¢), Site (Fz, Cz, Pz) and Group (CUD, Control)] revealed the expected Site main effect [$F(1.3,43)=9.5$, $p<0.01$] and Site by Trial interaction [$F(1.7,57.6)=20.0$, $p<0.0001$], whereby P300 amplitudes were higher for Pz (and Cz) than Fz (Pz=Cz>Fz), especially during the 'Go' trials. This analysis also revealed a Group main effect [$F(1,34)=4.6$, $p<0.05$; CUD>control subjects], driven by the Fz [$F(1,34)=4.3$, $p<0.05$] and Cz [$F(1,34)=5.7$, $p<0.05$] electrodes but not by the Pz electrode [$F(1,34)=0.8$, $p>0.4$]. All other multivariate effects did not reach significance [$F(2,33)<2.0$, $p>0.2$].

P300 at Pz

See Table 3.2 for the means and standard deviations of all P300 amplitudes and latencies as a function of Trial, Money, and Group. The main 2 × 3 × 2 ANOVA for P300 amplitude revealed significant Trial ["Go">"No-Go"; $F(1,34)=14.4$, $p<0.01$] and Money [45¢>0¢, $F(2,33)=4.4$, $p<0.05$] main effects. Although the Money by Group interaction was not significant [$F(2,33)=0.4$, $p>0.7$], a planned contrast revealed that the monetary effect was only significant in the control but not the CUD subjects, as best demonstrated during the "Go" trials [45¢>0¢; paired $t(17)=-2.2$, $p<0.05$; "No-Go"; paired $t(17)=-1.8$, $p<0.09$] (Figure 3.2). There were no significant correlations between these Pz P300 "Go" amplitudes with depression, in the complete group or separately in both study subgroups (all $r<|0.38|$, $p>0.1$). Similarly, inspected with independent t-tests separately for each monetary condition and subject group (and for the complete sample), these amplitude measures did not differ by history of cigarette smoking (all $t<|1.43|$, $p>0.2$). For the current smokers, frequency of smoking and time since last cigarette were not associated with these amplitude measures. Thus, this differential P300 amplitude to money in the control group but not CUD subjects cannot be attributed to the differential effects of depression or cigarette smoking.

For the P300 latencies at Pz, significant Trial ["Go"<"No-Go", $F(1,34)=23.0$, $p<0.0001$] and Group [CUD<control; $F(1,34)=5.5$, $p<0.05$] main effects demonstrated faster latencies for the "Go" trials and for the CUD subjects. Planned monetary contrasts did not reveal differences between the monetary conditions for any of the study groups or combined across all subjects [paired $t<|2.0|$,

p>0.07]. Further, both main effects remained significant after entering depression as a covariate [F(1,33)>6.7, p<0.05]. After entering history of cigarette smoking, the Trial by Group interaction reached significance [F(1,33)=6.7, p<0.05], indicating faster latency in the CUD subjects for the "Go" trials only. For the current smokers, frequency of smoking and time since last cigarette were not associated with these latency measures.

Behavioral Results

See Table 3.2 for the means and standard deviations of RT, accuracy, and the three rating scales as a function of Trial (where relevant), Money and Group. The main 2 × 3 × 2 mixed ANOVA on percent accuracy showed a Trial main effect ["No-Go">"Go"; F(1,34)=38.8, p<0.0001], a Money main effect (0¢>1¢; F(2,33)=4.6, p<0.05), and a Money by Trial interaction [F(1.7,57)=14.6, p<0.0001]. Non-parametric comparisons showed that the monetary differences were driven by the "No-Go" trials, where the 1¢ condition was least accurate [45¢=0¢>1¢; Z>-5.5, p<0.0001]; the latter is an unexpected result that requires follow-up with clear hypotheses (e.g., could it reflect increased inhibitory control requirements under conditions of relative uncertainty/frustration?). Importantly, there were no differences between the study groups in any of these comparisons. Accuracy did not correlate with depression and was also not associated with history of cigarette smoking (including frequency of smoking and time since last cigarette).

There was a significant Money linear contrast for RT (analyzed for the "Go" trials only) [F(1,34)=5.1, p<0.05], such that there was a trend for faster RT for the highest monetary condition. Planned comparisons revealed that the control subjects were somewhat faster than the CUD subjects, a difference that reached significance for the 1¢ condition [t(34)=2.1, p<0.05], with a trend for the 45¢ condition [t(34)=1.8, p<0.09]. Most importantly, the 45¢ vs. 0¢ differential was only significant for the control subjects [45¢<0¢; paired t(17)=2.7, p<0.05]. Entering depression as a covariate did not impact the monetary main effect and moved the Money by Group interaction closer to significance [Quadratic within-subjects contrast, F(1,33)=3.2, p<0.09]. History of cigarette smoking (including frequency of smoking and time since last cigarette) was not associated with RT.

Both interest and excitement rating scales showed a significant Money main effect [45¢>1¢≥0¢; F(1.4,46.9)>17.2, p<0.0001] and a significant Group main effect [CUD>control; F(1,34)>4.5, p<0.05] (Figure 3.3). The Money by Group interaction was not significant. There were no significant results for ratings of frustration. When depression was entered as a covariate, results did not change for the interest ratings; the diagnosis main effect was no longer significant for the

excitement ratings. Cigarette smoking (including frequency of smoking and time since last cigarette) was not associated with these rating scales.

P300-Behavioral Correlations

Because the amplitude and latency P300 group differences were noted mostly during the "Go" trials as described above (P300 at Pz section), the following correlations with behavior were focused on the "Go" trials. There was a positive correlation between the P300 amplitude differential for the 45¢ minus 0¢ condition with the respective accuracy differential in the control subjects only; the higher the P300 amplitude differential, the better the accuracy for the high monetary condition as compared to the neutral cue ($r=0.64$, $p<0.01$; Figure 3.4, left; this correlation remained significant after excluding the outlier on the upper right-hand corner of this figure: $r=0.61$, $p<0.01$). Similarly, a negative correlation with RT was only observed in the control subjects: the higher the P300 amplitude for the 1¢ minus 0¢ condition, the faster the respective change in RT ($r=-0.6$, $p<0.01$; Figure 3.4, right). Further, only for the control subjects, there was a negative correlation between latency and accuracy (this reached significance for the 0¢ condition: $r=-0.66$, $p<0.01$): the faster the P300 latency, the higher the accuracy. Controlling for depression or cigarette smoking (with partial correlations), these correlations remained significant ($r>|0.49|$, $p<0.05$). The parallel correlations in the CUD were not significant ($r<|0.29|$, $p>0.3$). None of the correlations between the P300 measures (during "Go" trials) and the rating scales survived the nominal significance level. The parallel correlations for the "No-go" trials (except with RT) were not significant ($r<|0.46|$, $p>0.06$).

Finally, we conducted analyses between these six variables (that showed P300-behavioral intercorrelations: P300 amplitude and accuracy differentials for 45¢ minus 0¢, P300 amplitude and RT differentials for 1¢ minus 0¢, and P300 latency and accuracy at 0¢ condition, all during the "Go" trials) and the selected 10 drug use variables in the CUD subjects (Table 3.1). One correlation reached nominal significance level: the higher the 45¢ minus 0¢ accuracy, the less frequent the cocaine use during the 12 months preceding this study ($r=-0.80$, $p<0.0001$; this correlation also reached significance for the 45¢ minus 1¢ accuracy differential, $r=-0.72$, $p=0.001$) (Figure 3.5). These correlations remained significant after controlling for depression and history of cigarette smoking (including current frequency and time since last use; $r>-0.66$, $p<0.01$). Parallel correlations for the "No-go" trials did not reach statistical significance ($r<|0.4|$, $p>0.1$).

DISCUSSION

The goal of this study was to investigate the P300 modulation by sustained monetary reward vs. non-reward in adults with current CUD as compared to age-matched healthy control adults. As hypothesized, sensitivity to monetary reward was compromised in the CUD subjects: while in the control subjects the amplitude of the P300 component (recorded at Pz during expectation of reward) was higher in the 45¢ condition than the 0¢ condition, a similar P300 response to money was not significant in the CUD subjects (Figure 3.2). In parallel, only the control subjects reacted faster to the highest monetary condition (45¢) as compared to the neutral cue (0¢). Further, only in the control subjects these P300 amplitude differentials intercorrelated with the respective behavioral adjustments to the monetary incentive (45¢>0¢ with accuracy and 1¢>0¢ with RT, Figure 3.4); in the CUD subjects, the better the accuracy adjustment for the high monetary condition, the less frequent the cocaine use during the year preceding this study (Figure 3.5). Overall, the compromise in the P300 and behavioral responses to monetary reward in the CUD subjects could not be attributed to general decreases in P300 amplitude or latency (P300 amplitudes at Pz did not differ between the study groups and P300 latencies at Pz were *faster* in the CUD than the control subjects), differential monetary gain during the task or to the inspected individual factors (e.g., depression, history of cigarette smoking). Further, these results could not be attributed to decreased task engagement in the CUD subjects who instead reported being *more* interested in the task than the control subjects (Figure 3.3).

Our results in the control subjects confirm modulation of the P300 by monetary reward magnitude [53, 55]. Similarly, using another S1-S2 RT task, fast trials resulted in larger P300 amplitudes in a condition where healthy subjects could earn money [155]. Our results extend these previous studies by showing parallel reward-driven adjustments in both the P300 amplitudes and behavioral performance; their direct intercorrelations support a previously described role of the P300 in motivation [156]. Our results are thus consistent with the recent locus coeruleus-norepinephrine theory that predicts a covariation between the P300 and behavior (accuracy and RT) as modulated by experimental factors known to affect task-focused performance [including feedback salience used in the current study; [157]].

Our main results in the CUD subjects are consistent with a compromised sensitivity to monetary reward and with a potential disruption in the ability to change behavior in response to perceived inner motivational drives (i.e., impaired insight) in cocaine addiction as we previously suggested based on an fMRI study [66, 158]. Specifically, these conclusions are based on the apparent

disparity, in the CUD subjects, between measures obtained objectively (lack of significant reward-driven P300 or behavioral adjustments) vs. those relying on subjective self-report (reward-driven interest in the task). In general, these results are consistent with ERP studies showing compromised P300 sensitivity to other neuropsychological tasks in CUD [41, 60-64]. This P300 compromise is also observed in other types of drug addiction and indeed it may be a marker for addiction susceptibility. For example, a compromised P300 response - specifically to incentives - has been documented not only in individuals with alcohol addiction [159] but also in non-addicted individuals with a family history of alcoholism [50].

Of note are the correlations in the CUD subjects between reward-driven behavioral performance and frequency of shorter-term (1 year) cocaine use. These correlations suggest that recent cocaine self-administration (as documented by positive urine results in all CUD subjects) could also contribute to the faster P300 latencies and higher self-reported task interest in the CUD as compared to the control group. This account remains to be experimentally tested (e.g., with test-retest longitudinal designs); however, it is consistent with studies where stimulants such as caffeine [160-161] and methylphenidate [162-163] decreased P300 latency.

Limitations of this study include the following: (1) the blocked nature of the experimental design allowed us to study sustained responses to monetary reward. However, it may have also introduced habituation effects that need to be studied separately; (2) future studies could compare additional or more disparate reward conditions (e.g., $2 vs. $1 vs. 10¢ or use a logarithmic formula to choose the different levels of reward) and also add monetary loss [55, 164-165]; (3) in the current study we a priori focused on the P300, an ERP component previously associated with the processing of reward value; the study of other ERP components, such as the N2 (to be elicited with appropriate/non-equiprobable conflict/inhibitory control tasks), could prove crucial in understanding impairments in inhibitory control/impulsivity in drug addicted individuals. Also, future studies could employ other analyses (e.g., with LORETA) to refine the location of the neuroanatomical generators that are sensitive to reward salience; (4) performance variability was restricted (at ceiling) by the current simple task (chosen to sustain attention similarly in all three reward conditions). Tailoring the paradigm to observe accuracy differences (e.g., by decreasing ratio of "No-go" to "Go" trials) would allow for a more sensitive investigation of the ERP error-related signal changes as previously reported in alcoholism [166-167]; (5) future studies need to establish reliability of these results by increasing sample size and studying different subgroups within CUD (e.g., comparing current users vs. individuals with longer-term withdrawal/abstinence

periods or treatment-seekers). The impact of comorbid psychopathologies in drug addicted individuals also remains to be explored; although preliminary analyses indicated no significant differences in our main dependent variables between the seven CUD subjects with other comorbid disorders and the 11 CUD subjects without such comorbidity, this effect needs to be systematically studied in larger sample sizes.

In summary, the current results demonstrate compromised sensitivity to monetary reward (as compared to non-reward) at both the behavioral (RT) and neural (P300 at Pz, where P300 is most pronounced) levels in adults with current CUD as compared to age-matched healthy control subjects. This compromise was evident despite using a higher than usual monetary incentive ($50 vs. <$10 in many other studies) and although reward was contingent on behavior (and not a priori determined as in studies that use guessing tasks). This compromise was also evident despite faster P300 latency and enhanced self-reported interest in the task in the CUD as compared to the control subjects. Because we further controlled for all other stimulus properties (the 0¢ condition was identical to the 45¢ condition in all properties but the amount of expected reward), we cannot attribute this specific compromise to a generalized impairment in information processing. Instead, we attribute this compromise to specific deficits in the neural network that underlies reinforcement learning (i.e., sensitivity to changing reinforcement contingencies to control goal-directed behavior). A potential candidate encompasses the anterior prefrontal cortex that showed a similar compromise when cocaine addicted individuals were expecting monetary reward in our previous fMRI study [66].

Despite this specific compromise in responding to reward vs. non-reward as documented in the current study, contingency management (use of reinforcers) improves retention and associated abstinence outcomes in cocaine and methamphetamine abusers [67]. This indicates that abstinent drug abusers are able to respond to reinforcers in well-structured and constrained environments that also incorporate treatment programs. However, these behaviors may not generalize to the everyday environments of drug addicted individuals, where external or predictable reinforcement for advantageous behaviors are not readily available. It is therefore possible that alternative treatment modalities (e.g., targeting improvements in reinforcement learning, inhibitory control or advantageous decision-making in the absence of overt reward) may help minimize longer-term relapse in drug addiction.

Table 3.1. *Demographic Characteristics and Drug Use by Study Subjects*

	Cocaine (N=18)	**Comparison (N=18)**
Gender (male/female)	11/7	12/6
Ethnicity (African- American/Caucasian/Hispanic/Asian)	16/2/0/0	9/6/2/1
First language (English/other)	18/0	17/1
History of cigarette smoking (current or past/never)‡	15/3	4/14
Education (years)	13.4 (1.9)	13.8 (1.7)
Age (years)	43.8 (6.0)	39.9 (8.0)
Handedness: Laterality Quotient[168]	0.93 (0.1)	0.90 (0.2)
Socio-economic Status [169]	31.4 (12.7)	37.2 (11.5)
Nonverbal Intellectual Functioning[170]	9.6 (3.0)	10.8 (2.5)
Self-Reported State Depression[143] †	8.5 (6.7)	3.4 (4.3)
Monetary Gain on the Task ($)	48.0 (2.2)	48.1 (1.7)
Age at onset of cocaine use (years)	22.6 (6.0)	--
Duration of use (years)	18.5 (5.0)	--
Frequency of use (days/week) last 30 days	3.8 (2.0)	--
Frequency of use (days/week) last 12 months (N=17)	3.8 (2.2)	--
Current use in $ per use (min – max, median) (N=15)	20-360 (60)	--
Duration of current abstinence (days) (min – max, median)	0-4, 1.5	--
Length of longest abstinence (days) (min – max, median)	0-5110, 365	--
Total Score on the Cocaine Selective Severity Index	16.7 (11.0)	--
Severity of Dependence Scale (0-15) (N=17)	6.4 (3.3)	--
Cocaine Craving Questionnaire (0-45) (N=16)	17.8 (10.1)	--

† $t(34)=2.7$, $p<0.05$; ‡ $\chi^2(1)=13.5$, $p<0.0001$

Note: min is minimum; max is maximum. Values are frequencies for categorical variables or mean (standard deviation) for continuous variables; for group differences in the categorical variables, χ^2 was used, for the continuous variables independent t-tests were used.

Table 3.2. *The P300 Amplitude and Latency at Pz and Behavioral (reaction time, accuracy, and self-reported ratings) Dependent Variables for All Study Subjects as a Function of Group, Monetary Reward, and Trial Type ('Go' vs. 'No-Go').*

	Cocaine (N=18)			Comparison (N=18)		
	$0.00	**$0.01**	**$0.45**	**$0.00**	**$0.01**	**$0.45**
Go: amplitude (μV)	6.7 (4.0)	7.3 (4.0)	7.5 (4.0)	5.8 (4.2)	6.3 (4.0)	7.0 (3.4)
No-Go: amplitude (μV)	5.6 (3.6)	4.9 (2.8)	5.9 (2.8)	4.2 (2.7)	4.6 (2.7)	5.0 (3.3)
Go: latency (msec)	376.5 (63.5)	368.8 (63.9)	349.8 (47.0)	423.4 (62.5)	412.6 (52.7)	414.6 (64.4)
No-Go: latency (msec)	436.1 (80.5)	415.9 (85.4)	431.9 (85.9)	452.0 (76.0)	431.6 (69.6)	465.5 (68.0)
Reaction time (Go)	254.1 (47.7)	257.4 (41.8)	252.1 (44.5)	236.2 (40.4)	231.0 (34.8)	227.0 (39.6)
Percent correct (Go)	.94 (.05)	.94 (.04)	.93 (.08)	.92 (.08)	.93 (.06)	.92 (.06)
Percent correct (No-Go)	.996 (.01)	.96 (.004)	.99 (.02)	.997 (.007)	.96 (0.0)	.99 (.01)
Interest ratings	4.3 (2.5)	4.9 (2.0)	5.9 (1.5)	2.8 (2.0)	3.4 (1.6)	4.4 (1.7)
Excitement ratings	4.4 (2.1)	4.7 (2.0)	6.0 (1.5)	3.3 (2.1)	3.7 (1.8)	4.4 (1.8)
Frustration ratings	5.3 (2.1)	5.2 (2.0)	5.2 (2.4)	4.9 (1.9)	4.8 (2.0)	5.3 (1.9)

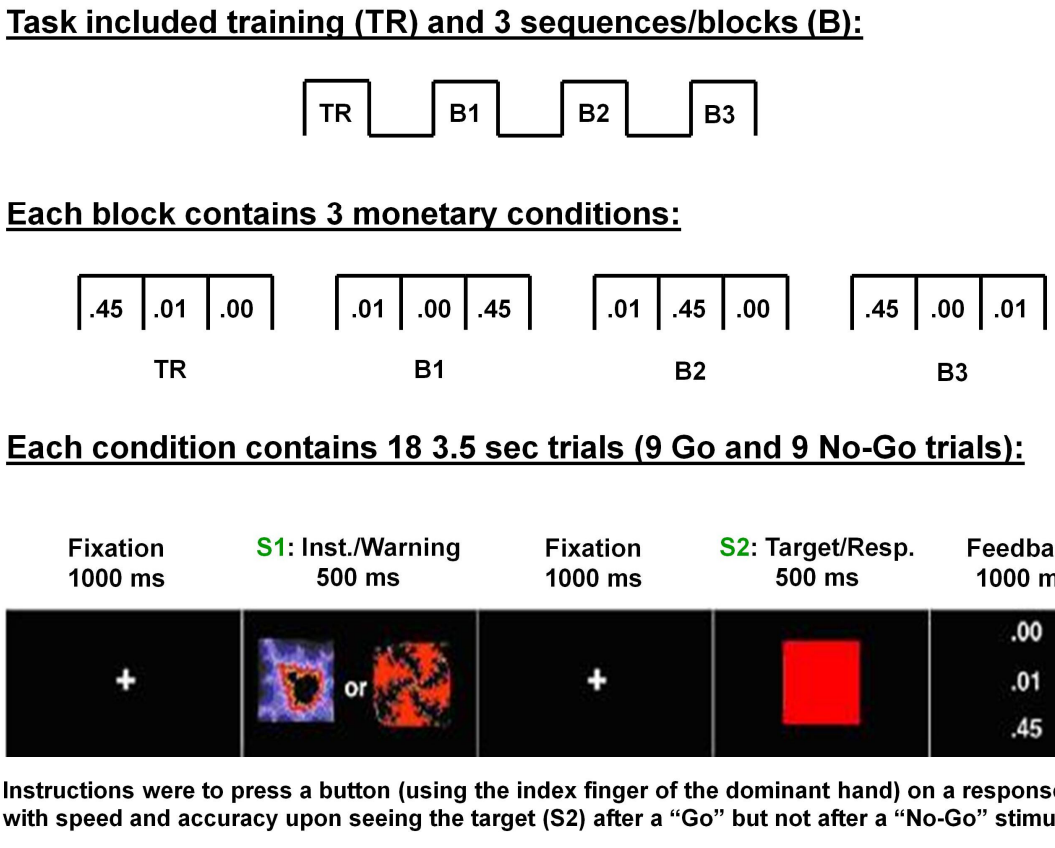

Figure 3.1: Experimental paradigm for the monetary incentive task. Overall design and experimental conditions are depicted at the top; at each condition onset (conditions were separated by 30 s), a 5 s screen (not depicted) displayed the monetary reward (45¢, 1¢, 0¢). Together with the feedback delivered at the end of each trial, this 5 s screen (similar in appearance to the feedback screen) guaranteed the subjects were continuously aware of the reward contingencies. Inst. is Instruction. Resp. is Response.

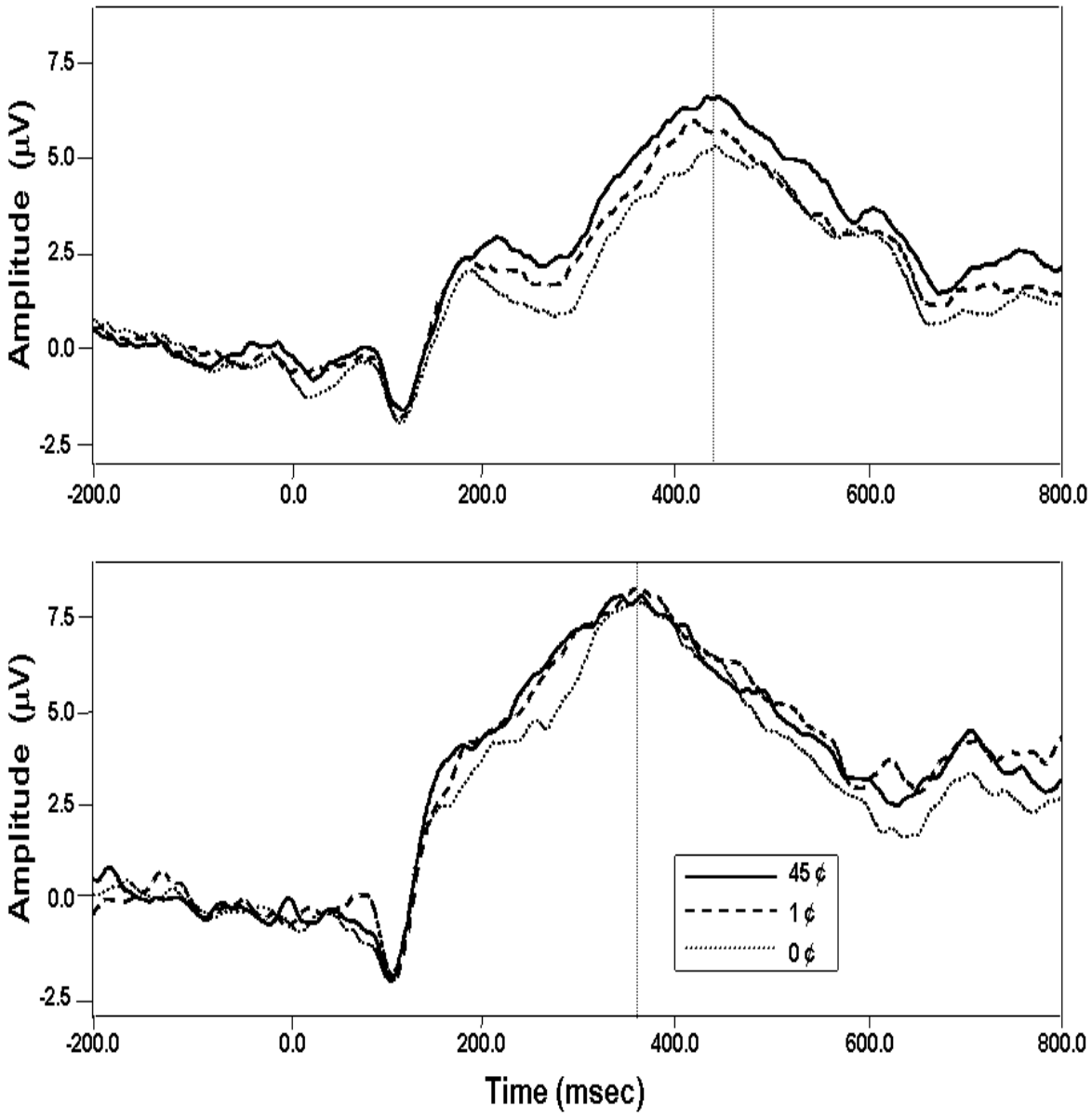

Figure 3.2. Grand averaged waveforms for control subjects (top) and individuals with current cocaine use disorders (bottom) reflecting 200 msec before to 800 msec after the target stimulus (S1) for each monetary reward condition (45¢, 1¢, 0¢) during the 'Go' trials (N=18 in each group).

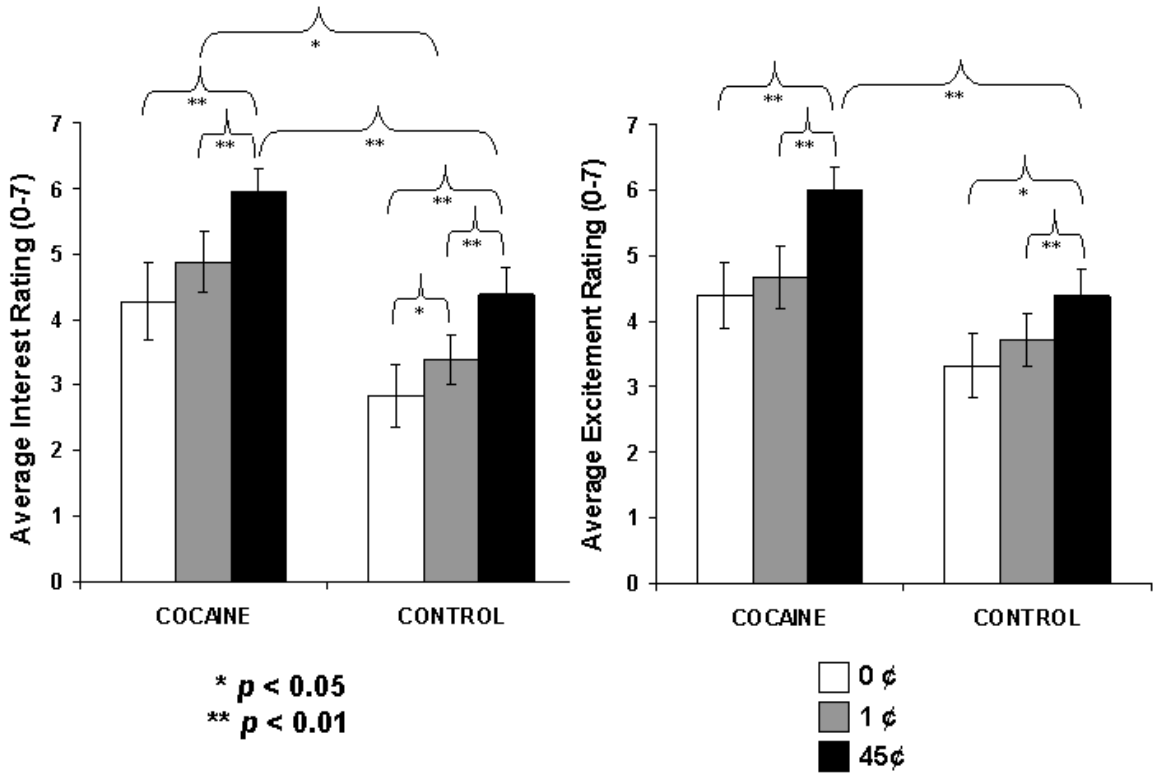

Figure 3.3. Average post-task subjective ratings for interest and excitement for control subjects and individuals with current cocaine use disorders as a function of monetary reward condition (45¢, 1¢, 0¢). Error bars represent standard error of the mean (N=18 in each group).

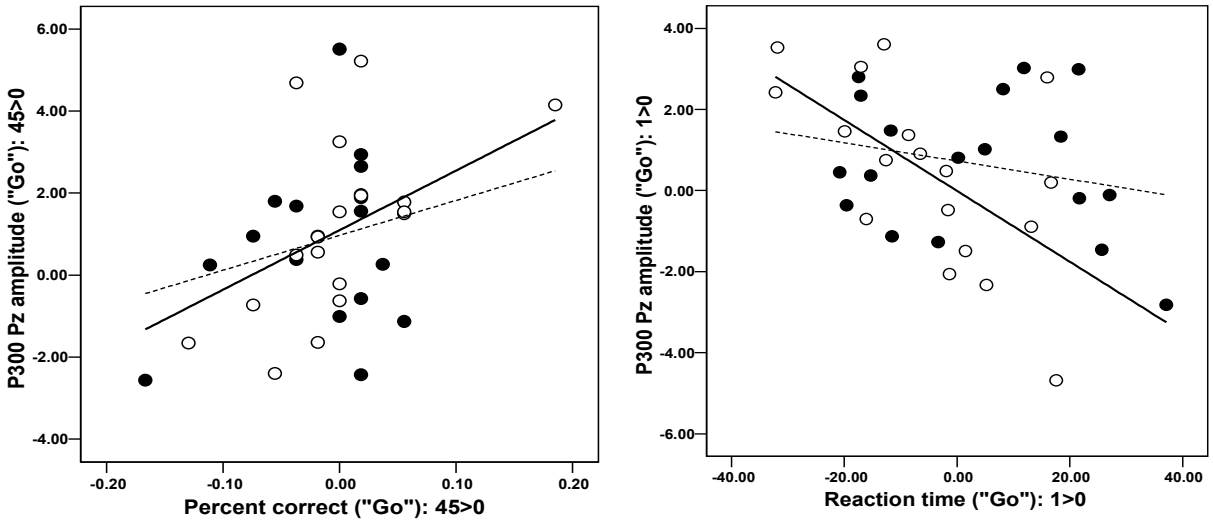

Figure 3.4. Correlations between the P300 and behavioral dependent variables. Left: positive correlation (R^2=.32, p<.01, regression line in bold; R^2=.23, p<.01 when one outlier is removed) between the P300 amplitude differential for the 45¢ minus 0¢ monetary conditions and the respective percent accuracy differential in healthy control subjects (white circles) but not individuals with current cocaine use disorders (black circles). Right: negative correlation (R^2=.36, p<.01, regression line in bold) between the P300 amplitude differential for the 1¢ minus 0¢ monetary conditions and the respective differential reaction time in healthy control subjects (white circles) but not individuals with current cocaine use disorders (black circles) (N=18 in each group).

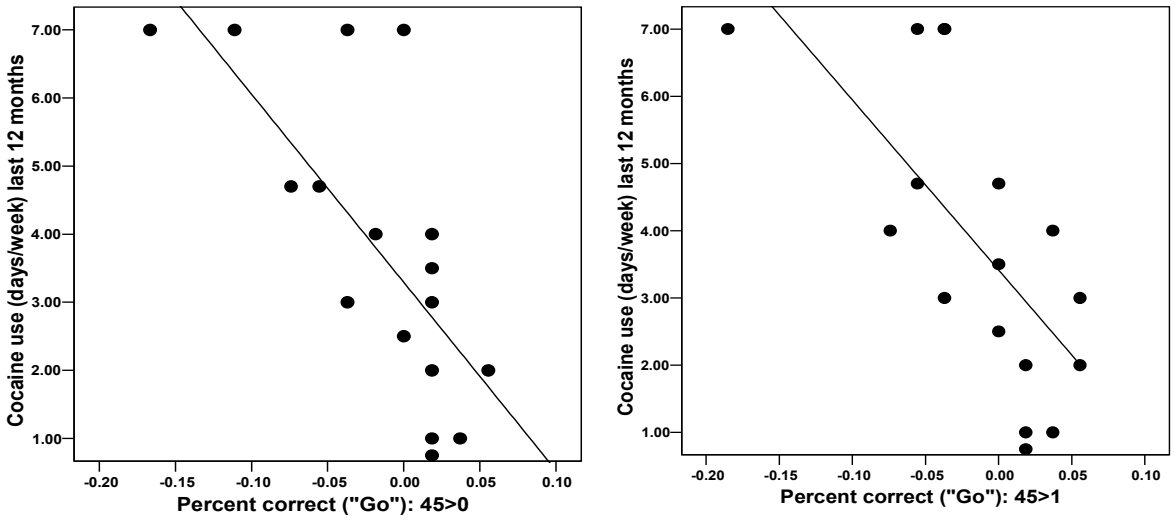

Figure 3.5. Correlations between accuracy differentials on the monetary incentive task and cocaine use. Left: negative correlation (R^2=.53, p<.01) between frequency of cocaine use in the last year and the differential accuracy for the 45¢ minus 0¢ monetary conditions in individuals with current cocaine use disorders (black circles). Right: negative correlation (R^2=.47, p<.01) between frequency of cocaine use in the last year and the differential accuracy for the 45¢ minus 1¢ monetary conditions in individuals with current cocaine use disorders (black circles) (N=18).

CHAPTER 4

(Submitted to Biological Psychology)

Title: Sensitivity to Monetary Reward is Most Severely Compromised in Recently Abstaining Cocaine Addicted Individuals: An ERP Study

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ABSTRACT

Recent studies suggest that drug addicted individuals have a dampened cortical response to *non*-drug rewards. For example, the P300, an event related potential (ERP) component sensitive to the incentive value of reinforcers, failed to show enhancement to monetary reward in individuals with current cocaine use disorder (CUD). However, it remains unclear whether recency of cocaine use impacts this impairment. Therefore, in the current study, recency of cocaine use was objectively determined by measuring cocaine in urine on study day. Thirty-five CUD [21 testing positive (CUD+) and 14 testing negative (CUD-) for cocaine in urine] and 23 matched healthy controls completed a sustained attention task with graded monetary incentives (0¢, 1¢ and 45¢). Unlike in healthy controls, in both CUD subgroups P300 amplitude was not modulated by the varying amounts of money; the CUD- showed the most severe impairment as documented by the lowest P300 amplitudes and task accuracy. In addition, while frequency of recent drug use was associated with *better* accuracy and higher P300 amplitudes, chronic drug use (lifetime duration of use) was associated with lower sensitivity to money. The current results extend our previous findings of decreased sustained sensitivity to monetary reward in CUD+ to CUD- (recently abstaining individuals), where level of impairment was most severe. Taken together with the correlations, the importance of these results is in supporting the self-medication hypothesis, where CUD may be self-administering cocaine to avoid or compensate for underlying cognitive and emotional difficulties albeit with a long-term detrimental effect on sensitivity to non-drug reward.

INTRODUCTION

(Edited to reduce redundancy)

Our previous ERP results corroborated prior reports of reduced P300 response in addicted individuals [62, 64], although null results in a similar population have also been reported [171-172].

One reason that may have contributed to these inconsistencies in the literature can be attributed to variability in recency of drug use. Drug use availability (and the perceived drug use opportunity) has been suggested to enhance cortical drug cue reactivity [81, 173]. It could also enhance cognitive function in addicted individuals. For example, we have recently reported that current users of cocaine show less impairment on neuropsychological tests of learning, memory and executive functioning than abstinent CUD [84], possibly consistent with the self-medication hypothesis, where repeated drug self-administration is posited to ameliorate emotional and cognitive deficits while escaping aversive withdrawal symptoms [82-83, 174]. Together, these studies suggest that abstinence from cocaine would be related to lower cortical response to reinforcement, although this has never been directly tested before.

In the current study we therefore measured P300 amplitude to monetary reward in abstinent CUD as compared to current CUD and matched controls. We hypothesized that while all CUD would show compromised P300 sensitivity to monetary reward, this compromise would be most severe in abstinent CUD. In addition to the P300, we explored an earlier fronto-central component, the P200a (150 – 280 msec post-stimulus) that has recently been described in the context of task relevance and motivational spillover [175-179], and the N200, another mid-latency ERP component (190 – 300 msec post-stimulus) that has been associated with biologically significant events [180] and stimulus novelty [181]. Analyses pertaining to these earlier components were exploratory.

METHODS

Participants

Thirty-five CUD and 23 healthy comparison subjects (all right-handed native English speakers) were recruited through advertisements in local newspapers and by word-of-mouth; one CUD was recruited from a treatment facility. Of these 58 subjects, 36 (18 CUD and 18 controls) were included in our previous report [65], representing an increase of more than 50% in the

population of the CUD recruited for the specific goals of the current study. Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board. *Other details regarding subject recruitment and screening are outlined in Appendix A.*

In addition to the self-reported cocaine use history, the recency of cocaine use was indexed objectively by cocaine urine screening conducted on study day using the triage urine panel for drugs of abuse (Biopsych^{TM}, detects drug use within 72 hours of study). This test results divided our CUD sample into two subgroups: those who tested positive for cocaine (current users, CUD+: N=21) and those who tested negative for cocaine (abstinent users, CUD-: N=14) on study day.

Reward Processing Task

*[Same as the study in Appendix A (**Figure 3.1** of Chapter 3)]*

Psychophysiological Recording and Behavioral Measures

(Same as the study in Appendix A)

Analyses

Event-Related Potentials and Data Reduction.

Given the very pronounced nature of the P200a and N200 peaks, a base-to-peak algorithm was employed to determine the most positive and negative amplitudes in the 150 msec to 300 msec post-stimulus time window with respect to the pre-stimulus baseline. Consistent with other studies, considering their fronto-central scalp topography, both peaks were scored at FZ and CZ electrodes [178, 182-184]. However, P300, being seemingly contaminated by other slow positive potentials (Figure 4.1A), was isolated using temporal principal components analysis (PCA) [Matlab (Mathworks Inc., Natick, MA) based ERP PCA Toolbox (version 1.35)], reported here for the first time. Temporal PCA assesses variance across time to maximize the separation of overlapping ERP components [185]. We used all time points as variables and all subjects, monetary conditions, and recording sites as observations. Based on the resulting Scree plot, temporal factors were extracted for Kaiser normalization [185] and Promax rotation [186]. We identified the first of these factors (explaining 19.2% of the total variance) as the P300 waveform, based on both its time-course [occurring 250-600 msec after S1 [57-58]] and scalp

topography [lowest amplitude in frontal electrodes (e.g., FZ), and highest in the parietal electrodes (PZ), [48]]. The current analyses of P300 were restricted to the PZ, which showed the most pronounced P300 response to money in previous studies [53, 55, 65, 187] as also confirmed by quantitative methods [e.g., spatial PCA [188-189]].

The P200a and N200 amplitudes were analyzed using a 2 [Electrodes (FZ and CZ] × 3 [*Money* (45¢, 1¢ and 0¢)] × 3 [*Group* (Controls, CUD+ and CUD-)] repeated measures analysis of variance (ANOVA), while the PZ P300 amplitudes from the first PCA component were analyzed using a 3 [*Money* (45¢, 1¢ and 0¢)] × 3 [*Group* (Controls, CUD+ and CUD-)] repeated measures ANOVA.

Behavior: Reaction Time and Accuracy. Similarly to the P300 analyses, RT of all correct trials and percentage of correct responses (accuracy) were analyzed using 3 × 3 mixed ANOVAs.

In all analyses, the Greenhouse-Geisser correction was applied for cases where Mauchly's test showed the assumption of sphericity was not met. Significant main effects and interactions were followed with paired (within group) or independent (between group) t-tests for ERP components and RT (which were normally distributed) and with the equivalent non-parametric tests (paired: Wilcoxon; or independent: Mann-Whitney U) for accuracy (not normally distributed). Cigarette smoking history, which differed significantly between the groups (Table 4.1), was covaried in subsequent ANCOVAs if it was significantly related to our dependent variables (ERP and behavioral variables). To test our *a priori* hypotheses (most severe impairment in P300 sensitivity to magnitude of monetary reward in CUD- compared to CUD+ and similar pattern of results for all CUD compared to controls), planned between- and within-group comparisons were conducted for P300 amplitude, even when the main effects or interactions were not significant. This practice, of reporting results of post-hoc tests even when main effects are not significant is recommended in case of strong a priori hypotheses (e.g., to avoid Type II error) [190], and has been widely used especially in studies of populations (e.g., with select psychopathologies) that are difficult to recruit/engage [191-192]. Note that, given our prior ERP (Goldstein et al., 2008) and fMRI [193] results, task accuracy and RT were similarly treated. All other effects were only followed if main or interaction effects were significant.

Correlations. Correlations between ERP amplitudes and all behavioral variables were examined separately for all three monetary conditions and also for differential scores (45¢ minus 0¢, 45¢

minus 1¢, and 1¢ minus 0¢, to specifically target sensitivity to monetary reward controlling for all other effects). These correlations were calculated for all subjects, and separately per study group (controls, all CUD, and both CUD subgroups separately). Finally, we conducted correlations between all our dependent measures (including the differential scores for all ERP amplitudes and behavioral variables) with the drug use measures listed in Table 4.1; these correlations were examined across all CUD and also for each CUD subgroup. To protect against Type I error, a significance level of $p<0.01$ was required for all correlations, while $p<0.05$ was reported as trend. In all correlation analyses, cigarette smoking history was controlled through partial correlations when it was associated with our dependent variables [194].

RESULTS

Cigarette smoking history was not significantly associated ($p > 0.1$) with any of our task-specific dependent variables (ERP or behavioral, absolute or differential scores) and therefore will not receive further consideration in Results.

ERP Results (Table 4.2 and Figure 4.1B)

a. P200a Results:

The mixed ANOVA did not reveal significant group [$F(2,55)=2.0$, $p=0.14$] and electrode [$F(1,55)=1.9$, $p=0.18$] main effects, although there was a significant money main effect [$F(2,54)=5.85$, $p=0.005$]. Post-hoc paired t-tests showed this money main effect to be driven by significantly higher P200 amplitude for 45¢ condition as compared to 0¢ condition across all subjects [FZ: $t(57)=2.8$, $p=0.007$; CZ: $t(57)=3.5$, $p=0.001$]. None of the interaction effects reached significance ($p>0.1$).

b. N200 Results:

All three main effects were significant: group [$F(2,54)=3.4$, $p=0.04$], money [$F(2,54)=4.4$, $p=0.017$], , and electrode [$F(1,55)=23.5$, $p<0.0001$]. None of the interaction effects reached significance ($p>0.1$). Post-hoc t-tests revealed these main effects to be driven, respectively, by more negative N200 waveforms in controls compared to CUD+ ($p=0.046$), non-reward compared to reward [0¢ > 45¢: $p=0.08$; 0¢ > 1¢: $p=0.02$], and at FZ compared to CZ ($p<0.0001$) across all groups and money conditions. Thus, N200 was greatest in control subjects and in the non-reward task condition at FZ.

c. P300 Results:

Results of the 3 × 3 mixed ANOVA did not reveal a significant group main effect [$F(2,55)=1.93$, $p>0.1$], although there was a trend for a money main effect [$F(2,54)=2.73$, $p<0.1$]. Although the money by group interaction was not significant [$F(4,110)=0.95$, $p>0.1$], to test for our a priori hypotheses, planned follow-up between-group analyses showed that CUD- exhibited a blunted response in all reward task conditions when compared to the other two study groups: compared with controls for 45¢ [$t(34)=2.1$, $p=0.05$; and a similar trend for the 1¢ condition: $t(33.3)=1.9$, $p<0.1$] and compared with CUD+ for 1¢ [$t(32)=2.1$, $p=0.05$; with a similar trend in the other two task conditions [$t(33)<1.9$, $p<0.1$]. The CUD+ and controls did not differ in any of the monetary conditions [$t(42)>0.2$, $p>0.5$]. Planned within-group comparisons revealed differential responsiveness to money in controls [45¢=1¢>0¢: paired $t(22)<-2.50$, $p<0.02$] but not in CUD [CUD+: $t(20)<0.40$, $p>0.2$; CUD-: $t(13)<-0.14$, $p>0.8$; combined CUD: $t(34)<0.19$, $p>0.3$]. Thus, consistent with our first *a priori* hypothesis, the P300 showed sensitivity to money in the controls but not in CUD. Consistent with our second *a priori* hypothesis, P300 amplitudes were lowest in the CUD- as directly compared to both controls and CUD+.

Behavioral Results (Table 4.2)

Accuracy: Results of the 3 × 3 mixed ANOVA revealed a group main effect [Controls=CUD+>CUD-: $F(2,55)=5.9$, $p=0.005$], such that CUD- were significantly less accurate than both controls and CUD+. Neither the main effect of money [$F(2,54)=0.7$, $p>0.1$] nor the money by group interaction [$F(4,110)=0.7$, $p>0.1$] reached significance. Planned non-parametric paired comparisons did not reveal any within-group differences [$Z<-0.13$, $p>0.1$], while Mann-Whitney U tests showed that the group main effect was driven by the lowest accuracy in the CUD- compared to CUD+ in the 0¢ condition [$Z=-2.3$, $p=0.02$; with the same trend observed during the 1¢ condition, $Z=-1.9$, $p<0.1$; given this preponderance of group differences in accuracy in the 0¢ and 1¢ conditions, and not in the 45¢ condition, lack of group differences in task earnings was not unexpected (Controls: \$48.50 ± 1.33; CUD+: \$47.31 ± 3.02; CUD-: \$48.71 ± 1.07; $F(2,54)=2.52$, $p=0.09$)].

Reaction time: The 3 × 3 mixed ANOVA did not reveal a significant group main effect [$F(2,55)=0.7$, $p>0.1$], but did reveal a significant money main effect such that responses were fastest for the highest monetary condition across all study subjects [45¢<0¢: $F(2,54)=4.9$,

p=0.01]. Although the money by group interaction was not significant [F(4,110)=0.6, p>0.1], planned within-subject comparisons revealed that the monetary main effect was driven by the CUD+ [45¢<0¢: t(20)=3.2, p=0.004; with a similar trend for 45<1¢: t(20)=1.9, p<0.1], while the parallel comparisons were not significant in controls [t(22)<1.2, p>0.1] or CUD- [t(13)<1.6, p>0.1]. Between-group comparisons did not reveal any significant differences [t(35)<1.2, p>0.1].

Post task rating scales

Upon task completion, participants were asked to rate their interest (ranged from 0-7: boring to interesting, respectively), excitement (0-7: dull to exciting) and frustration (0-7: extremely frustrating to not at all frustrating) for all three monetary conditions. Each rating scale was analyzed with a 3 (Money) × 3 (Group) mixed ANOVA, followed by non-parametric t-tests.

The mixed ANOVA for interest ratings did not show a group main effect [F(2,54)=1.3, p>0.1], while the money main effect reached significance [45¢>1¢=0¢; F(2,108)=26.4, p<0.01]. The money by group interaction revealed a trend [F(4,108)=2.3, p<0.1], driven by group differences between CUD+ and controls in rating 45¢ [CUD+>controls, Z=-2.2, p<0.05] but not in rating the 1¢ or 0¢ conditions [Z<-0.9, p>0.1] (Figure 4.2). There were no differences between CUD- and the other two groups although CUD- was the only group where the difference between the 1¢ and 0¢ conditions did not reach significance.

Similar to interest ratings, the mixed ANOVA for excitement ratings did not reveal a group main effect [F(2,54)=1.9, p>0.1], while the money main effect reached significance [45¢>1¢=0¢; F(2,108)=31.5, p<0.01]. The money by group interaction revealed a trend [F(4,108)=2.1, p<0.1], again driven by group differences between CUD+ and controls in rating 45¢ [CUD+>controls, Z=-2.2, p<0.05] but not in rating the 1¢ and 0¢ conditions [Z<-1.0, p>0.1] (Figure 4.2). There were no differences between CUD- and the other two groups. Here, differences between the 1¢ and 0¢ conditions did not reach significance in any of the study groups.

The mixed ANOVA for frustration ratings did not reveal a group main effect [F(2,54)=1.9, p>0.1], while the money main effect again reached significance [45¢>1¢=0¢; F(2,108)=9.5, p<0.01]. The money by group interaction did not reach significance [F(4,108)=0.4, p>0.1]. Planned non-parametric tests did not reveal significant results.

Thus, all groups rated the 45¢ condition as more interesting and exciting and less frustrating than either the 1¢ or 0¢ conditions. In these ratings, the CUD+ subgroup also rated the 45¢ condition as more interesting and exciting than controls.

Correlation analyses (Spearman) revealed a positive association between the frustration ratings and the P300 amplitudes during the 0¢ condition [$r=0.37$, $p=0.005$], with similar trends emerging during the 1¢ condition [$r>0.2$, $p<0.05$], as evident across all study subjects. That is, the lower the frustration (high rating scores) for the no- or low-monetary conditions, the higher the P300 amplitude for these conditions.

Within the subgroups, the CUD+ showed a significant positive correlation between severity of cocaine use (determined by the severity of dependence scale) and interest ratings during the 0¢ condition [$r=0.6$, $p=0.005$], with a similar trend during the 1¢ condition [$r=0.5$, $p<0.05$]; similar trends were also revealed for the excitement ratings, again in the 0¢ and 1¢ conditions [$r>0.49$, $p<0.05$]. These associations suggest that the more severe the self-reported cocaine dependence, the higher the interest and excitement ratings in CUD+ for the no- or low-monetary reward conditions only.

In CUD-, there were positive correlations between duration of current abstinence (days) and frustration ratings during the 0¢ condition [$r=0.71$, $p=0.005$] and 1¢ condition [$r=0.67$, $p=0.008$], with a similar trend in the 45¢ condition [$r=0.62$, $p<0.05$], suggesting that longer abstinence is associated with lower self-reported frustration.

P300, Behavior and Drug Use Correlations

Across all CUD, there was a significant positive correlation between frequency of maximum cocaine use (days per week during the self-reported period of maximum cocaine use) with task accuracy during the 1¢ condition [$r=0.52$, $p=0.002$] (Figure 4.3A), with similar trends in the other two monetary conditions [$r>0.35$, $p<0.05$], as driven by the CUD+ group [$r>0.53$, $p<0.05$; in CUD- $r<0.40$, $p>0.1$). A similar correlation was observed between frequency of recent cocaine use (days per week in past 12 months) with task accuracy during the same monetary condition [$r=0.45$, $p=0.006$] (Figure 4.3B), again driven by CUD+ [$r=0.45$, $p=0.04$; in CUD- $r=0.12$, $p>0.1$]. In contrast, across all CUD, duration of cocaine use (years) was negatively correlated with a task accuracy differential (45¢>1¢: $r=-0.50$, $p=0.002$; again driven by CUD+: $r=-0.44$, $p=0.05$), such that the shorter the cocaine use, the better the accuracy response to high vs. low money (Figure 4.4). Finally, in CUD- only, a significant positive correlation was

observed between frequency of recent cocaine use (days of cocaine use per week in past 30 days) and P300 amplitude again during the 1¢ condition [r=0.75, p=0.002; in CUD+ r=-0.30, p>0.1] (Figure 4.3C). Taken together, these correlations suggest that the more frequent the acute drug use, the *better* the task accuracy in the CUD+ and the *higher* the P300 amplitudes in the CUD-, as evident especially during the lowest monetary reward available (this is also the only condition associated with an actual coin). In contrast, chronic drug use was associated with lower behavioral accuracy to money across all CUD.

DISCUSSION

In the current study we tested for the first time the impact of recency of drug use/abstinence in cocaine addicted individuals on cortical reward processing as measured with the P300, an ERP component reliably modulated by reward magnitude in healthy individuals [51-53] . For this purpose, we used a sustained (and predictable) monetary reward and compared its impact on the P300 between three subject groups: healthy controls, cocaine addicted individuals who tested positive for cocaine in urine (current users) and those who tested negative (i.e., abstinent); drug urine status, an objective measure of recency of cocaine use, was used as an indirect assessment of the self-medication hypothesis [82, 174]. Earlier ERP components (P200a and N200) were used in exploratory analyses.

Extending results of our previous study that was conducted in controls and CUD+ only [65], P300 sensitivity to monetary reward as directly compared to non-reward (45¢ > 0¢) was not observed in CUD- or CUD+ (or when combining them to a single large CUD group) while such effect was observed in the controls, explaining the lack of a money main effect in these results. These results in controls are consistent with results in healthy individuals from other laboratories [51-52, 55]. In the current larger CUD+ sample, this P300 compromised response to money is all the more striking given these individuals' faster RT and increased self-reported interest and excitement during the reward versus non-reward trials. These differential ERP-RT results may reflect a brain-behavior dissociation or asynchrony, as we have previously suggested [65]. Note that similar neural-behavioral dissociations have also been reported in other populations of substance abusers [e.g., smokers [195]] as potentially associated with orbitofrontal cortical damage [196]. Together, these results do not fully support the 'motivational spillover' effect [197].

Consistent with our second *a priori* hypothesis, severity of impairment (in P300 amplitudes and task accuracy) was most pronounced in the CUD- compared to CUD+ and control subjects (this differential pattern in the CUD subgroups explains lack of a money by group interaction in these results). That is, deficits were most pronounced in the addicted individuals with the *least* frequent recent cocaine use and a relatively *longer* abstinence. Note that these results cannot be directly attributed to the effects of withdrawal given that the CUD subgroups did not differ in these symptoms as measured by the cocaine selective severity assessment scale (Table 4.1); the cognitive signs and symptoms of withdrawal remain to be fully quantified using more appropriate measures. These results are generally consistent with previous studies where abstinent CUD (6 – 24 days of complete abstinence) showed decreased P300 amplitudes in response to auditory oddball paradigms even when self-reported signs of withdrawal were minimal [60, 64]; the current study for the first time extend these results to monetary reward, a secondary generalizable reinforcer, providing important evidence for a deficient response to a socially acquired and abstract reward despite its strong motivational and arousal value (i.e., association with drug procurement).

Taken together, the results in CUD-, and the RT results in the CUD+, are consistent with cocaine's neurocognitive enhancing effects [198], providing support to the self-medication hypothesis, where drug abusers are postulated to use their preferred drug for the relief of negative symptoms such as anhedonia, boredom susceptibility, low self-esteem [82], including avoidance of withdrawal symptoms [83], or underlying cognitive deficits [84]. The *positive* correlations between P300 and frequency of recent cocaine use in the CUD-, and similar correlations with task accuracy driven by the CUD+, provide further support for the self-medication hypothesis. The negative correlation between lifetime duration of cocaine use and sensitivity to monetary reward (as measured by task accuracy differential), however, provides a reminder that acute drug self-administration has a detrimental long-term effect, calling for the development of less harmful interventions to ameliorate underlying cognitive and emotional dysfunction in addiction. In considering alternative explanations of results in the CUD, one could invoke drug use expectation [173] and hypersensitivity to reward [199] especially as related to RT and ratings in the CUD+, not mutually exclusive with the self-medication hypothesis and not fully congruent with the P300 results.

Both earlier ERP components, the P200a and N200, showed monetary modulation across all study subjects. The P200a has been implicated in heightened attention to relevant cues [200] including reward-related stimuli [178, 201]. Following earlier speculations that the P200a represents a necessary (although not sufficient) step before a P300 can be elicited [202], results suggest that early (as compared to more sustained) processing of money (and potentially of other motivational stimuli) may not be impacted in CUD (indeed, in contrast to the P300, a direct 45¢ vs. 0¢ P200a contrast was significant in CUD, $p<0.05$). The N200 revealed significantly higher negativity for the non-reward (0¢) as compared to both reward conditions (1¢ and 45¢), in addition showing lowest amplitudes in the CUD+ (as compared to controls). Given earlier reports linking the N200 with discrimination of negatively emotional stimuli [180, 203-204], these results may be driven by negative arousal, most pronounced during the no reward task condition and in the current users. An alternative explanation invokes role of the N200 in indexing stimulus novelty arising from deviation from a predominant stimulus category [181], with non-reward reflecting a deviation from the other reward trials. The attenuated N200 response in CUD+ may thus reflect higher response uncertainty and false-alarm rates [205]. However, there were no differences between CUD+ and controls in task accuracy, possibly due to task ceiling effects. Therefore, these intriguing results warrant a follow-up study using tailored tasks to specifically investigate medial frontal negativity and error related negativity ERP components, the former implicated in processing external evaluative feedback/utility information including losses [206-207] and the latter associated with the evaluation of performance along a correct-error dimension [179, 208-210].

We recognize the following limitations in the present report: (1) the blocked nature of the experimental design may have introduced habituation effects that need to be studied separately; (2) increasing sample size especially in the CUD- subgroup would allow examination of generalizability of results to longer abstinence periods; and (3) to more reliably test the self-medication hypothesis, the cognitive and emotional deficits medicated by cocaine remain to be measured prior to initiation of cocaine use (i.e., in a longitudinal design). Future directions are therefore to (1) compare current results with longitudinal or protracted abstinence studies using test-retest within-subject designs (such that one can study the same individual for impact of current use vs. abstinence); (2) compare additional or more disparate reward conditions (e.g., $2 vs. $1 vs. 10¢) and also add monetary loss [55]; (3) employ other analyses (e.g., LORETA) to

refine the location of the neuroanatomical generators that are sensitive to reward salience; and (4) investigate the possibility of a reversal (or amelioration) of the reported deficits in the CUD- by administering a dopamine agonist (e.g., methylphenidate) or other (e.g., cognitive-behavioral) interventions.

In summary, the current results for the first time demonstrate that the more severe impairment in reward sensitivity characterizes CUD with *less* recent cocaine use/*longer* short-term abstinence, while corroborating our previous results showing decreased neural sensitivity to sustained monetary reward in a larger group of CUD (CUD+ and CUD- combined) as compared to healthy controls. Collectively, these results support the self-medication hypothesis where CUD may be acutely using cocaine to temporarily normalize underlying cognitive and emotional disruptions, albeit at the expense of longer-term detrimental impact on sensitivity to non-drug reward. These results emphasize the importance of developing treatment modalities, including pharmacological interventions, which would target improvements in neuropsychological function without reducing sensitivity to non-drug reward.

Table 4.1: *Demographics and drug use-related measures of all study subjects*

	Test (χ^2, F, or Z)	Control (N = 23)	CUD+ (N = 21)	CUD- (N = 14)
Demographics				
Gender: Male / Female	1.0	15 / 8	16 / 5	11 / 3
Race: African-American / Other	6.3	13 / 10	18 / 3	13 / 1
Age (years)	1.4	40.7 ± 7.0	43.1 ± 6.1	43.9 ± 5.5
Education (years)	2.9	13.9 ± 1.9	13.0 ± 1.7	12.5 ± 2.1
Non-Verbal IQ: Wechsler Abbreviated Scale of Intelligence : Matrix Reasoning Scale [211]	1.9	10.8 ± 2.6	9.5 ± 3.3	11.3 ± 2.6
Depression: Beck Depression Inventory II [143]	1.4	3.7 ± 4.4	5.7 ± 4.0	4.0 ± 4.0
Socioeconomic Status: Hollingshead Index	2.8	35.5 ± 14.6	31.5 ± 11.3	25.4 ± 10.4
Drug Use				
Cigarette Smokers (current or past / nonsmokers)	26.5†	6 / 17	18 / 3	12 / 2
Daily cigarettes (current smokers: N = 3/17/10)	0.4	6.0 ± 7.4	8.4 ± 7.4	6.8 ± 5.0
Age of onset of cocaine (years)	-0.4	--	24.2 ± 5.9	24.1 ± 7.3
Duration of use of cocaine (years)	-0.5	--	16.8 ± 6.2	16.1 ± 6.3
Duration of current abstinence (days)	-3.8†	--	1.9 ± 1.6	7.2 ± 5.6
Cocaine use during last 30 days: Days/week	-3.1†	--	4.3 ± 2.1	2.0 ± 1.7
Cocaine use during last 12 months: Days/week	-2.4*	--	4.3 ± 2.3	2.4 ± 2.0
Maximum cocaine use (Days/week)	-0.6	--	5.9 ± 1.6	5.3 ± 2.5
Total score on the Cocaine Selective Severity Assessment Scale (measure of withdrawal symptoms) (0-126) [147]	-1.1	--	16.7 ± 10.2	13.1 ± 9.5
Severity of Dependence Scale (0-15) [149]	-1.2	--	6.7 ± 2.9	5.4 ± 4.3
Cocaine Craving Questionnaire (0-45) [212]	-2.4*	--	21.5 ± 10.9	11.9 ± 9.0

*p<.05; †p<.01;
Race: Other (Caucasian / Hispanic / Asian);
χ^2 tests were used for categorical variables; Mann-Whitney U for all drug-related variables (continuous non-normally distributed variables) and ANOVAs for all comparisons between the three groups;
Values are frequencies or means ± standard deviation (SD).

Table 4.2: *The P200a, N200, P300 Amplitudes and Behavioral (reaction time and accuracy) Dependent Variables for all Study Subjects as a Function of Group and Monetary Reward.*

		P200a (µV)		N200 (µV)		P300 (µV)	Reaction Time (msec)	Accuracy (%)
		FZ	**CZ**	**FZ**	**CZ**	**PZ**		
Control (N=23)	**$0.00**	7.08 (2.71)	7.16 (2.42)	-3.41 (3.42)	-2.76 (3.76)	4.91(1.36)	241.4 (21.8)	93.1(5.8)
	$0.01	7.23 (2.83)	7.43 (2.66)	-3.28 (3.94)	-2.18 (4.40)	5.93 (1.58)	238.1 (20.2)	92.8 (6.3)
	$0.45	7.89 (3.01)	8.39 (2.77)	-3.46 (3.95)	-1.96 (4.36)	6.15 (1.62)	237.3 (22.6)	93.4 (5.6)
CUD+ (N=21)	**$0.00**	8.57 (3.80)	8.56 (3.42)	-1.50 (4.20)	0.28 (3.59)	5.71 (1.86)	235.2 (16.0)	94.7 (11.1)
	$0.01	9.54 (3.62)	9.36 (2.93)	-0.72 (4.29)	0.67 (3.54)	6.15 (1.60)	232.8 (14.6)	95.5 (6.7)
	$0.45	9.20 (3.70)	9.17 (3.48)	-0.55 (4.12)	1.02 (3.51)	5.93 (1.72)	227.1 (15.0)	95.3 (5.5)
CUD- (N=14)	**$0.00**	7.72 (2.74)	6.72 (2.46)	-3.50 (3.46)	-2.29 (3.28)	3.67(1.28)	225.9 (18.0)	87.5 (12.4)
	$0.01	8.08 (3.33)	7.07 (2.79)	-2.50 (3.95)	-0.99 (3.49)	3.82 (1.69)	219.5 (21.2)	85.6 (11.1)
	$0.45	9.38 (3.94)	7.63 (3.03)	-2.92 (3.28)	-1.83 (3.81)	3.93 (1.63)	221.4 (18.6)	87.4 (9.7)

Mean (SD)

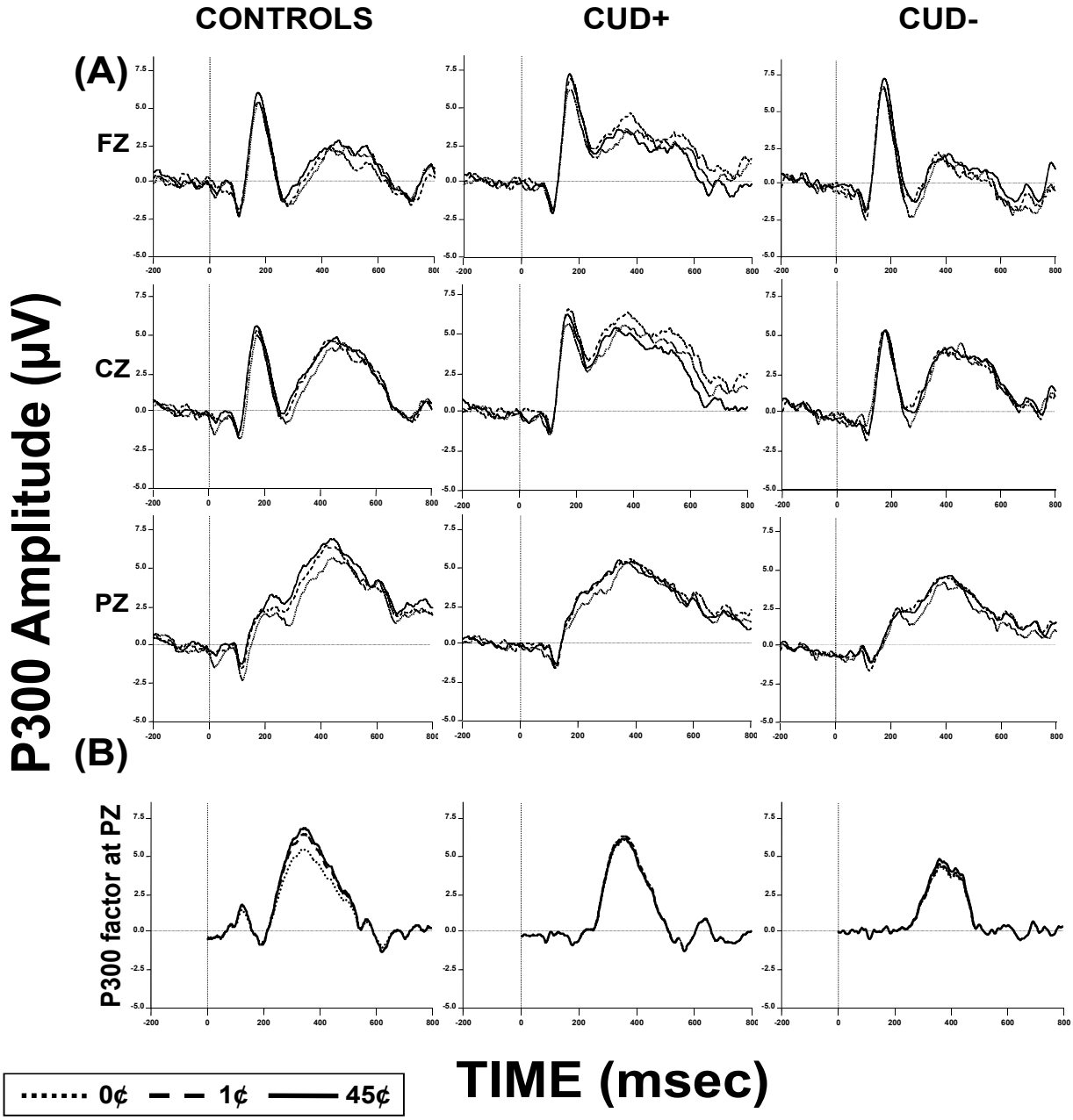

Figure 4.1: (A) shows grand averaged ERP waveforms for control subjects (left; N=23), CUD+ (center; N=21) and CUD- (right; N=14) reflecting 0 msec to 1000 msec after the target stimulus (S1) for each monetary reward condition (45¢, 1¢, 0¢) during the 'Go' trials. (B) shows P300 factor isolated by PCA for the three study groups for each monetary reward condition (45¢, 1¢, 0¢).

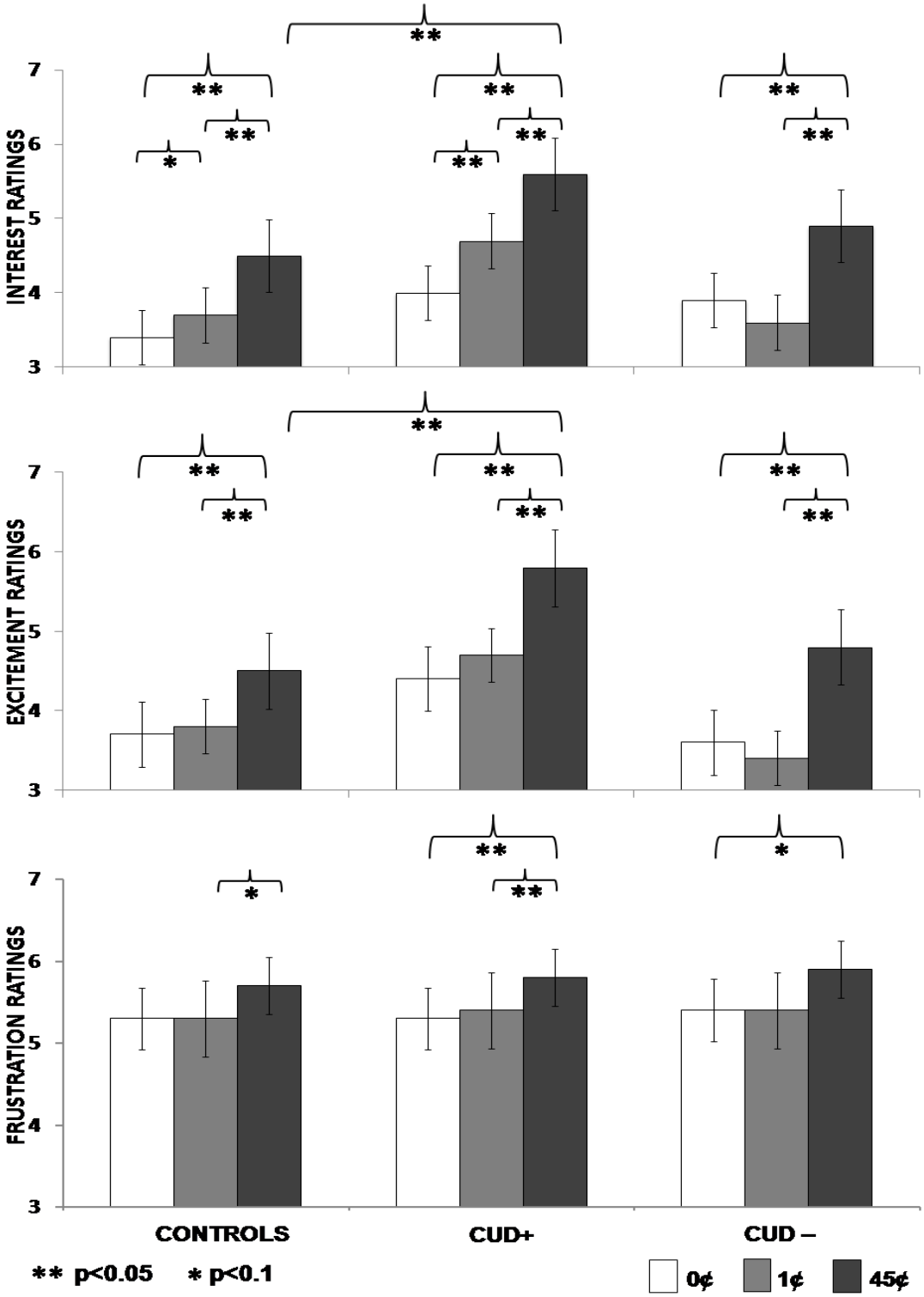

Figure 4.2: *Post Task Ratings across all monetary conditions and all groups.*

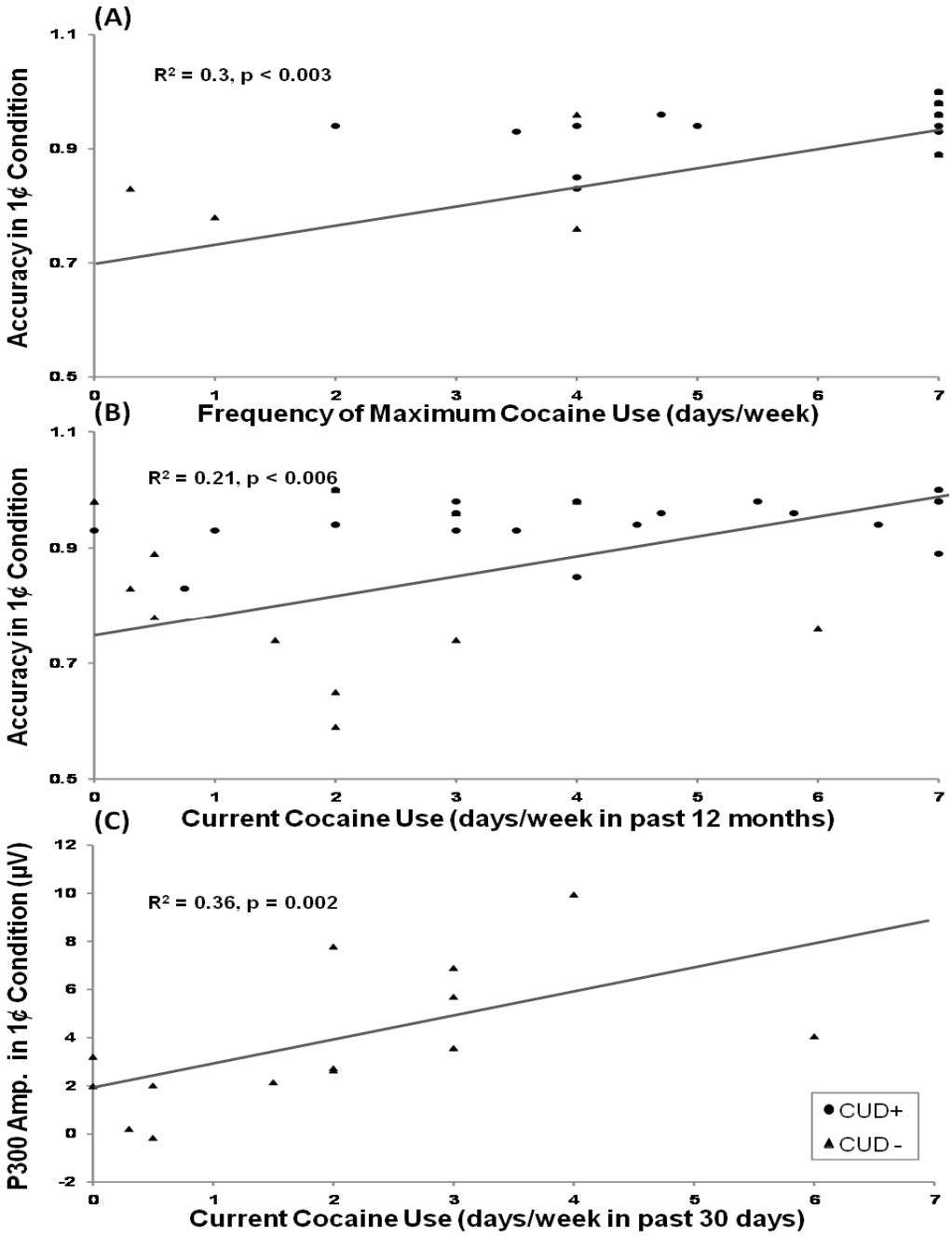

Figure 4.3: Correlation between frequency of cocaine use and task-related variables. (A) and (B) show correlation between task accuracy for the 1¢ conditions and frequency (days per week) of maximum cocaine use and cocaine use in past 12 months in CUD (CUD+: •; CUD-: ▲), respectively, while (C) shows correlation between the P300 amplitude for the 1¢ conditions and frequency of recent (in last 30 days) cocaine use in CUD- (▲).

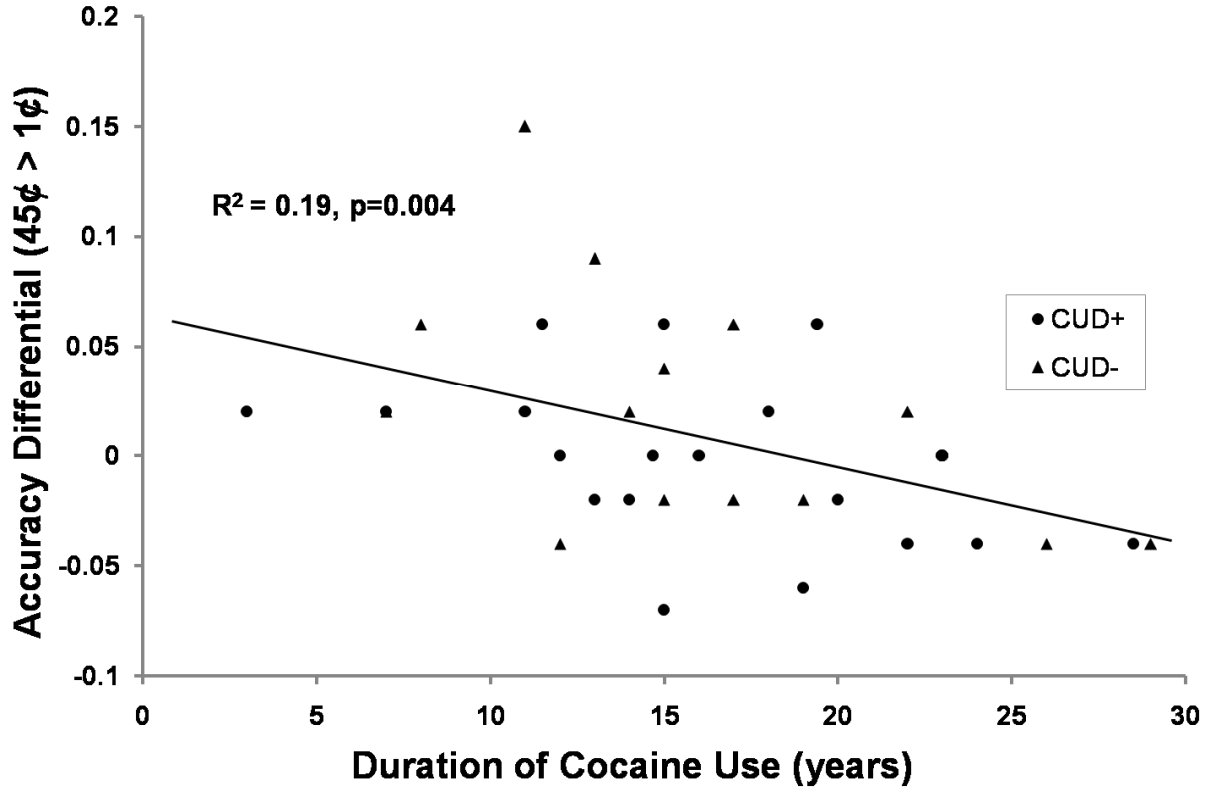

Figure 4.4: Correlation between accuracy differential (45¢ > 1¢) and duration of cocaine use (years) in CUD (CUD+: •; CUD-: ▲).

CHAPTER 5

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Title: Motivated Attention to Cocaine and Emotional Cues in Abstinent and Current Cocaine Users: An ERP Study

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ABSTRACT

Background: Event-related potentials (ERPs) are a direct measure of neural activity and are ideally suited to study the time-course of attentional engagement with emotional and drug-related stimuli in addiction. In particular, the late positive potential (LPP) appears enhanced following cocaine-related compared to neutral stimuli in individuals with cocaine use disorders (CUD). However, previous studies have not directly compared cocaine-related to emotional stimuli while examining potential differences between abstinent and current cocaine users. **Methods:** The present study examined ERPs in 55 CUD (27 abstinent and 28 current users) and 29 matched healthy controls while they passively viewed pleasant, unpleasant, neutral, and cocaine-related pictures. To examine the time-course of attention to these stimuli, we analyzed both an early and later window in the LPP as well as the early posterior negativity (EPN), established in assessing motivated attention. Behavioral ratings of valence, arousal, and liking and wanting of cocaine were collected after picture viewing. **Results:** Cocaine pictures elicited increased electrocortical measures of motivated attention in ways similar to affectively pleasant and unpleasant pictures in all CUD; however, current users exhibited deficient processing of all emotional stimuli in a later LPP time window. Results were unique to the LPP and not EPN. Whereas all CUD rated cocaine pictures as pleasant, controls rated them as unpleasant; current users rated cocaine pictures as more pleasant and arousing than abstinent users. **Conclusions:** Taken together, results suggest that recent cocaine use impairs sustained processing of emotional stimuli among CUD, an effect not captured by self-report.

INTRODUCTION

(Edited to reduce redundancy)

Drug-related compared to neutral stimuli elicit a unique pattern of reactions in drug addicted individuals. For instance, exposure to drug-related stimuli (e.g., pictures, paraphernalia) increases physiological reactivity and cognitive interference in drug addicted individuals [213-214]. Mechanisms underlying these effects include attentional bias and increased motivational salience attributed to drug-related stimuli [215].

A parallel line of research similarly demonstrates unique reactions to emotional compared to neutral stimuli in healthy individuals [216-218]. Termed 'motivated attention', it is hypothesized that motivational systems are responsible for automatically allocating attention to, and enhancing the salience of, emotional stimuli [216]. Two event-related potentials (ERP), the early posterior negativity (EPN) and the late positive potential (LPP), are larger for both pleasant and unpleasant compared to neutral visual stimuli; they are interpreted to reflect increased attention to motivationally relevant stimuli [68-72, 219-220].

Specifically, only a few ERP studies directly compared drug-related to other emotional stimuli in both drug addicted and control individuals [77-78]. This is a crucial comparison considering that more general emotion-related abnormalities have been implicated among substance dependent individuals [79-80]. In addition, recency of drug use may relate to aberrant neural reactivity to drug cues among addicted individuals [81]. Therefore, the current sample of individuals with cocaine use disorders (CUD) included both those who tested positive (CUD+) versus negative (CUD-) for recent cocaine use.

We hypothesized that in both CUD groups, LPPs elicited by cocaine pictures would be larger than neutral LPPs and similar to other emotional picture LPPs, suggestive of enhanced processing of drug-related cues. The EPN analyses were more exploratory. Consistent with data implicating enhanced drug cue reactivity with perceived drug opportunity [221], we further hypothesized that cocaine-related LPPs would be most pronounced in CUD+. After picture viewing, participants rated all stimuli on valence, arousal, and liking and wanting of cocaine so that we could examine whether patterns of neural reactivity were associated with self-report. We hypothesized that neural measures would better differentiate attentional processes in CUD since recent findings have suggested impaired insight in this group [222].

METHODS

Participants

Fifty-five individuals with CUD and 29 healthy control subjects participated in the current study. A positive urine screen indicated cocaine use within 72 hours (maximal resolution of the urine test) of study day in 28 participants (CUD+), while 27 participants tested negative (CUD-). Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board. *Details regarding subject recruitment and screening procedures were same as outlined in Appendix A.*

Stimuli

Ninety pictures were selected from the International Affective Picture System IAPS; [223] based on normative ratings of valence and arousal, such that pleasant and unpleasant pictures would be more arousing than neutral pictures, and that each category of pictures would differ in their respective valence scores (see Supplementary Materials for analyses). Of these 90 pictures, there were 30 pleasant (e.g., smiling faces, nudes), 30 unpleasant (e.g., sad faces, violent images), and 30 neutral scenes (e.g., neutral faces, household objects).

We created a fourth category that included 30 pictures of cocaine and individuals preparing or using cocaine (e.g., snorting or smoking), collected from freely available online sources and adapted (as still images) from a cocaine video used previously in our laboratory [224]. Cocaine pictures were matched to the IAPS pictures on size of presentation and ratio of human to non-human content.

One of 10 sequences of completely randomized pictures (across all four picture categories) was randomly assigned to each subject. Within each sequence, four blocks of 30 randomized pictures were presented during the task. All 120 pictures were presented for 2000 ms, with a 2500 ms inter-trial interval; each picture was viewed only once.

Procedure

After a brief description of the experiment, electroencephalograph (EEG) sensors were attached and participants were given more detailed task instructions. Participants were told that they would be viewing pictures depicting a wide range of scenes; some pleasant, unpleasant, neutral, or drug-related. Participants were asked to focus on the screen and simply watch all of the pictures as they were displayed. Following the EEG task, subjects then rated each picture on

valence ("rate how pleasant or unpleasant you felt about this picture"), arousal ("rate how strong of an emotional response you had to this picture"), like cocaine ("rate how much you like (or do not like) cocaine in response to this picture"), and want cocaine ("rate how much you want (or do not want) cocaine in response to this picture"). Subjects responded using a computerized version of the Self-Assessment Manikin SAM; [225]. The SAM depicted five characters that ranged on valence (happy to unhappy) or arousal (strong visceral response to no response); these same SAM scales were used to assess liking and wanting of cocaine. Subjects chose the numbers '1' through '9' ('1' corresponded to happy/liking/wanting/high visceral response, '9' corresponded to unhappy/not liking/not wanting/no response) that appeared below the SAM characters. Thus, low numerical ratings correspond to higher levels of pleasantness, arousal, and liking and wanting cocaine.

Psychophysiological Recording and Data Reduction

(Same as Appendix A)

Analyses

Event-related potentials. The ERPs were constructed by separately averaging trials based on picture type: pleasant, unpleasant, neutral, and cocaine-related pictures. For each ERP averaged waveform, the average activity in the 200 ms window prior to picture onset served as the baseline. Previous research indicates that the EPN is maximal at temporo-occipital electrode sites during a 200-300 ms window after stimulus onset [69, 219, 226]; therefore, we defined the EPN as the average activity at the Oz, POz, O1, and O2 electrode sites in a 200-300 ms time window after picture onset. For the LPP, previous research among both non-addicted [68, 71-72, 220] and addicted see [74-76, 227] samples has assessed multiple windows, as best captured by a recent principal components analysis of the LPP that pointed to early (indicative of initial attention capture; similar to the P300) and later parietal components reflecting additional processes relevant for sustained emotional processing; [72]. Therefore, we defined the LPP as the average activity in an early (400-1000 ms) and late (1000-2000 ms) time window after picture onset. Previous investigations also indicate that drug-specific LPP modulation is maximal at fronto-central recording sites [227-228]; scalp topographies in the present study corroborated this effect (Figure 5.1). Therefore, the LPP was scored as the average activity at the Cz, FCz, FC1, FC2, and Fz electrodes. For each time window, the averaged LPP was analyzed with a 4 (Picture

Type: pleasant, unpleasant, neutral, cocaine-related) x 3 (Group: CUD+, CUD-, controls) mixed-model analysis of variance (ANOVA). The EPN was similarly analyzed. All averaged ERP amplitudes are presented in Table 5.2.

If significant interaction effects were present in the normally distributed EPN and LPP data, paired samples *t*-tests were used to assess within-group differences. Interaction effects were further explored through ERP difference scores, computed by subtracting neutral from all other picture types (pleasant, unpleasant, cocaine); these difference scores were then used to examine between-groups differences via independent *t*-tests. This approach controls for general differences in ERPs across participants, examining the degree of emotional modulation of the EPN and LPP across groups.

Picture Ratings. The averaged valence and arousal rating scales were analyzed using two separate 4 (Picture Type: pleasant, unpleasant, neutral, cocaine-related) x 3 (Group: CUD+, CUD-, controls) mixed-model ANOVAs. Since ratings of liking and wanting cocaine were only meaningful in the CUD groups, two separate 4 (Picture Type: pleasant, unpleasant, neutral, cocaine-related) x 2 (Group: CUD+, CUD-) mixed-model ANOVAs were used in these analyses (results in Supplementary Materials). Interaction effects for the non-normally distributed ratings were followed with Wilcoxon tests to assess within-group differences. Similar to the procedure used for the ERP data, ratings difference scores were created and used for testing between-groups differences via Mann-Whitney tests. Means and standard deviations for all rating scales are presented in Table 5.3.

Correlations. Correlations were conducted between ERPs and all picture rating scales (using raw scores; across all subjects and within each group separately) and between ERPs and selected drug use variables (in CUD only: whole sample and both subgroups separately). Since ratings and drug use variables were distributed non-normally, non-parametric Spearman correlations were used. All correlations were corrected for a family-wise error rate ($p<0.01$).

All Analyses and Effects of Possible Covariates. SPSS (Version 16.0) was used for all analyses. For ANOVAs, the General Linear Model was used and Greenhouse-Geisser correction was applied for violations of sphericity. In all analyses, $p<0.05$ was considered statistically significant. To control for the effects of possible covariates, we conducted correlations between dependent variables (ERPs and picture ratings) with depression (drug use variables that differed

between CUD subgroups were similarly treated). For history of cigarette smoking, differences in the dependent variables were inspected with *t*-tests. If significantly associated with the dependent variables across all study subjects ($p<0.05$), these variables were entered as covariates in the relevant ANOVA see Supplementary Materials for analyses; [229].

RESULTS

EPN

The EPN varied as a function of Picture Type ($F(3,243)=14.80$, $p<0.001$), but not group ($F(2,81)=.41$, $p>0.65$); the interaction between Picture Type and Group was also not significant ($F(6,243)=.86$, $p>0.50$). The main effect was driven by more negative EPNs for pleasant, unpleasant, and cocaine pictures than neutral pictures (all significant ts$>|3.60|$, ps<0.001); the emotional pictures did not differ from each other (all ts$<|1.76|$, ps>0.05). Hence, affective (including cocaine) compared to neutral pictures elicited increased EPNs across *all* study groups.

Early LPP (400-1000 ms)

The LPP varied as a function of Picture Type ($F(3,243)=26.57$, $p<0.001$) and was qualified by a significant interaction between Picture Type and Group ($F(6,243)=4.84$, $p<0.001$). Groups did not differ overall ($F(2,81)=.28$, $p>0.70$). The interaction was driven by significantly larger cocaine-related compared to neutral LPPs in both CUD subgroups (CUD+: $t(27)=-3.25$, $p<0.005$; CUD-: $t(26)=-5.05$, $p<0.001$) but not control subjects ($t(28)=-.79$, $p>0.40$) (Figures 5.1 and 5.2). Also, only in the CUD, cocaine LPPs did not differ from either pleasant (CUD+: $t(27)=-.86$, $p>0.35$; CUD-: $t(26)=.58$, $p>0.55$) or unpleasant (CUD+: $t(27)=-.38$, $p>0.70$; CUD-: $t(26)=-1.27$, $p>0.20$) LPPs, while in controls cocaine LPPs were significantly smaller than both pleasant ($t(28)=6.23$, $p<0.001$) and unpleasant ($t(28)=4.62$, $p<0.001$) LPPs. Furthermore, pleasant and unpleasant pictures elicited larger LPPs than neutral pictures ($t(28)=6.17$, $p<0.001$ and $t(28)=5.80$, $p<0.001$, respectively), but did not differ from each other ($t(28)=1.22$, $p>0.20$) in the healthy subjects (Figure 5.1, bottom; Figure 5.2, bottom). The same pattern was observed in the CUD+ (pleasant and unpleasant>neutral: $t(27)=3.86$, $p<0.001$ and $t(27)=4.12$, $p<0.001$, respectively; pleasant=unpleasant: $t(27)=-.69$, $p>0.45$). In CUD-, pleasant and unpleasant LPPs were similarly larger than neutral LPPs ($t(26)=6.15$, $p<0.001$ and $t(26)=3.99$, $p<0.001$,

respectively), also showing enhanced pleasant than unpleasant LPPs ($t(26)=2.26$, $p<0.05$) (Figure 5.1, middle; and Figure 5.2, middle).

In examining LPP difference scores, between-group analyses for each picture category revealed that both CUD groups had larger cocaine LPPs than controls (all significant ts$>|2.24|$, ps<0.05), CUD- and controls had larger pleasant LPPs than CUD+ (all significant ts$>|2.25|$, ps<0.05), and there were no group differences for the unpleasant LPPs (all ts$<|1.04|$, ps>0.30).

Thus, for all CUD, the magnitude of LPPs elicited by cocaine, pleasant, and unpleasant pictures was larger than the LPP elicited by neutral pictures; further, the cocaine and other emotional picture LPPs did not differ from each other. In controls by contrast, LPPs elicited by cocaine and neutral pictures were comparable in magnitude and both significantly smaller than LPPs elicited by the pleasant and unpleasant pictures. Direct group comparisons showed that compared to controls, both CUD groups exhibited increased response to cocaine pictures. Interestingly, the CUD+ group also displayed reduced processing of pleasant pictures in the early LPP window.

Late LPP (1000-2000 ms)

In the late window, the LPP again varied as a function of Picture Type ($F(3,243)=10.40$, $p<0.001$) and was qualified by a significant interaction between Picture Type and Group ($F(6,243)=32.49$, $p<0.001$); a main effect of group was not significant ($F(2,81)=.26$, $p>0.75$). The interaction was driven by a similar pattern of results as for the early LPP in controls (all significant ts$>|4.15|$, ps<0.001; Figure 5.1, bottom; Figure 5.2, bottom) and largely in the CUD- (all significant ts$>|2.55|$, ps<0.05; the only change included a significant difference between cocaine-related and unpleasant LPPs, $t(26)=-2.52$, $p<0.05$; Figure 5.1, middle; Figure 5.2, middle) but not in CUD+ where no statistically significant differences emerged between any of the LPPs (all ts$<|1.83|$, ps>0.05; Figure 5.1, top; Figure 5.2, top).

In comparing difference scores across groups, results were similar to the earlier window, except that in this later window, enhanced processing of the cocaine pictures was only discernible in the CUD- group (CUD->Controls, $t(54)=3.16$, $p<0.005$; CUD+=Controls, $t(55)=1.42$, $p>0.15$; CUD-=CUD+, $t(53)=-1.91$, $p>0.05$). Further, CUD+ displayed decreased processing of *both* pleasant (CUD+<Controls, $t(55)=-2.7$, $p<0.01$) and unpleasant (CUD+<Controls, $t(55)=-2.60$, $p<0.05$) pictures.

Thus, in the late LPP window, CUD- maintained enhanced processing of cocaine pictures; both CUD- and controls continued to show an increased LPP in response to both pleasant and unpleasant compared to neutral pictures. Of note, the CUD+ group demonstrated an attenuated late LPP to pleasant, unpleasant, and cocaine stimuli.

Picture Ratings

Valence. Main effects of Picture Type ($F(3,237)=207.76$, $p<0.001$) and Group ($F(2,79)=19.43$, $p<0.001$), and an interaction between Picture Type and Group ($F(6,237)=19.22$, $p<0.001$) were all significant. Within-group comparisons showed higher pleasant>cocaine>neutral>unpleasant ratings for CUD+ (all significant Zs>|2.23|, *p*s<0.03), for CUD- the rating pattern was pleasant>neutral=cocaine>unpleasant (all significant Zs>|3.50|, *p*s<0.001), and for controls it was pleasant>neutral>unpleasant=cocaine (all significant Zs>|4.39|, *p*s<0.001).

In examining valence difference scores, between-group analyses revealed differences in ratings of cocaine (CUD+>CUD->Controls; all significant Zs>|2.67|, *p*s<0.01) and pleasant pictures (CUD+>CUD-, Conrols=CUD+ and CUD-; $Z=-2.05$, $p<0.05$). Valence ratings for unpleasant pictures did not differ between groups (all Zs<|1.41|, *p*s>0.15). Hence, for all groups, pleasant pictures were rated as most pleasant. Further, both CUD groups rated cocaine pictures as more pleasant than unpleasant pictures, but controls rated cocaine and unpleasant picture valence equally. Finally, CUD+ rated cocaine and pleasant pictures as more pleasant than CUD-.

Arousal. For arousal ratings, results revealed significant main effects of Picture Type ($F(3,237)=15.46$, $p<0.001$) and Group ($F(2,79)=7.76$, $p<0.005$), qualified by a significant interaction between Picture Type and Group ($F(6,237)=5.07$, $p<0.001$). This interaction was driven by different patterns of arousal ratings within each group: for CUD+ it was pleasant=cocaine>neutral=unpleasant (all significant Zs>|2.89|, *p*s<0.005), for CUD- it was pleasant>unpleasant=neutral, cocaine=all picture types (all significant Zs>|2.39|, *p*s<.02), and for controls it was pleasant>neutral=cocaine, unpleasant=pleasant>cocaine (all significant Zs>|3.49|, *p*s<0.001). Examination of arousal difference scores revealed differences in cocaine pictures (CUD+=CUD->Controls; all significant Zs>|2.42|, *p*s<0.015). Therefore, CUD+ rated cocaine and pleasant pictures highest and indistinguishable on arousal, whereas controls rated cocaine pictures as less arousing than both pleasant and unpleasant pictures. Also, CUD+ and CUD- found cocaine pictures more arousing than controls.

Correlations

The more money spent per each cocaine use in the last 30 days, the larger (more positive) the cocaine-related LPPs in the late window (r_s=0.676, p<0.001) for CUD+ (Figure 5.3). This was the only correlation reaching family-wise correction level (see Supplementary Materials Table S1 for all correlations between LPPs and drug use variables).

DISCUSSION

In the present study we examined the EPN as well as the early and late LPP, neurophysiological measures of increased attention to motivationally relevant stimuli, to study processing of drug-related versus other emotional stimuli in drug addicted individuals. By focusing on early to late ERPs, we were able to determine at what stage cocaine-related stimuli differed from other emotional stimuli among individuals with CUD; we were particularly interested in examining these markers as a function of recent drug use—and for the first time in this type of study examined CUD who were positive and negative for recent cocaine use. EPN results suggested that very early attentional allocation to emotional stimuli, including cocaine images, was similar across all groups. In addition, and in line with previous reports, all subjects displayed increased motivated attention to pleasant and unpleasant compared to neutral pictures in the early LPP time window [68, 70-72, 220, 226, 230]. However, for both CUD groups compared to controls in the early LPP window, cocaine pictures elicited electrocortical activity on par with highly appetitive and aversive images and greater than neutral picture activity. These results support our first a priori hypothesis and extend results by others [75-76, 227], and suggest that cocaine stimuli are similar to other emotional stimuli in increasing motivated attention in CUD—and this effect is first evident in the time window of the early LPP. In line with previous research in healthy controls [69, 219], this suggests that early processing of emotional stimuli also remains intact in CUD.

Even during the early LPP response to emotional stimuli, however, CUD sub-groups began to differ from one another: compared to CUD-, CUD+ showed attenuated responses to pleasant pictures. Abnormalities in the LPP were even more pronounced among CUD+ in the later window, which reflects sustained attentional engagement and processing of motivationally significant stimuli. Here, CUD+ did not differentiate any emotional pictures (including cocaine) from neutral. On the other hand, a processing bias to cocaine images remained significant for CUD-: the LPP was larger for cocaine than both neutral and unpleasant images. Thus, results did not support our second hypothesis that LPPs to cocaine stimuli would be most pronounced in

CUD+. Instead, we observed *decreased* processing of cocaine pictures (no differences from controls in the late window), pleasant pictures (compared to controls and CUD- in the early window and compared to controls in the later window), and unpleasant pictures (compared to controls during the late window) in CUD+.

The dramatic group differences observed during the late LPP window suggests that current cocaine use might be uniquely associated with deficits in *sustained* attention to emotional stimuli – results broadly consistent with previous work. Specifically, Lubman et al. [78] demonstrated lack of the typical startle-elicited P300 attenuation during pleasant versus neutral or drug pictures in opiate dependent individuals compared to controls. Also, the bilateral dorsolateral prefrontal cortex was activated to pleasant pictures in 18 healthy controls but not in 16 inpatient (abstinent 1-24 weeks) male heroin addicts [231]. Taken together, the present ERP results shed light on differences in the time course of motivated attention to emotional stimuli as a function of current cocaine use.

The overall pattern of LPP and arousal ratings across picture types in the control group were in line with previous work: only pleasant and unpleasant pictures elicited increased LPPs—these were also the pictures rated as more arousing. Yet, several dissociations between LPPs and self-report ratings are of mention. For instance, there were no significant correlations between LPPs and arousal ratings. It is possible that the psychophysiological and self-report measures assessed unique information [232]—the LPP may index neurobiological processes that only map broadly to self-reports or processes not readily accessible to self-report in the present study. Also, despite decreased LPPs to pleasant (both windows) and cocaine pictures (late window), CUD+ compared to the other groups rated pleasant pictures highest in arousal and valence; they also rated cocaine images highest in valence, arousal, and liking and wanting of cocaine. Thus, the largest dissociation between LPP and self-report data was evident in CUD+, consistent with a recent report suggesting that this subgroup displays the most severe behavioral insight deficits [222]. Other investigations in CUD have also reported dissociations between self-report and behavior to monetary reward [66], task performance and the P300 [233], and self-report and choice behavior [234]. In this vein, a recent meta-analysis demonstrated a modest overall correlation (r=0.19) between various measures of attentional bias and drug craving across several addiction types. In our study, we attribute lack of a significant correlation between LPPs with craving to

our high nominal statistical threshold as confirmed by inspection of the raw correlations (consistent with the meta-analysis results, r=|.14 - .25|, Supplementary Table S1).

Limitations of the study include: 1) one could question our choice of dividing the CUD into two subgroups based on cocaine in urine. We therefore report in Supplementary Materials results where the CUD are treated as a single group further exploring correlations with time since last cocaine use; results were largely unchanged from those reported here; 2) results pertain mainly to males and remain to be further substantiated in women; results in males only (excluding females) are reported in the Supplementary Materials, again with no major change to current conclusions. For purposes of generalizability, we included females in the current report; 3) depression and history of cigarette smoking differed between the groups. However, depression did not correlate with LPPs, and all original effects remained significant after controlling for cigarette smoking (see Supplementary Materials); and 4) clinical significance of these findings needs to be studied. For example, it will be important to examine whether differences in LPPs predict treatment outcomes (e.g., especially of longer-term relapse or using a longer-term abstinent sample).

In conclusion, we found that cocaine pictures capture attention in ways similar to affectively pleasant and unpleasant pictures in abstinent and current users of cocaine but not in matched healthy controls. Further, we found that current compared to abstinent cocaine users and controls exhibited *deficient sustained* processing of emotional (including cocaine) stimuli; this objective deficit was not present in self-report, where, compared to the other study groups, current users rated both cocaine and pleasant images as highly arousing. ERPs could be examined in future cocaine addiction research for possible utility as biomarkers in treatment outcomes.

Table 5.1: *Demographic Characteristics and Drug Use by Study Subjects*

	CUD+ (N=28)	CUD- (N=27)	Controls (N=29)
Gender (male/female)	27/1	26/1	25/4
Ethnicity (African-American/Caucasian/Hispanic)	20/5/3	19/5/3	20/8/1
History of cigarette smoking (current or past/never or tried)[1]	21/7[c]	21/6[c]	6/23[a,b]
Education (years)	13.09 (1.76)	12.69 (1.82)	13.81 (2.02)
Age (years)	45.55 (4.81)	42.47 (8.82)	41.17 (7.32)
Socio-economic status (Hollingshead, 1975)	32.32 (11.03)	33.06 (11.63)	32.90 (13.56)
Non-verbal intellectual functioning: Wechsler Abbreviated Scale of Intelligence: Matrix Reasoning scaled score (Wechsler, 1999)	9.43 (3.72)	9.92 (3.06)	11.03 (2.72)
Self-reported state depression (Beck et al., 1996)[2]	7.57 (7.56)[c]	7.63 (6.38)[c]	1.48 (2.87)[a,b]
Age at onset of cocaine use (years)	26.68 (5.23)	25.04 (6.47)	--
Duration of use (years)	16.56 (7.09)	14.46 (8.80)	--
Frequency of use (days/week) last 30 days[3]	4.23 (2.40)[b]	1.53 (2.29)[a]	--
Current use in $ per use (min – max, median) last 30 days	62.36 (2-200, 50)	109.23 (0-300, 80)	--
Duration of current abstinence (days) (min – max, median)[4]	2.25 (0-14, 2)[b]	214.85 (2-2555, 25)[a]	--
Length of longest abstinence (days) (min – max, median)	869.89 (19-3650, 365)	818.63 (25-2555, 560)	--
Total score on the Cocaine Selective Severity Assessment Scale (measure of withdrawal symptoms; 0-126)	19.11 (10.84)	15.74 (10.36)	--
Severity of Dependence Scale (0-15)[5]	6.61 (3.40)[b]	8.44 (3.15)[a]	--
Cocaine Craving Questionnaire (0-45)[6]	22.18 (10.66)[b]	10.96 (9.58)[a]	--

Note. Values in parentheses are standard deviations unless otherwise indicated. [1] $\chi^2(2)=23.79$, $p<.001$ (Kruskal-Wallis); [2] $\chi^2(2)=25.07$, $p<.001$ (Kruskal-Wallis); [3] $Z=-4.00$, $p<.001$ (Mann-Whitney); [4] $Z=-5.71$, $p<.001$ (Mann-Whitney); [5] $t(53)=-2.08$, $p<.05$; [6] $t(53)=4.10$, $p<.001$. Superscript letters designate group differences ([a] significantly different from CUD+; [b] significantly different from CUD-; [c] significantly different from control group).

Table 5.2: *Averaged ERP (EPN and LPP) Amplitudes to Each Picture Type in CUD+, CUD-, and Controls*

	EPN (200-300 ms)			LPP (400-1000 ms)			LPP (1000-2000 ms)		
	CUD+	CUD-	Controls	CUD+	CUD-	Controls	CUD+	CUD-	Controls
Pleasant	3.50 (2.16)	4.16 (3.15)	3.68 (3.01)	-1.70 (2.31)	-0.81 (3.04)	-0.85 (3.30)	-2.17 (1.97)	-1.30 (2.34)	-0.96 (2.57)
Unpleasant	3.07 (2.27)	4.05 (2.76)	3.53 (3.15)	-1.34 (3.24)	-1.86 (2.83)	-1.38 (3.91)	-2.06 (2.64)	-2.02 (2.27)	-0.95 (3.52
Neutral	4.17 (2.19)	4.54 (2.76)	4.47 (3.60)	-3.23 (2.92)	-3.63 (3.27)	-3.78 (3.32)	-2.64 (2.79)	-3.30 (2.97)	-3.40 (3.08)
Cocaine	3.11 (2.47)	3.72 (2.73)	3.72 (3.20)	-1.10 (4.18)	-1.16 (3.87)	-3.43 (3.63)	-1.55 (3.04)	-0.63 (3.14)	-3.64 (3.51)

Note. Mean (standard deviation). Averaged ERP amplitudes are in microvolts (μV).

Table 5.3: *Averaged Self-reported Ratings of All Picture Types*

	CUD+	CUD-	Controls
Pleasant Picture Valence	2.26 (.93)	2.88 (1.41)	2.92 (1.09)
Pleasant Picture Arousal	3.55 (2.05)	4.28 (1.90)	4.70 (1.97)
Pleasant Picture Like Cocaine	5.57 (2.04)	7.11 (2.00)	8.50 (1.11)
Pleasant Picture Want Cocaine	5.96 (2.14)	7.67 (1.63)	8.56 (1.63)
Unpleasant Picture Valence	7.90 (1.12)	7.55 (1.09)	7.77 (1.15)
Unpleasant Picture Arousal	6.12 (2.58)	5.99 (2.04)	5.71 (2.15)
Unpleasant Picture Like	7.44 (1.88)	7.58 (2.02)	8.57 (0.99)
Unpleasant Picture Want	7.58 (1.91)	8.06 (1.75)	8.55 (1.61)
Neutral Picture Valence	4.46 (1.05)	4.57 (1.38)	4.63 (1.40)
Neutral Picture Arousal	5.70 (1.85)	6.28 (2.16)	6.33 (2.11)
Neutral Picture Like Cocaine	6.52 (2.01)	7.54 (2.04)	8.46 (1.22)
Neutral Picture Want Cocaine	6.87 (2.08)	8.05 (1.65)	8.56 (1.59)
Cocaine Picture Valence	3.30 (1.76)	5.54 (2.30)	7.88 (1.46)
Cocaine Picture Arousal	3.62 (2.16)	5.21 (2.15)	7.25 (2.00)
Cocaine Picture Like Cocaine	3.41 (2.02)	5.99 (2.56)	8.67 (0.91)
Cocaine Picture Want Cocaine	3.52 (2.02)	6.15 (2.54)	8.68 (1.43)

Note. Mean (standard deviation). Low numerical ratings correspond to higher levels of pleasantness, arousal, and liking and wanting of cocaine.

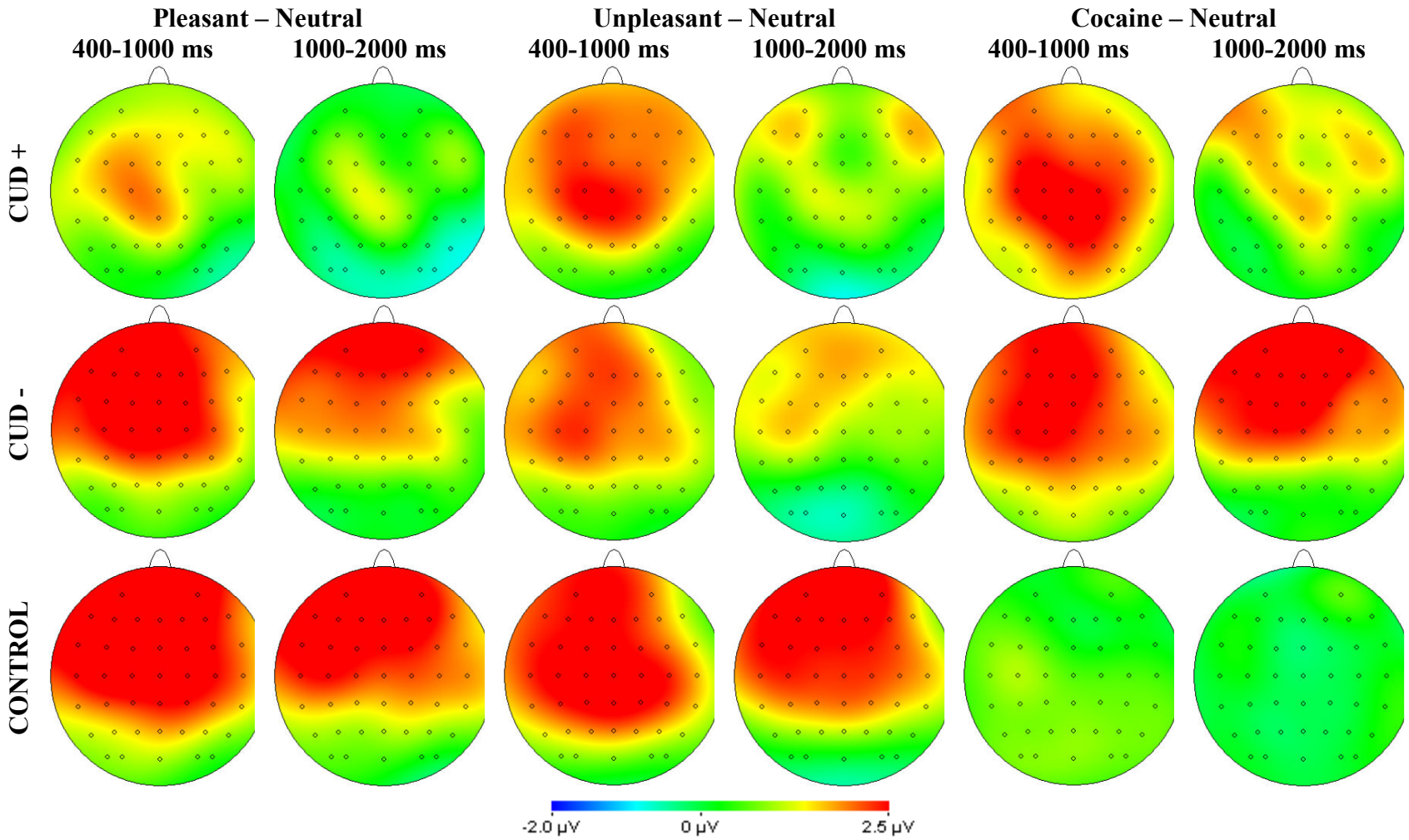

Figure 5.1. Scalp topography of pleasant minus neutral (left columns), unpleasant minus neutral (middle columns), and cocaine minus neutral (right columns) differences in both the early (400-1000 ms) and late (1000-2000 ms) windows during passive viewing in CUD+ (top row), CUD- (middle row), and controls (bottom row).

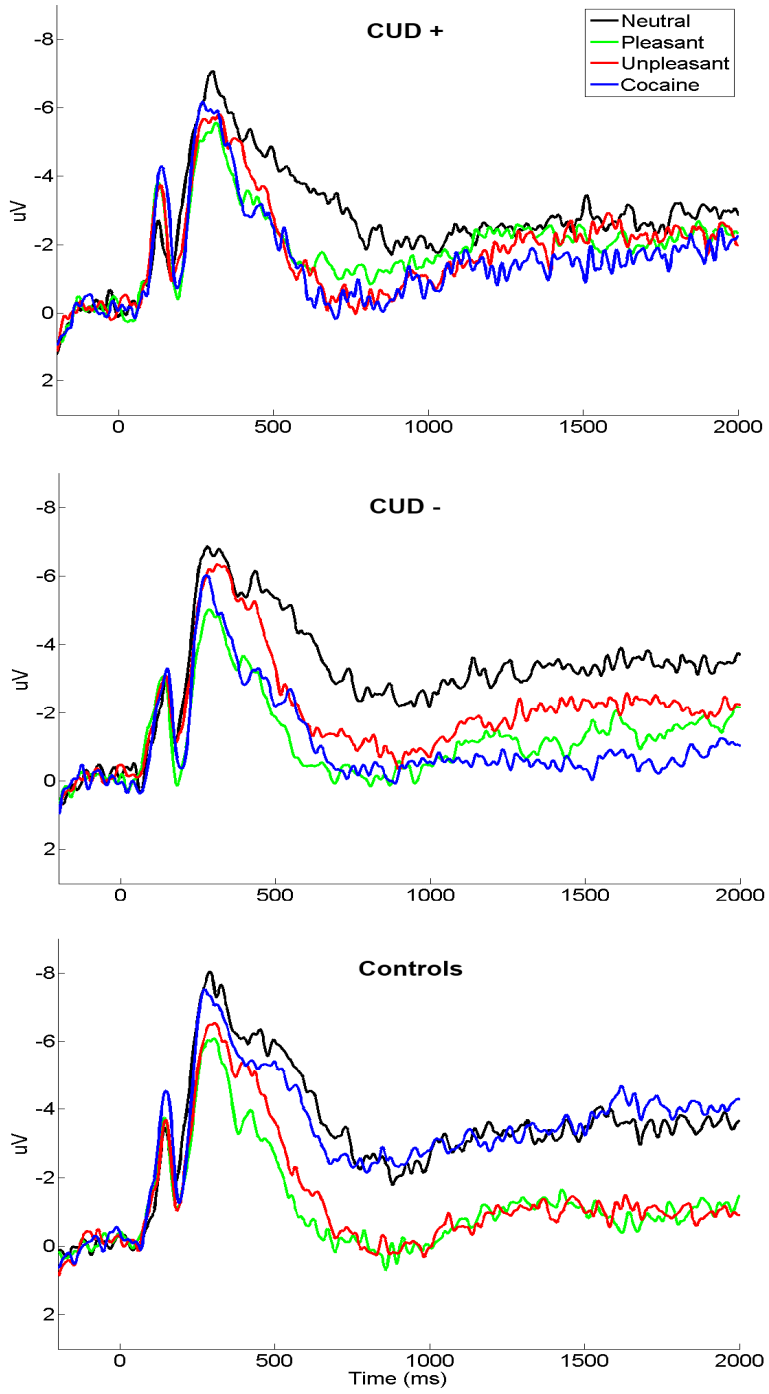

Figure 5.2. Grand averaged late positive potentials (at the average of sites Cz, FCz, FC1, FC2, and Fz) elicited by neutral, pleasant, unpleasant, and cocaine-related pictures for CUD+ (top), CUD- (middle), and control subjects (bottom). Stimulus onset occurred at 0 ms.

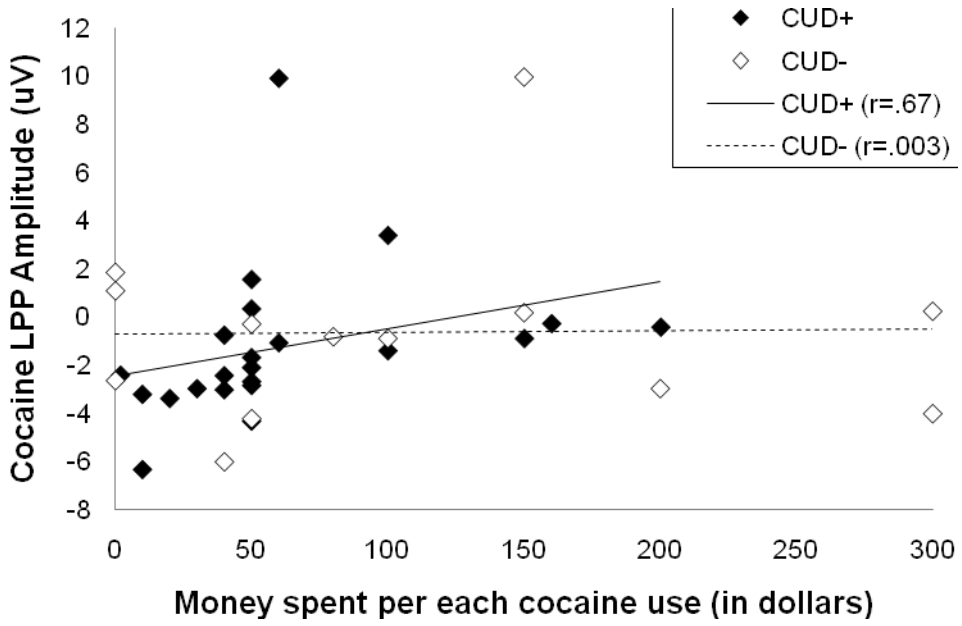

Figure 5.3. Scatterplot of the correlation between cocaine-related LPPs (late window) and money spent per each cocaine use in the past 30 days (US dollars) in CUD+ (*N*=22) and CUD- (*N*=13) groups. Spearman correlation coefficients are presented.

CHAPTER 6

(Submitted to Journal of Cognitive Neuroscience)

Title: Structural Integrity of Prefrontal Cortex Mediates Electrocortical Sensitivity to Reward

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ABSTRACT

The P300 is a known event-related potential (ERP) component assessing stimulus value, including the value of a monetary reward. In parallel, the incentive value of reinforcers relies on the prefrontal cortex (PFC), a central module of the mesocortical neural reward pathway. Here we show a significant positive correlation between P300 response to money vs. no money with PFC gray matter integrity, encompassing the orbitofrontal cortex, anterior cingulate cortex, and dorsolateral PFC in healthy control subjects. In contrast, individuals with cocaine use disorder (CUD) showed compromises in both P300 sensitivity to money and PFC structural integrity, and in their interdependence. These results document for the first time the importance of structural integrity of the limbic PFC to reward-modulated P300 response. In CUD, results may represent a disadvantageous reorganization of the brain systems responsive to reward.

INTRODUCTION

(Edited to reduce Redundancy)

Our objective in the present study was to evaluate whether P300 response to the expectation of monetary gain (reward to be obtained for correct performance on a sustained attention task) was associated with PFC volumetric integrity in a healthy subject group. Here we hypothesized that reward-sensitive P300 response will be positively correlated with preferontal cortex (PFC) gray matter volume. Demographically-matched individuals with cocaine use disorders (CUD) were included for comparison to a condition known to impact both reward processing [as measured with both functional magnetic resonance imaging [235] and ERP [65]] and PFC integrity [89, 91-92]. Given the uncoupling between reward-driven behavioral (task accuracy and reaction time) and autonomic (P300) responses in CUD as we previously demonstrated [65], and as similarly observed following PFC [specifically orbitofrontal cortex (OFC)] lesions [196], we also postulated null correlations for the CUD.

METHODS

Subjects

Full written informed consent was obtained from 39 subjects [17 controls (7 females), and 22 CUD (4 females)] in accordance with the local institutional review board. *Details regarding subject recruitment and screening procedures were same as outlined in Appendix A.*

Task Paradigm

(Same as in Appendix A)

Preprocessing and Reduction of EEG Data

(Same as in Appendix A)

Structural MRI

MRI acquisition was performed on a 4-Tesla Varian/Siemens scanner, with a self-shielded whole-body SONATA gradient set. A T_1-weighted anatomical MRI scan was obtained from all subjects using a 3D-MDEFT (3 dimensional modified driven-equilibrium Fourier transform) sequence [236] (TE/TR = 7/15 ms, 0.94 × 0.94 × 1.00 mm^3 spatial resolution, axial orientation, 256 readout and 192 × 96 phase-encoding steps, 16 minute scan time). The MDEFT is particularly effective for tissue differentiation producing the most precise characterization of gray matter

(GM) tissue compared to other sequences [237]. A T_2-weighted hyperecho scan was also obtained to rule out any gross morphological abnormalities. Structural scans were obtained from all subjects within 1 week (1.79 ± 2.88 days) of completing the psychophysiological recordings and clinical interviews, with no differences between the groups in this time gap (p>0.41).

Image Preprocessing. Data preprocessing and analyses were performed using the statistical parametric mapping (SPM5) suite (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab version 7.0 (Mathworks Inc., Natick, MA). Voxel-based morphometry (VBM), a whole-brain, fully automated, unbiased, and operator-independent MRI analysis technique commonly used to detect regionally specific differences in brain tissue composition using a voxel-wise comparison across subjects [85], was conducted with the VBM toolbox (VBM5.1) (Gaser, C, University of Jena, Department of Psychiatry, Germany; http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM5, which combines spatial normalization, tissue segmentation, and bias correction. The MDEFT scans were first spatially normalized to standard proportional stereotaxic space and segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) tissue classes according to *a priori* tissue probability maps [85, 238]. A hidden Markov random field [239] was applied to minimize the noise level by "removing" isolated voxels of one tissue class that are unlikely to be members of that tissue class, thereby increasing the accuracy of the segmentation. Jacobian modulation was also applied to compensate for the effect of spatial normalization and to restore the original absolute GM volume in the segmented GM images. Total brain volume (TBV) was computed as a sum of the extracted total GM and WM volumes for each subject, calculated as an adjustment factor to account for the effect of overall head size on regional GM volume. TBV, and not total intracranial volume (that encompasses CSF), was chosen because of known artifact susceptibility associated with CSF volume calculation in SPM5 (e.g., if voxels are not fully differentiated as GM or WM, they can be mislabeled as CSF). The use of TBV is also appropriate when comparison groups are matched on age [240] and is frequently employed in studies assessing regional GM in clinical populations [e.g., substance addiction [92], obesity [241], and obsessive-compulsive disorder [242]]. CUD and control subjects did not differ in their TBV (t_{37}= 1.28, p=0.21) or total GM volume (t_{37}= 0.34, p=0.74). Statistical analysis of regional GM volume was performed after smoothing the normalized and modulated segments with a 10 mm^3 full-width at half-maximum Gaussian kernel.

Statistical Analyses

Morphometry Analyses. In SPM5, multiple regression analyses were performed with P300 peak amplitudes as seed variables regressed against regional GM volume in healthy controls and CUD separately using whole-brain VBM. That is, across subjects within a group, the P300 component amplitudes [computed using the Principle Component Analysis (PCA)] in response to 45¢, 1¢ and 0¢ trials separately (**Fig. 6.1B**), and the differentials 45¢ minus 0¢, 45¢ minus 1¢, and 1¢ minus 0¢, served as the reward-modulated P300 seed variables regressed – one at a time – against the subjects' regional GM volumes (used as the contrast maps). Age and TBV were included as covariates in all analyses. Statistical maps were thresholded at $p<0.001$ voxel-level uncorrected, with a minimum cluster extent of 50 contiguous voxels and significance was reported at $p<0.05$, FWE-corrected at cluster level for multiple comparisons using Random Field Theory [243]. *A priori* regions of interest were defined at the OFC, anterior cingulated cortex (ACC), dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC). For completeness, we also report results of 1) Money (45¢, 1¢, and 0¢) by Group (Controls and CUD) mixed ANOVAs for the PCA-derived P300, task performance and ratings conducted to assess modulation of these variables by money and group in this sample; and 2) a whole-brain independent samples t-test conducted to assess regional differences in GM volume between the groups (**Fig. 6.2A**). Here we used an exploratory voxel-level threshold of $p<0.005$ uncorrected and 50 contiguous voxels. Anatomical specificity for all analyses was corroborated with the Anatomy toolbox [244], which provides probabilistic cytoarchitectonic neuroanatomical localization maps. Subjects' individual cluster volume measures were extracted using the EasyROI toolbox in Matlab (http://www.sbirc.ed.ac.uk/cyril/cp_download.html) and plotted to check for potential outliers. Analyses in SPSS 11.5 (SPSS Inc., Chicago, IL) were used to confirm whole-brain VBM results.

Correlations with Drug Use. We conducted partial correlations, controlling for age and TBV, between the GM cluster volumes (all regions from **Table 6.2** and the Control>CUD t-test contrast reported in **Fig. 6.2A**) and drug use (cocaine and alcohol) history for CUD (variables in **Table 6.1**). Inter-correlations within cocaine, alcohol, and nicotine histories in CUD, and their impact on results, were also explored. To protect against Type I error, nominal significance level for these correlation analyses was set at $p<0.01$ with $p<0.05$ reported as trend. Significant correlations in SPSS were repeated with whole-brain analyses in SPM.

RESULTS

Task Behavior and Ratings Results (Table 6.3)

A 3 (Money: 45¢, 1¢, and 0¢) x 2 [Group: control or cocaine use disorder (CUD)] analysis of variance (ANOVA) revealed a main effect of money for reaction time (RT) [$F(2,74)= 3.14$, $p=0.049$], such that RT decreased linearly with increasing money value across all 39 subjects (linear contrast for Money: $F(1,37)=5.65$, $p=0.02$; quadric contrast, n.s.). These results were driven by CUD [RT was faster for 45¢ > 0¢ and 45¢ > 1¢, $t(21)>|2.17|$, $p<0.04$; while 1¢ vs. 0¢ did not significantly differ, $p=0.91$] but not controls [$t(16)<|1.21|$, $p>0.24$]. All other main and interaction effects did not reach significance [$F(2,74)<|0.29|$, $p>0.75$]. As expected (given our prior results and the low level of difficulty of the current task), accuracy on the task did not differ among the three monetary conditions [$F(2,74)= 0.59$, $p=0.56$] or between the groups [$F(1,37)= 0.76$, $p=0.39$] and there was no significant money by group interaction [$F(2,74)= 0.03$, $p=0.97$]. There were no significant correlations between P300 amplitude, including the differentials for 45¢ minus 0¢, 45¢ minus 1¢, or 1¢ minus 0¢, with the respective RT and accuracy measures in either group [controls: $r<|0.32|$, $p>0.22$; CUD: $r<|0.31|$, $p>0.16$; note Spearman-r was used for correlations with accuracy].

All subjects reported being fully engaged in the experiment, as assessed by self-reported ratings obtained immediately following the task. A main effect of money was observed such that subjects in both groups reported being more interested [$F(2, 72)= 13.24$, $p<0.001$] and more excited [$F(2,74)= 16.64$, $p<0.001$] during high reward trials than low or non-reward trials on the task, with no group main effects [$F(1,36)< 0.25$, $p>0.62$], or significant money by group interactions [$F(2,72)< |1.91|$, $p>0.17$] on either of these scales. Follow-up paired t-tests confirmed these money effects separately in each study group [for interest: controls (45¢>1¢>0¢), $t(16)> |2.14|$, $p<0.05$; CUD (45¢>1¢=0¢), $t(20)> |3.14|$, $p<0.005$ with 1¢ vs. 0¢, n.s.; and for excitement (45¢>1¢=0¢): controls, $t(16)> |2.87|$, $p<0.01$; CUD, $t(20)> |3.40|$, $p<0.003$; for both groups, 1¢ vs. 0¢, n.s.]. There was also a significant main effect of money on ratings of frustration [$F(2,72)= 6.83$, $p=0.01$], such that less frustration was reported with increasing money value across all subjects (linear contrast for Money: $F(1,36)=6.16$, $p=0.02$; quadric contrast: $F(1,36)=9.24$, $p=0.004$). Follow-up paired t-tests revealed that these results were driven by CUD who reported significantly less frustration for high reward versus low or non-reward [45¢>1¢ and 45¢>0¢, $p<0.02$; 1¢=0¢, $p=1.0$] but not by controls [45¢=1¢=0¢,

p>0.21]. However, again there was no significant group main effect [F(1,36)= 0.01, p=0.92] or money by group interaction [F(2,72)= 0.98, p=0.38] on frustration. There were no differences between the groups on any of these scales for any of the three monetary conditions even in follow-up independent t-tests (p>0.22).

There was a significant positive correlation between frustration ratings for the 0¢ condition and P300 amplitude at 0¢ in CUD (r=0.53, p=0.01; note Spearman-r was used for correlations with frustration ratings which were non-normally distributed) and between frustration at 1¢ and P300 at 1¢ in controls (0.52, p=0.03). All other correlations between self-reported task ratings and P300 amplitude were not significant (p>0.06). Thus, the higher the P300 amplitude during low or non-reward trials, the lower the self-reported frustration on those trials.

Taken together, deficits currently reported in CUD cannot be attributed to lack of task engagement or impaired task performance (in fact, CUD showed faster reaction time and lower frustration to money vs. no money than controls).

Psychophysiological Results

A 3 (Money: 45¢, 1¢, and 0¢) × 2 (Group: controls, CUD) mixed analysis of variance (ANOVA) showed the money main effect we previously reported [65] [F(2,74)=5.87, p=0.004], such that PZ P300 amplitudes increased linearly with money value across subjects (linear contrast for Money: F(1,37)=10.30, p=0.003; quadric contrast, n.s.). Although there was no significant group main effect [F(1,37)=0.11, p=0.75], or money by group interaction [F(2,74)=0.44, *p*=0.65], planned within group two-tailed t-tests showed the money main effect to be driven by healthy controls specifically for the highest reward versus non-reward conditions [45¢ > 0¢, t(36)=-3.49, *p*=0.003; while 45¢ vs. 1¢ and 1¢ vs. 0¢ did not significantly differ, t(16)<|1.63|, *p*>0.12] but not by CUD [45¢ = 1¢ = 0¢, t(21)<|1.57|, *p*>0.13]. Despite using a slightly different sample and for the first time applying PCA to identify P300 component amplitudes, these results corroborate our previous findings [65]. Note that similarly to our prior report [65], we carried out these planned comparisons even when main effects and interactions did not reach significance given of our *a priori* hypothesis (of P300 amplitude response to reward magnitude within controls but not CUD). This technique has been shown to be statistically viable [190].

VBM Results

As expected, the psychophysiological task results were consistent with our prior report (Goldstein et al., 2008) where the P300 was sensitive to monetary reward in the controls but not CUD. Results from a two-sample t-test directly assessing differences in GM between the groups and GM correlations with lifetime drug use history are presented in **Fig. 6.1**; here again results support previously reported drug-related OFC GM volume reductions in CUD as compared to controls [91] as we recently observed in a larger sample of CUD [245]. Importantly and uniquely to the current study, in control subjects only, unbiased whole-brain analyses showed that psychophysiological sensitivity to money (45¢ minus 0¢) was significantly correlated with GM volumes in four distinct clusters encompassing the right DLPFC (BA 46), right ACC (BA 32, after small volume correction), left VLPFC (BA 44), and right lateral OFC (BA 47) [cluster level $p<0.05$, FWE-corrected for multiple comparisons unless otherwise stated] (**Table 6.2**, **Fig. 6.3A**). No other regions survived this whole-brain correction even at a reduced set threshold level of $p<0.01$ uncorrected. Scatter plots between the adjusted [for age and TBV] GM volumes in these regions and the P300 differential amplitude (45¢ minus 0¢) as a function of study group are presented in **Fig. 6.3B**. Overall tests of coincidence (Primer of Biostatistics software, Version 4.02, McGraw-Hill) of the groups' regression lines were significant for all four regions [$F_{2,35}=8.86$, $p<0.001$ for DLPFC; $F_{2,35}=8.73$, $p<0.001$ for VLPFC; $F_{2,35}=7.90$, $p=0.001$ for lateral OFC; and $F_{2,35}=4.68$, $p=0.01$ for ACC], confirming that the correlation between P300 differential amplitudes and prefrontal GM volume differs significantly between the study groups. There were no significant correlations at the set significance threshold level in CUD with the maximal differential P300 response (45¢ minus 0¢) or within either study group between regional GM volume and P300 responses to 45¢, 1¢, and 0¢ (absolute amplitudes) or 45¢ minus 1¢ and 1¢ minus 0¢ as separately inspected.

Between-group Comparison of Regional GM Volume

A direct whole-brain between-group t-test assessing regional differences in gray matter (GM) between CUD and healthy controls was performed controlling for the effects of age and total brain volume (TBV). Threshold was set at exploratory voxel-level $p<0.005$ uncorrected, with 50 adjacent voxels. Results indicated that healthy controls had increased GM of the orbitofrontal cortex (OFC), a cluster encompassing the bilateral rectal gyri (BA 11, x=-20, y=28, z=-20, peak t=3.75, peak Z=3.42, 2259 voxels, p=0.046 cluster-level corrected) and the left inferior frontal

gyrus (BA 48, x=-37, y=18, z=29, peak t=4.36, peak Z=3.87, 864 voxels, voxel-level p=0.038 FWE-corrected, p=0.011, FDR-corrected), after small volume correction [sphere (21.8 resels) at center] (see **Fig. 6.2A**). There were no regions of significantly increased GM in CUD compared with control subjects using the same whole-brain cluster-level correction for multiple comparisons.

Results in CUD are consistent with previously documented compromises in PFC volume including the OFC [90-92, 246], a region where damage is associated with an impaired ability to differentiate between rewarding and non-rewarding situations and appropriately altering behavior in the face of changing reward contingencies [247].

GM Correlations with Drug Use

Region of interest correlations between GM volume (all regions from main **Table 6.2** and the Control > CUD t-test contrast reported in **Fig. 6.2A**) and drug use history showed significant associations in CUD between lateral OFC GM (BA 47, x=37, y=49, z=-15, from P300 regression results in controls) with duration of lifetime cocaine use (r= -0.52, p=0.02), consistent with results in a bigger sample size [245]; this region also correlated with age of cocaine use onset (r= 0.54, p= 0.01), such that, together, longer duration and earlier age of onset of cocaine use were associated with lower GM volume in the lateral OFC. Although CUD who met criteria for current alcohol dependence were excluded from the study, duration of lifetime alcohol use was significantly associated with lower GM in all four regions of interest (main **Table 6.2** from P300 regression results in controls, right dorso-lateral prefrontal cortex (DLPFC), BA 46: r= -0.49, p=0.03; right anterior cingulate cortex (ACC), BA 32: r= -0.63, p=0.003; left ventro-lateral PFC (VLPFC), BA 44: r= -0.55, p=0.01; and right lateral OFC, BA 47: r= -0.52, p=0.02) and with OFC, BA 11 from the Controls > CUD t-test contrast (r= -0.54, p=0.01). Results in the OFC survived follow-up whole-brain analyses in SPM [set threshold p<0.001 uncorrected and 50 voxels; for duration of cocaine use, right lateral OFC, BA 47: x=51, y=41, z=-12, peak t=6.06, peak Z=4.42, 459 voxels, p=0.056 cluster level corrected, voxel-level p=0.008 FWE-corrected and p=0.01 FDR-corrected after small volume correction, sphere (21.9 resels) at center, see **Fig. 6.2B**; for duration of alcohol use, right OFC, BA 11: x=30, y=53, z=-8, peak t=5.10, peak Z=3.96, 2103 voxels, p=0.03 cluster-level corrected, see **Fig. 6.2C**]. Age of onset and lifetime

use of nicotine were not significantly correlated with any of the reported ROIs ($r<|0.32|$, $p>0.19$), as confirmed by whole-brain analyses.

Inter-correlations between cocaine, alcohol, and nicotine use histories among CUD are reported in **Table 6.4**. Including duration of lifetime alcohol and nicotine use as well as alcohol use in the past 30 days (the variables that significantly correlated with lifetime cocaine use) as additional (to age and TBV) separate covariates in the analysis between lifetime cocaine use and lateral OFC GM did not impact the significance of the results ($r> -0.69$, $p<0.002$). Similarly, the analysis with lifetime alcohol use and medial OFC GM remained significant when taking into account lifetime cocaine and nicotine use and number of cigarettes smoked in the past 30 days ($r> -0.73$, $p<0.001$).

Consideration of Potential Confounds

State depression scores were not significantly correlated with P300 amplitudes in the entire group or separately in either study subgroup (all Spearman-r < |0.08|, $p>0.76$). Similarly, as inspected with independent t-tests separately for each subject group, these amplitude measures did not differ by history of cigarette smoking (past or current vs. non-smokers; for both groups, $t<$ |1.08|, $p>0.29$; this analysis was not conducted across the entire sample given the almost parallel distribution with study group). Further, for current smokers (16 CUD/3 controls), the differential P300 response was not associated with number of cigarettes smoked per day (r=0.04, p=0.88). Cocaine urine status in CUD also did not significantly impact P300 modulation ($t_{20}<$ |0.28|, $p>0.78$).

State depression scores separately or for the whole group were also not significantly correlated with regional GM volume (regions of interest in main **Table 6.2**) [all Spearman-r < |0.25|, $p>0.13$]. Non-smokers as compared to past or current smokers had significantly higher GM volume in the ACC within controls (t_{15}= 2.34, p= 0.034; for all other regions, $t<$ |1.37|, $p>0.19$) and in the ACC (t_{20}= 2.67, p= 0.015) and lateral OFC (t_{20}= 2.44, p= 0.024) within CUD (all other regions, $t<$ |1.73|, $p>0.099$). Although similar ACC GM results were previously reported in larger sample sizes of healthy cigarette smokers vs. non-smokers [248-249], in our study across all current smokers, cigarettes smoked per day were not significantly associated with GM in any of the regions of interest ($r<|0.25|$, $p>0.29$). Nevertheless, the impact of cigarette smoking on PFC GM remains to be studied in paradigms that allow causality attributions (e.g., animal

models). Finally, GM volume also did not differ by cocaine urine status in CUD (t_{20}< |0.89|, p>0.38).

The study groups differed in their self-reported state depression scores and history of cigarette smoking (**Table 6.1**). In addition, of the 22 CUD, 13 were urine positive for cocaine on study day. We tested these variables' potential impact on significant results [including on the psychophysiological (45 minus 0¢ differential) and neuroanatomical measures, and on their intercorrelations], separately for controls, CUD, and for the combined group of all 39 subjects. Note that the groups did not differ on gender (p>0.1), therefore gender effects were not further investigated.

When separately controlling for these three potential covariates, the observed GM-P300 correlations were unchanged (all p<0.001 in controls; all p>0.26 in CUD).

DISCUSSION

To the best of our knowledge, this study is the first to specifically explore the neuroanatomical correlates of reward sensitive P300 amplitudes. We found a robust positive correlation between P300 differential amplitude response to the expectation of monetary reward and GM volume in brain regions functionally involved in reward sensitivity and salience attribution, namely the dorso- and ventro-lateral PFC, ACC, and lateral OFC, in healthy controls. In contrast, cocaine addicted individuals demonstrated – in addition to the expected compromised psychophysiological sensitivity to money and reduced PFC GM volume (specifically in the OFC, as associated with longer drug use history, **Fig. 6.2B, C**) – lack of interdependence between these two measures. Taken together, although correlation analyses are inconclusive about direction, causality or predisposition, results suggest that structural integrity of the PFC mediates electrocortical sensitivity to monetary reward. These findings extend the study of reward processing, commonly accomplished with a single modality to a multimodal functional-structural investigation.

P300 amplitude is proposed to primarily reflect brain mechanisms facilitating the focal attention needed for salience processing [250]. Subregions of the PFC comprise such a neural network where attention [251] and higher-order executive function [252-254] interface reward processing and salience attribution. Within this network, the specific functions of the DLPFC (sustained attention, behavior monitoring) [255], ACC (error monitoring, inhibitory control) [256], and OFC (reward processing, reinforcement learning) [254, 257] make these regions likely candidates for

reward-related modulation of P300 response, as indeed supported by correlations in the controls in the current study. These correlations further point to a preponderant role of *right* PFC GM in P300 response (**Table 6.2**). It has been suggested that the level of activity (and likely structural integrity) of the right PFC is specifically related to reward-modulated inhibitory control [258] where transient inhibition of right but not left PFC using low frequency repetitive transcranial magnetic stimulation impairs performance ("riskier choices") on a rewarded gambling task [259]. Before drawing sound laterality conclusions, however, results remain to be validated in lesion models.

The conspicuous absence of such correlations in CUD is supported by lesion studies, where, compared to controls, patients with chronic traumatic frontal lesions manifest deficits in P300 amplitudes on auditory tasks [260] and in response to predictive contextual processing cues [261]. Similarly, albeit at trend level, ACC GM density reductions correlate with irregularities in auditory P300 amplitudes in patients with posttraumatic stress disorder [262]. The deficits seen in the present study, both in psychophysiological response to money (maximal reward-related P300 differential, 45¢ minus 0¢) and relationship to GM volume only in reward-related regions (as observed in the controls), point to a specific reward-driven disruption in CUD. Nevertheless, although not directly supported by current results (where group differences in P300 were not significant), a more general dysfunction in P300 response generation cannot be ruled out as remains to be studied separately (e.g., by comparing current results to non-reward related P300 processing in CUD).

Results of this study need to be considered in light of its main limitations. First, the VBM approach is susceptible to the potential confounds inherent to indirect measures of neural integrity (e.g., spatial normalization of atypical brains and robustness of standard parametric tests) [263]. Because the precise GM histopathological characteristics that influence MRI segmentation are not yet known, results of this study remain to be validated with a direct inspection of brain tissue (e.g., postmortem studies). Future studies should also consider other reward-sensitive ERP components or direct neural source waveforms as is now possible with advanced MRI-guided source localization techniques. Finally, although the effects of depression, cigarette smoking, alcohol use, and urine status for cocaine were statistically inspected, their potential impact on results remains to be separately investigated. For example, given that it is not practical to exclude cigarette smoking CUD [where concomitant use of nicotine and comorbid

nicotine dependence are much higher than in the general population: 70-80% for nicotine use and 50% for nicotine dependence as compared to 22% and 13% in controls, respectively [264-268], a future study would need to recruit more cigarette smoking controls.

In sum, we showed that reward-related modulation of P300 amplitude is correlated with GM volume of prefrontal brain regions centrally involved in reward processing in healthy controls but not in CUD. This is an important finding as it highlights the potential utility of reward-modulated P300 amplitude as a functional marker for underlying neural integrity of these brain regions. Given that EEG is a substantially less expensive alternative to other imaging techniques and that MRI is not ubiquitously available (especially in clinical or international settings), establishing the P300 response to reward as an indirect biomarker of PFC integrity would be beneficial for numerous future studies, spanning healthy development (and emotional traits) to monitoring disease course or impact of treatment in clinical settings, specifically in psychopathologies affecting the PFC. The application of results to the individual subject, rather than to groups of individuals, remains to be explored.

Table 6.1. Demographic and drug use variables for healthy control and CUD subjects.

	Test	Control	CUD
Gender: Male / Female	χ^2_2=2.5	10 / 7	18 / 4
Race: African-American / Other	χ^2_2=2.6	9 / 8	17 / 5
Laterality Quotient	Z=-1.1	0.96 ± 0.07	0.92 ± 0.09
Age (years)	t=1.3	40.3 ± 6.7	42.9 ± 6.2
Education (years)	t=-1.4	14.1 ± 2.1	13.2 ± 1.9
Verbal IQ: WRAT-3 Reading	t=-1.6	98.8 ± 10.4	92.4 ± 13.3
Non-Verbal IQ: WASI - Matrix Reasoning Scale	t=-0.5	10.8 ± 2.6	10.3 ± 3.2
Depression: Beck Depression Inventory II	Z=-2.3*	2.0 ± 2.6	4.2 ± 3.1
Socioeconomic Status: Hollingshead Index	Z=-1.4	35.1 ± 15.5	27.9 ± 11.4
Cigarette Smokers (current or past / nonsmokers)	χ^2_2=11.1†	4 / 13	17 / 5
Daily cigarettes (current smokers: N = 3 / 16)	t=0.2	10.0 ± 7.0	10.7 ± 6.1
Age of onset of cocaine use (years)	--	--	24.1 ± 6.5
Duration of current abstinence (days)	--	--	4.5 ± 4.9
Severity of Dependence Scale[1]	--	--	6.1 ± 3.9
Withdrawal symptoms: 18-item CSSA	--	--	15.9 ± 9.1
Cocaine Craving: 5-item Questionnaire[2]	--	--	15.3 ± 10.6
Cocaine Use (past 30 days)	--	--	15.1 ± 8.3
Cocaine Use (lifetime)	--	--	17.8 ± 6.9
Alcohol Use (past 30 days)	--	--	5.9 ± 6.9
Alcohol Use (lifetime)	--	--	15.0 ± 12.0

Note. *p<0.05; †p<0.01

[1] Missing data for 1 subject; [2] Missing data for 2 subjects;

χ^2 tests were used for categorical variables; t-tests (or the non-parametric Mann-Whitney U in cases of skewed distributions) for all other comparisons between the two groups;

Values are frequencies or means ± standard deviation (SD);

Race: Other (Caucasian / Hispanic / Asian); WRAT-3 = Wide Range Achievement Test (3rd edition); WASI = Wechsler Abbreviated Scale of Intelligence; CSSA = Cocaine Selective Severity Assessment Scale.

Table 6.2. Regression results in 17 healthy controls between regional gray matter volume and psychophysiological sensitivity to reward.

Region	MNI Coordinates			Peak *T*	Peak *Z*	Voxels	R^2	*p*
	X	*Y*	*Z*					
R DLPFC, BA 46	25	44	26	6.86	4.39	4433	0.6730	<0.0001
R ACC, BA 32	9	49	13	6.24	4.17	629	0.4946	0.022, svc
L VLPFC, BA 44	-42	19	30	6.12	4.13	4861	0.6645	<0.0001
R Lateral OFC, BA 47	37	49	-15	5.69	3.96	1595	0.5917	0.032

P300 amplitude differential responses to money (45¢ minus 0¢) were regressed against regional gray matter volume using a whole-brain approach. Statistical maps were thresholded at cluster-level $p<0.05$, family-wise error corrected for multiple comparisons (voxel-level $p<0.001$ uncorrected) with a minimum cluster extent of 50 contiguous voxels. Age and total brain volume were used as covariates in all analyses. DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; VLPFC, ventrolateral PFC; OFC, orbitofrontal cortex; R=right and L=left; svc= small volume correction; BA, Brodmann Area.

Table 6.3. ERP task performance and ratings. Task behavior (reaction time and accuracy) and post-task self-reported ratings for all study subjects as a function of group and monetary reward condition.

		Reaction Time (ms)	Accuracy (% correct)	Interest	Excitement	Frustration
Controls (N=17)	***45¢***	230.8 (14.4)	0.94 (0.02)	4.39 (0.38)	4.39 (0.46)	5.53 (0.47)
	1¢	233.6 (13.3)	0.93 (0.02)	3.98 (0.45)	3.75 (0.47)	5.18 (0.54)
	0¢	236.0 (13.9)	0.93 (0.01)	3.68 (0.46)	3.62 (0.48)	5.24 (0.53)
CUD (N=22)	***45¢***	228.6 (8.1)	0.91 (0.02)	5.14 (0.44)	5.14 (0.43)	5.85 (0.43)
	1¢	234.7 (8.3)	0.90 (0.02)	3.95 (0.46)	3.86 (0.45)	5.14 (0.45)
	0¢	234.4 (7.8)	0.91 (0.02)	3.86 (0.45)	3.67 (0.45)	5.14 (0.47)

Values are means (SEM).

Table 6.4. Inter-correlations between cocaine, alcohol, and nicotine histories among individuals with cocaine use disorders (CUD) (N=22).

		Cocaine			Alcohol		Nicotine		
		1. Age of Onset	**2. Years of Use**	**3. Frequency of use (past 30 days)**	**4. Years of Use**	**5. Frequency of use (past 30 days)**	**6. Age of Onset**	**7. Years of Use**	**8. Number of cigarettes smoked (past 30 days)**
Spearman-*r*)	**1.**	--	-0.39	-0.07	-0.12	-0.24	0.34	-0.26	-0.43*
	2.		--	-0.17	0.44*	0.57†	0.08	0.55†	0.37
	3.			--	0.14	0.13	0.37	-0.04	0.44*
	4.				--	0.36	0.18	0.57†	0.55†
	5.					--	-0.05	0.50*	0.35
	6.						--	-0.18	0.26
	7.							--	0.51*
	8.								--

*p<0.05; †p<0.01

Note: Number of cigarettes smoked in the past 30 days was calculated as cigarettes smoked per day multiplied by 30.

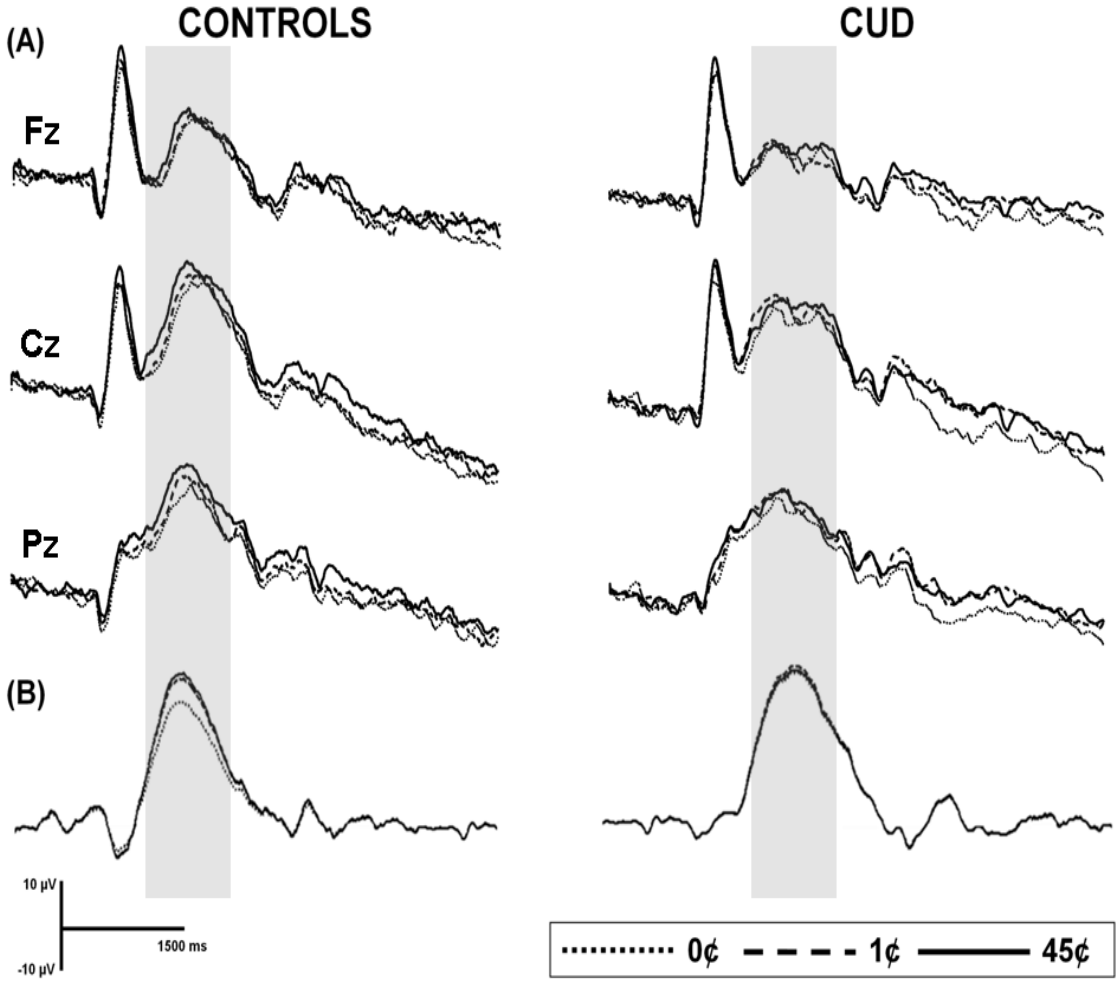

Figure 6.1. **(A)** Grand averaged P300 waveforms at FZ (top), CZ (middle) and PZ (bottom) electrodes for control subjects (left; N=17) and individuals with cocaine use disorders (CUD, right; N=22) reflecting 0 ms to 1500 ms after the onset of the expectation stimulus (S1) for each monetary reward condition (45¢, 1¢ and 0¢) during 'Go' trials on the task. **(B)** P300 factor isolated by PCA for the two study groups for each monetary reward condition (45¢, 1¢, and 0¢) at PZ.

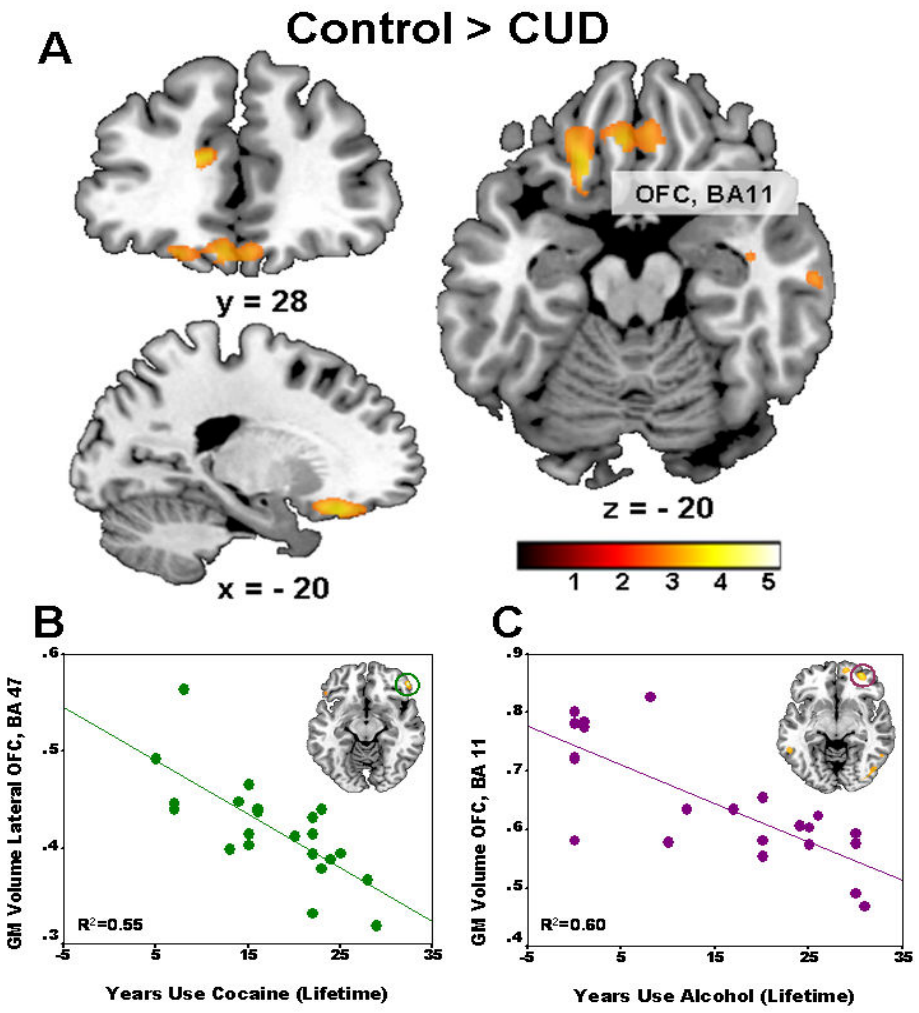

Figure 6.2. (A) Controls>CUD: Healthy controls had increased GM of the OFC, a cluster encompassing the bilateral rectal gyri (BA 11), and the left inferior frontal gyrus (BA 48). **CUD>Controls**: There were no regions of significantly increased GM in CUD compared with control subjects using the same whole brain cluster-level correction for multiple comparisons. Threshold was set at exploratory voxel-level $p<0.005$ uncorrected, with 50 adjacent voxels. Duration of lifetime cocaine use (**B**) and lifetime alcohol use (**C**) are negatively correlated with GM volume in the OFC. Threshold was set at $p<0.001$ and 50 voxels for analyses with drug use history. Age and total brain volume were used as covariates in all analyses. Color bar represents *t* values. Color maps are overlaid on a

single subject T_1-weighted template and images are presented in neurological view (right is right).

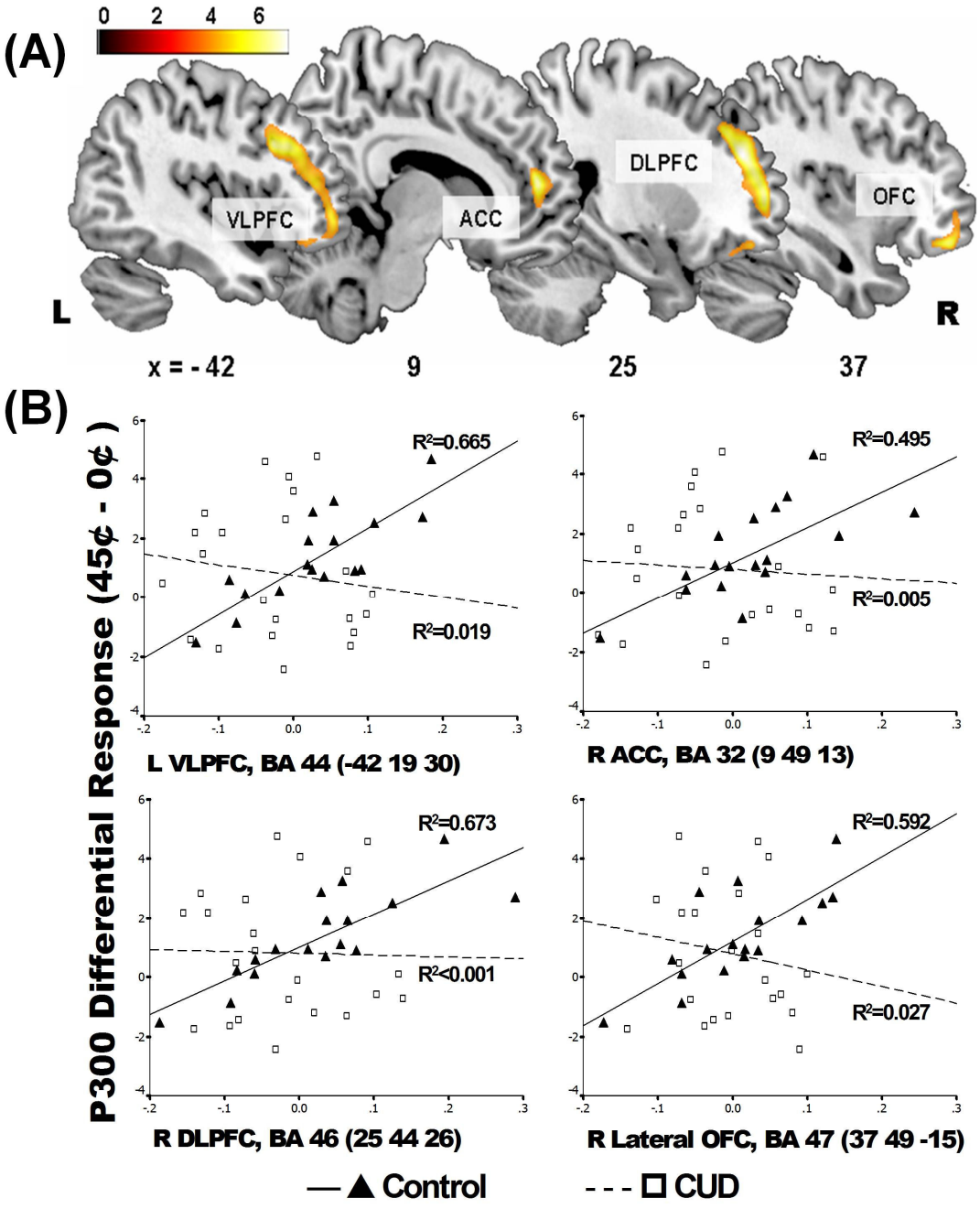

Figure 6.3. Neuroanatomical correlates of reward-sensitive P300 amplitudes. **(A)** Differential P300 responses to 45¢ (reward) versus 0¢ (non-reward) trials on the forced-choice sustained attention monetary reward paradigm (**Fig. 6.1**) correlated with gray

matter volume in four distinct clusters encompassing ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), dorsolateral PFC (DLPFC), and lateral orbital frontal cortex (OFC) in 17 control subjects (cluster-level $p<0.05$, family-wise error corrected for multiple comparisons with 50 contiguous voxels; threshold for display $p<0.001$ uncorrected). Color bar represents t values. Color map is overlaid on a single subject T_1-weighted template. **(B)** Scatterplots showing relationship between gray matter volume, adjusted for age and total brain volume, and P300 amplitude differential response (45¢ minus 0¢), displayed as a function of study group [17 controls and 22 individuals with cocaine use disorder (CUD)]. Coordinates are reported following MNI convention. Gray matter values were extracted from the significant clusters in **A**. All regressions in controls are significant ($p<0.001$) and all regressions for CUD are not ($p>0.46$). R=right; L=left.

CHAPTER 7

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Title: Event-related potentials in the prediction of choice: relevance to insight

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ABSTRACT

Event-related potentials (ERPs) index the salience/arousal of evocative stimuli, but their ability to predict choice behavior has not been tested. In the present study, we hypothesized that the ERP late positive potential (LPP), elicited by emotional images, would predict choice to view these same images independently of self-reports. The predictive ability of LPPs could be especially useful in individuals for whom insight into behavior (and, consequently, the validity of self-reports) is compromised. We recently documented such impairment in cocaine addiction. Therefore, 59 individuals with cocaine use disorder (CUD) and 32 healthy control subjects completed the following procedures in a fixed sequence: (i) underwent ERP recordings while passively viewing pleasant, unpleasant, neutral, and cocaine images; (ii) provided self-report ratings of each picture's arousal; (iii) completed a previously validated choice task to assess objective choice for viewing these same images; and (iv) completed a second previously validated probabilistic learning choice task to assess insight – whether perceived choice corresponds with actual choice. Results showed that pleasant relative to neutral LPPs predicted respective choice in all subjects. In contrast, cocaine relative to pleasant LPPs predicted respective choice only in CUD with impaired insight. Also in this CUD subgroup only, this choice behavior was associated with increased disease severity. Finally, although cocaine relative to pleasant arousal ratings predicted respective choice in both CUD groups, these ratings were associated with self-reported drug use only in CUD with unimpaired insight, suggesting that using ratings to predict behavior (drug use) remains valid when insight is intact. Collectively, these results show that LPPs elicited by salient stimuli (pleasant images in all subjects; cocaine images in impaired insight CUD) predict objective choice to view these same stimuli. These relatively inexpensive and portable ERPs could therefore provide a diagnostic tool to predict clinically relevant behavior (e.g., drug seeking in addiction) if self-reports are compromised.

INTRODUCTION

(Edited to reduce redundancy)

In addition to LPP's role in healthy individuals, we were interested in the predictive validity of LPPs in individuals whose self-reported behavior may be invalid such as those with *impaired insight* into behavior, commonly conceptualized as denial of (or failure to recognize) the severity of illness, compromised control of action, or unawareness of one's social deficits [269-270]. For this purpose, we studied individuals with cocaine use disorder (CUD), who show dysfunction of brain networks subserving insight and self-awareness [271]. Support for this specific deficit rests on accumulating evidence for discrepancies between self-reports and objectively measured goal-driven behavior or brain function in CUD [272-274]. Similarly, CUD inaccurately identify their own task-related errors [275] and choice behavior for viewing drug-related versus non-drug-related pictures, with the latter also associated with increased drug-seeking behavior [114]. Thus, objectively ascertained LPPs could provide a much-needed tool to predict behavior in psychopathologies marked by impaired self-awareness including drug addiction.

We hypothesized that LPPs elicited by salient pictures would predict - independently of self-reports - the choice to view these same salient pictures: pleasant or unpleasant images in all subjects, and cocaine images in CUD. In addition, given the high coupling between implicit, automatic measures and choice when insight into preference is lacking [276], we hypothesized that the automatic, bottom-up LPP would predict cocaine choice especially in CUD with impaired insight. In contrast, we hypothesized that self-reports would remain predictive of cocaine choice in CUD without impaired insight. The parallel associations with actual drug use were also expected.

METHODS

Subjects

Ninety-one participants (59 CUD and 32 healthy controls), all right-handed and native English speakers, underwent all study procedures described below. Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board. *Other details regarding subject recruitment and screening are outlined in Appendix A.*

Study Procedures

Study procedures encompassed four steps, all completed in a fixed sequence: LPPs, picture ratings, picture choice, and insight assessment.

Stimuli and Psychophysiological Recordings.

(Same as Appendix C)

Picture Ratings.

(Same as Appendix C)

Picture Choice Task. Immediately following the ERPs and picture ratings, subjects completed a choice task that assessed their *objective* preference for these same IAPS and cocaine images [274]. During this choice task, subjects chose via continued button pressing between two fully-visible side-by-side images (one image from one picture category and one image from a different picture category). Because there were no correct or incorrect responses, this choice exclusively reflected subjects' own preference for viewing the respective images. Choice for a desired image enlarged this chosen image to fully cover the screen, which subjects could view for the trial duration of 5000 msec by continued button pressing; 500 msec of non-response, however, returned the side-by-side image display. The total number of button presses for each picture category was summed across 70 choice trials.

Insight Assessment. A different choice task with probabilistic contingencies enabled insight assessment. Here, subjects indicated choice for viewing the IAPS and cocaine images via a single button press for pictures hidden under flipped-over cards, arranged in four decks [274]. During each trial, subjects chose from a particular "deck." Immediately after this choice, an image chosen from that deck was revealed, covering the entire screen for 2000 ms of passive viewing. Two task design features reduced certainty of choice to enable insight assessment. First, each deck contained 26/30 pictures from a particular category, allowing pictures from other categories to be interspersed within each deck. Second, at the conclusion of each run (which occurred when subjects selected from a particular deck for a total of eight times), deck location of the four picture categories shifted.

Immediately at the conclusion of this task, subjects were prompted with the following question, "What kinds of pictures do you think you chose to look at most often?" Subjects pressed a button corresponding to one of the four picture categories to indicate what they perceived was their most selected picture type. Following previous procedures [114], we compared this self-report with actual behavior (i.e., subjects' most selected picture category). The CUD with agreement between these subjective and objective measures were classified as having *unimpaired insight* (N=33), whereas the CUD lacking agreement were classified as having *impaired insight* (N=26). All control subjects included in this study had unimpaired insight. Previous findings suggested insight impairment to be a unique neuropsychological deficit in CUD, not mediated by impairments of other cognitive functions [i.e., incidental memory and executive functioning [277], verbal learning and memory [278], or non-verbal intelligence [211]] [114].

Statistical Analyses

Regression analyses tested our main hypothesis that LPPs elicited by emotional images predict subsequent choice to view those same images. Importantly, to inspect whether LPPs predict choice beyond self-reports, these regressions were performed while controlling for self-reported arousal ratings of these same pictures. To test for modulating effects of insight, all regressions were first conducted across all subjects and then split by subgroup (impaired insight CUD, unimpaired insight CUD, and controls).

A first set of regressions tested LPP associations with respective choice behavior. The variables in these regressions were scores for pleasant, unpleasant, or cocaine pictures each compared with neutral pictures (three scores each for LPPs, self-reports, and choice), reflecting the effects of salient images compared with a neutral baseline. In addition, cocaine pictures were compared with pleasant pictures, a comparison of interest in CUD to examine choice between two different salient image categories. All scores were calculated by examining residuals generated from univariate regression analyses in which the control variable (e.g., responses during neutral pictures) were used to predict the response variable (e.g., response during pleasant pictures); similarly derived residual scores were analyzed in a previous study of addicted individuals and healthy controls that also used a combined IAPS/physiological approach [279]. A final set of regressions, conducted in the CUD only, examined cocaine relative to neutral or pleasant LPP

associations with the drug use variables listed in Table 7.1. Because these drug use variables contained extreme outliers, these analyses were conducted with Spearman (rank) correlations (except the cocaine selective severity assessment, which was normally distributed and therefore examined with standard regressions). Given the number of drug use variables available for inspection, these drug use analyses were considered significant at $p<0.01$ to reduce the potential for type I error. Choice behavior analyses, our primary interest in the current study, were considered significant at $p<0.05$. For all regressions, missing data were excluded on a pair-wise basis (i.e., we included in each analysis the maximum number of participants with complete data for the variables involved).

RESULTS

LPP and Arousal Prediction of Picture Choice (Table 7.2)

As expected, pleasant relative to neutral LPPs predicted respective pleasant relative to neutral choice across all subjects, but only in the late (1000-2000 ms) LPP window (Figure 7.1A). Importantly, this late-window LPP explained unique variance beyond self-reported arousal, which also predicted choice in all subjects (Figure 7.1B). Unpleasant relative to neutral LPPs did not predict respective choice, likely because these unpleasant images, while still salient, were infrequently chosen.

Also as expected, cocaine (relative to pleasant) LPPs predicted respective choice independently of arousal only in impaired insight CUD (early window: Figure 7.2A; late window: Figure 7.2B). Tests of coincidence (i.e., comparison of slopes and intercepts of these regressions between the groups) showed that the magnitude of the cocaine relative to pleasant LPP-choice associations differed in the two cocaine subgroups [early window: $F(1,54)=6.1$, $p<0.05$; late window: $F(1,54)=7.6$, $p<0.01$]. In contrast, with one exception, cocaine relative to pleasant or neutral arousal ratings predicted respective choice in both CUD subgroups.

LPP and Arousal Associations with Drug Use Variables

Here associations were observed between the arousal ratings and drug use variables, clearly driven by the unimpaired insight CUD. In this subgroup only, arousal correlated with more money spent per use on cocaine (controlling for both LPP windows, for both cocaine relative to neutral or pleasant comparisons) and shorter current abstinence

(controlling for both LPP windows, for the cocaine>neutral comparison). Although drug use did not correlate with LPPs, withdrawal symptoms as assessed by the cocaine selective severity assessment (total score) correlated with cocaine relative to pleasant choice in impaired insight CUD (β=0.57, $p<0.01$), and such choice was indeed predicted by the respective late-window LPP also in this subgroup (described above). These results suggest an *indirect* effect of LPPs on withdrawal/addiction severity in impaired insight CUD, as supported by a significant Sobel test in this subgroup only ($Z=1.96$, $p<0.05$; Figure 7.3).

Effects of Covariates

Across all subjects, pleasant relative to neutral LPP continued to predict respective choice after controlling for cigarette smoking history (β=0.24, $p<0.05$) and depression (β=0.26, $p<0.05$). Impaired insight CUD and unimpaired insight CUD did not differ on any demographic variables (Table 7.1), indicating that these variables are unlikely to account for the current results pertaining to insight.

DISCUSSION

Despite extensive evidence that ERPs over parietal cortex covary with stimuli salience [280], their ability to predict choice behavior was previously unknown. Consistent with our first a priori hypothesis, our results show for the first time that LPPs elicited in response to salient pleasant images predict subsequent choice to view those same pleasant images. Interestingly, it was sustained emotional processing of these pleasant images as indexed by the late LPP (but not initial image processing as indexed by the early LPP) that translated into increased choice. A recent study of healthy individuals showed similar results, revealing a later but not earlier LPP to be associated with behavior (better recognition memory for pictures) [281]. Because in the current study the LPP accounted for unique variance in choice (not explained by the self-report LPP analogue, arousal), results support the important idea that self-report and physiological/neural measures assess unique and possibly complementary information [282-283].

Consistent with our second a priori hypothesis, the ability of LPPs to predict behavior was modulated by insight. Cocaine relative to pleasant LPPs predicted respective choice in impaired insight CUD, but not in unimpaired insight CUD, during

both the early and late LPP windows. By using LPPs to predict objective cocaine choice behavior, these findings extend previously revealed correlations between ERPs and self-reported craving [284], and suggest that the prediction of actual choice behavior in unawareness may benefit from these objectively ascertained LPPs. Cocaine-related LPPs in impaired insight CUD may also signal the actual severity of addiction, as revealed by its significant indirect effect on withdrawal symptoms uniquely in this cocaine subgroup. Such efforts to associate LPPs and drug use are crucial considering that CUD with impaired insight may have limited capacity to identify or report on their internal states [272-275], an interoceptive deficit that is associated with more severe drug seeking in addiction [114] and poor clinical outcome more generally [285].

In contrast, when insight is intact, behavior prediction may be amenable to conveniently administered self-report assessments (e.g., arousal). Indeed, although unexpectedly associated with choice behavior in both CUD subgroups, cocaine-related arousal ratings were associated with current drug use measures (the amount of money spent per use on cocaine, cocaine abstinence) uniquely in the unimpaired insight CUD. These results are consistent with the idea that the strength of association between self-reports and relevant drug use variables may vary as a function of individual characteristics [286]. The concept of insight in addiction could potentially inform the discussion on when self-reports can validly be used to predict important drug-relevant outcomes such as relapse [287], helping to ensure the efficient use of scarce clinical resources.

A limitation of this study pertains to the use of a categorical insight measure. A dimensional (i.e., quantitative) index of insight could improve prediction of behavior. A second limitation involves potential overlap of insight with other cognitive and psychological mechanisms. Although several alternative cognitive explanations have been previously ruled out [114], additional variables (e.g., coping, sustained attention) remain to be explored. A third limitation is that our study included mostly males, and therefore future studies will need to generalize these results to females.

Taken together, our results support the novel conclusion that a psychophysiological scalp-recorded measure (the LPP) predicts objective choice behavior, in both healthy individuals and individuals with impaired insight (those

addicted to cocaine). These findings contribute to recent efforts to use neural activity to ascertain choice [288], while also extending such findings to a clinically relevant psychopathology. It is becoming increasingly feasible to deploy ERPs at clinical intervention sites, as such techniques are relatively inexpensive (compared with other neuroimaging techniques), portable (e.g., they can now be transported and implemented via backpack), and non-invasive. Our findings suggest that ERPs could provide a powerful assessment tool to help forecast disadvantageous behaviors in select psychopathologies (e.g., drug seeking in CUD), with the goal of improving prevention and intervention efforts.

Table 7.1. Demographic Characteristics and Drug Use by Study Group.

	Impaired Insight CUD (N=26)	Unimpaired Insight CUD (N=33)	Healthy Controls (N=32)
Gender (male/female)	23/3	30/3	28/4
Ethnicity (African-American/Caucasian/Other)	18/5/3	19/9/5	21/8/3
History of cigarette smoking (current or past/never; available for N = 26/31/30)	23/3†	25/6†	6/24
Daily cigarettes (current smokers: N = 17/17/2)	7.3 ± 4.2	7.5 ± 6.1	7.0 ± 4.2
Time since last use (within 4 hrs/>4 hrs)	9/8	4/13	2/0
Education (years)	12.5 ± 1.3	13.1 ± 2.7	13.5 ± 2.2
Age (years)	44.3 ± 8.1	43.3 ± 7.2	41.4 ± 6.9
Socio-economic status (SES)	30.9 ± 9.1	32.7 ± 11.6	31.1 ± 11.5
Non-verbal intellectual functioning: Wechsler Abbreviated	9.4 ± 5.3	10.0 ± 3.0	11.4 ± 2.4
Self-reported state depression (BDI)	8.3 ± 5.8†	8.7 ± 8.7†	1.6 ± 2.6
Cocaine urine status (positive/negative)	11/15	11/22	--
Treatment-seeking status (no/yes)	18/8	18/15	--
Age at onset of cocaine use (years)	26.7 ± 7.9	26.0 ± 8.1	--
Duration of use (years)	15.1 ± 7.1	16.2 ± 8.3	--
Frequency of use (days/week): last 30 days (min – max, median)	0-7, 1	0-7, 1	--
Current use in $ per use (min – max, median): last 30 days	0-150, 40	0-200, 10	--
Duration of current abstinence (days) (min – max, median)	0-120, 0	0-1825, 4	--
Duration of longest abstinence (days) (min – max, median)	90-2920, 330	7-2192, 700	--
Total score on the Cocaine Selective Severity Assessment	15.2 ± 10.8	18.7 ± 11.3	--
Severity of Dependence Scale (range: 0-15)	11.0 ± 9.4	10.9 ± 9.3	--
Cocaine Craving Questionnaire (range: 0-45)	12.5 ± 10.8	13.5 ± 10.1	--

Note: Numbers are $M \pm SD$ or frequencies (unless otherwise noted); †differs significantly from controls; ***$P<0.001$.

Table 7.2. Standardized regression coefficients for the predictive effects of early-window (400-1000 ms) and late-window (1000-2000 ms) LPPs and self-reports on respective choice behavior, combined and separately for each study group.

	All Subjects		Impaired Insight CUD		Unimpaired Insight CUD		Healthy Controls	
	β_{LPP}	β_{Rat}	β_{LPP}	β_{Rat}	β_{LPP}	β_{Rat}	β_{LPP}	β_{Rat}
PICTURE CHOICE								
Pleasant (relative to Neutral)								
Early LPP	.15	.30*	.15	.37	.27	.35*	.15	.20
Late LPP	.24*	.31*	.28	.39	.26	.35	.29	.18
Unpleasant (relative to Neutral)								
Early LPP	.08	.14	.10	.23	.32	.05	-.11	.23
Late LPP	.03	.15	.08	.23	-.02	-.01	-.02	.20
Cocaine (relative to Neutral)								
Early LPP	-.01	.54*	.36	.50*	-.02	.59*	-.05	.34
Late LPP	-.03	.54*	.37	.55*	-.10	.57*	.00	.34
Cocaine (relative to Pleasant)								
Early LPP	-.06	.55*	.45*	.31	-.18	.60*	.13	.37
Late LPP	-.03	.55*	.53*	.42*	-.17	.58*	.05	.34

Note. *significant association (p<0.05), and not driven by outliers; β_{LPP} = standardized regression coefficient for the LPP; β_{Rat} = standardized regression coefficient for the arousal rating.

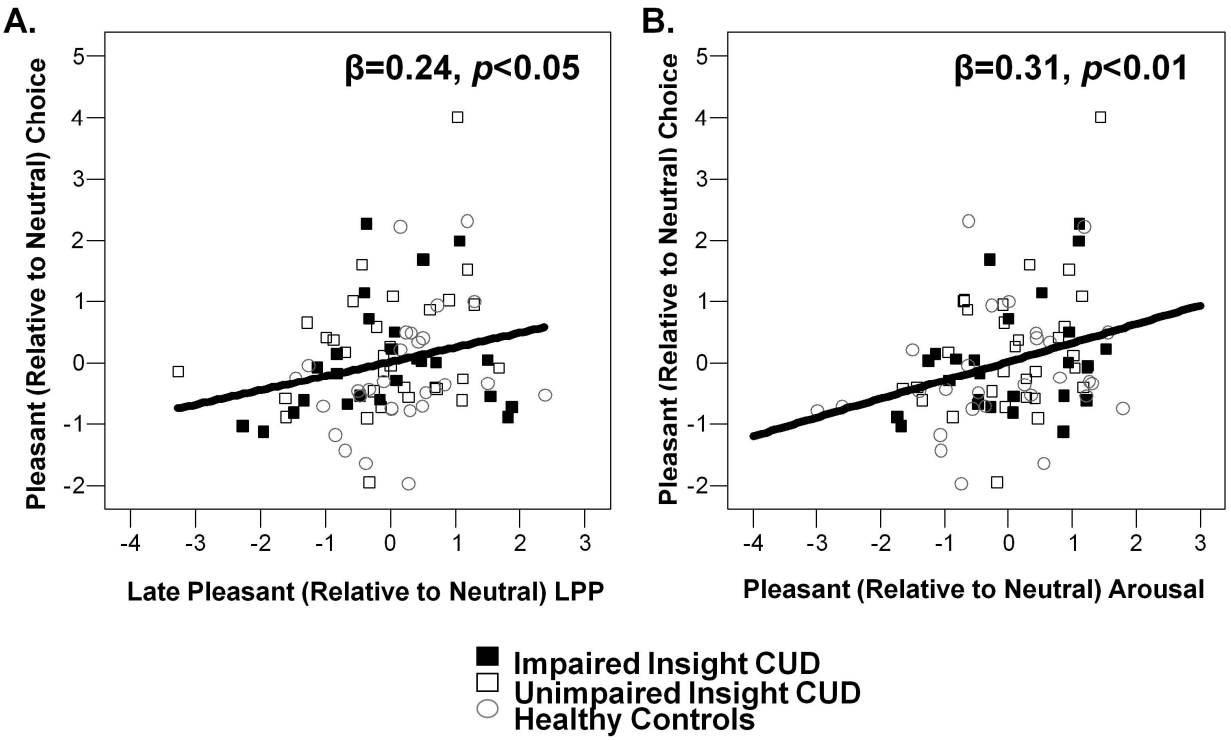

Figure 7.1. Prediction of pleasant-related choice by respective LPPs. Figure shows significant associations across all subjects (N=91) between pleasant relative to neutral choice with (A) pleasant relative to neutral LPP (late window: 1000-2000 ms) and (B) pleasant relative to neutral arousal. Abscissa and ordinate values are standardized residuals.

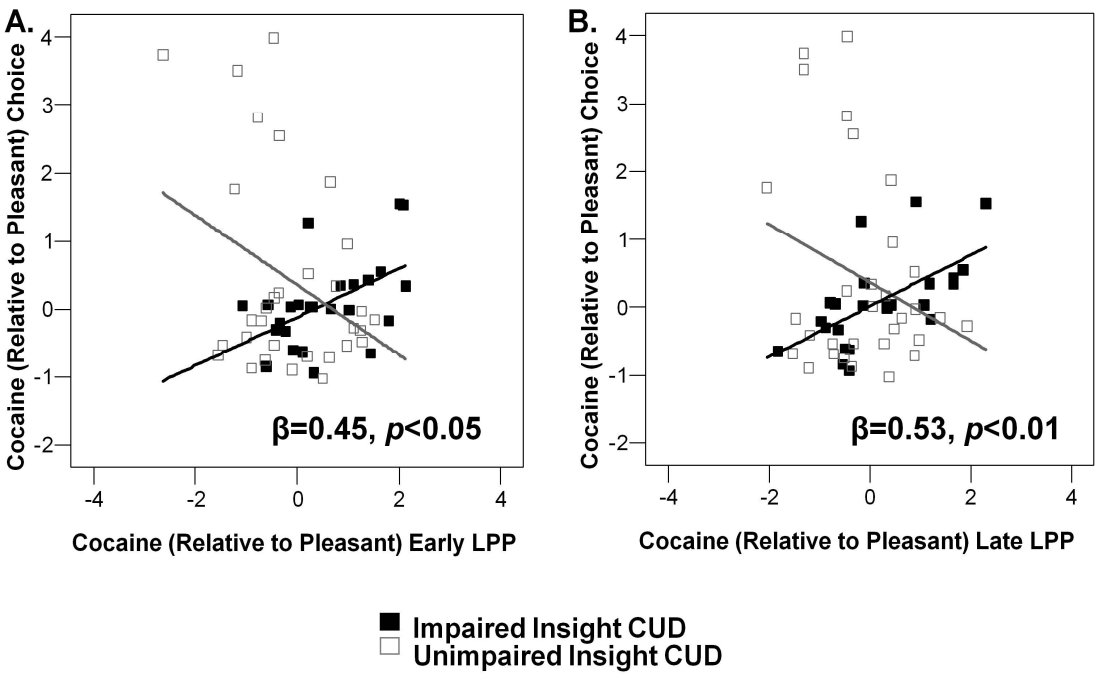

Figure 7.2. Prediction of cocaine-related choice by respective LPPs. Figure shows associations between cocaine relative to pleasant choice with respective LPPs as measured during both the (A) early window (400-1000 ms) and (B) late window (1000-2000 ms). Associations are significant in the cocaine subjects with impaired insight (N=26) (black line), but not in those with unimpaired insight (N=33) (gray line). Abscissa and ordinate values are standardized residuals.

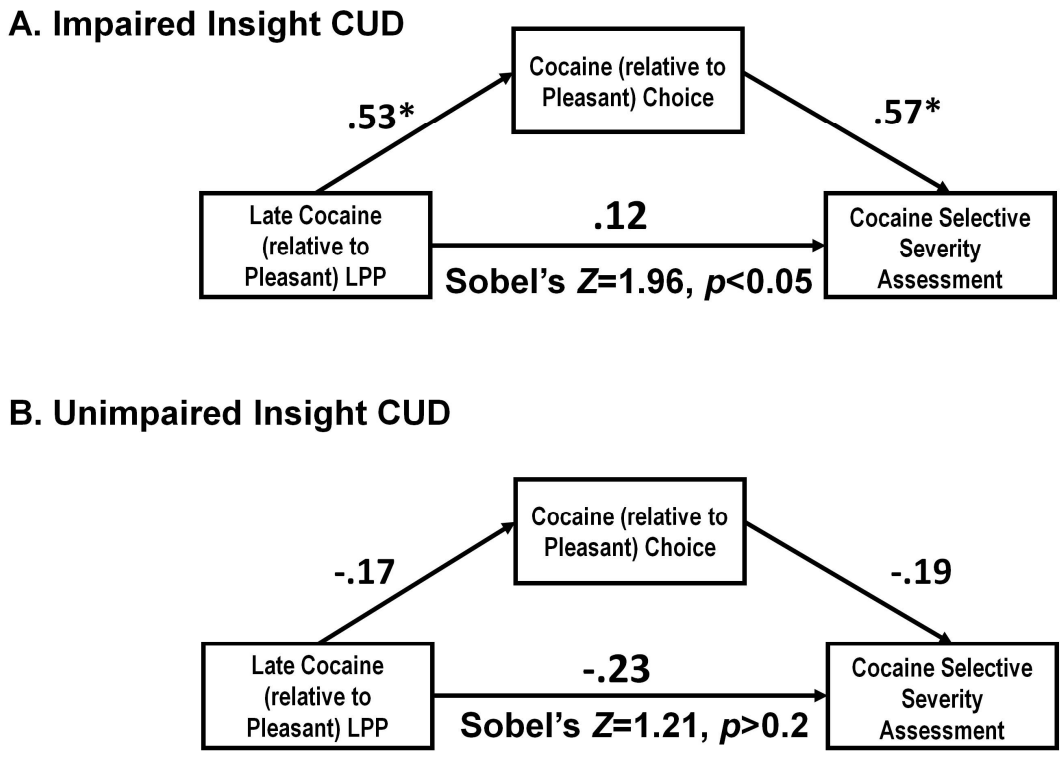

Figure 7.3. Indirect effect of the late-window (1000-2000 ms) cocaine relative to pleasant LPP on the cocaine selective severity assessment (total score; a measure of withdrawal symptoms) through cocaine relative to pleasant choice behavior. The indirect effect (as tested with Sobel's *Z*) was significant in (A) cocaine subjects with impaired insight (N=26), but not in (B) cocaine subjects with unimpaired insight (N=33); for both (A) and (B), the bolded, solid lines highlight this tested pathway. Figure shows standardized regression coefficients for the associations among all variables (cocaine relative to pleasant LPPs, arousal, and choice, as well as the cocaine selective severity assessment). Asterisks indicate significant associations *(*$p<0.05$ for choice, $p<0.01$ for the cocaine selective severity assessment).

CHAPTER 8

(Manuscript in preparation)

Title: Electrophysiological Correlates of Frontal Activation during Emotion Reappraisal

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ABSTRACT

Emotion reappraisal is a cognitive strategy that alters the emotional experience by reinterpreting the meaning of an emotional situation. Neuroimaging studies have highlighted the role of prefrontal cortical (PFC) regions in suppressing emotional experience during reappraisal. However, electrophysiological studies have only identified modulation of late positive potential (LPP) component during emotion reappraisal which only suggests altered emotional arousal and does not correspond to recruitment of PFC-mediated cognitive control mechanisms. Therefore, the aim of this study is to identify electrocortical marker of PFC activation during reappraisal. Forty-nine healthy undergraduate students viewed neutral and unpleasant pictures. At 1.5 sec after picture onset, subjects were instructed either to view the picture as they normally would, or to reduce their emotional response to the picture by reinterpreting its meaning. The results showed a significant suppression of LPP amplitudes in response to reappraised unpleasant pictures at frontal and parieto-occipital electrode sites. Moreover, there was a significant desynchronization of induced alpha in the reappraised compared to the attended trials at left frontal electrode sites. The modulation (normally viewed minus reduced) of LPP amplitude and alpha power were also positively correlated, indicating that these two neural indices covary as a function of emotion reappraisal. These results suggest that while modulation of LPP amplitude reflects altered emotional appraisal, desynchronization of induced frontal alpha band is reflective of prefrontal cortical activation during emotion reappraisal. These data are largely consistent with existing functional neuroimaging studies which highlight the role of the PFC is emotion regulation, and suggest that frontal alpha desynchronization could be an interesting metric for interactions between emotion and cognition that rely on the PFC.

INTRODUCTION

Emotion regulation typically refers to processes engaged when individuals try to influence the type or amount of emotion they experience and how these emotions are expressed [289]. Emotion regulatory behaviors (or strategies) are normally used to enhance or blunt emotional experiences, successful use of which is related to various psychological, social, and physical health outcomes [290].

One of the most flexible and efficacious regulation strategies is reappraisal, which involves reinterpreting the meaning of emotionally evocative stimuli [289, 291-292]. By changing a stimulus' affective value, reappraisal can effectively modulate subjective reports of emotion, facial expression, both autonomic and central measures of arousal [115, 293-298]. A recently proposed working model of the cognitive control of emotion [119] posits that emotion generation and regulation involve the interaction of appraisal systems, such as the amygdala (encoding the affective properties of the stimuli in a bottom-up fashion) with control systems implemented in the prefrontal cortex (PFC; supporting top-down cognitive control) [119-120, 299].

Functional neuroimaging studies of emotion regulation using a reappraisal strategy have provided evidence for this model of the cognitive control of emotion. These studies implicate increases in the ventromedial and lateral PFC activity [118-121], and decreases in the amygdala activity [300-301] when negative emotion is regulated by the reinterpretation of the emotional stimuli. Although most studies have reported left PFC activation during cognitive reappraisal to reduce negative emotion [118-119], others have also shown bilateral [300] and even right [121] ventral PFC activations during successful emotion reappraisal.

Event-related potentials (ERPs) have also been used to provide more temporally fine-grained indices of the effects of reappraisal. Specifically, the late positive potential (LPP), a widely distributed ERP component that is larger throughout the presentation of emotional compared to neutral pictures and words [70, 302-307] has shown to be sensitive to reappraisal instructions [115-117]. For example, Hajcak and Nieuwenhuis [115] found that when participants were asked to reappraise unpleasant pictures, the LPP was reduced relative to the control condition. Similar modulations of the LPP following more open-ended emotion regulation instructions have also been reported [116, 308]. Thus, the LPP seems to

index emotional arousal, and therefore may not be a suitable electrocortical metric of the PFC-mediated regulatory mechanisms during reappraisal.

Therefore, event-related EEG oscillations might be quantified to explore enhanced cortical activation during emotional reappraisal. Specifically, frontal alpha (i.e., 8 – 13 Hz) appears to mainly reflect the inhibition and disengagement of task-relevant cortical regions [122, 309-311] and therefore, can be understood as inversely related to cortical activity [122, 309]. For example, a number of studies have used alpha-band power to shed light on the asymmetrical involvement of the PFC in approach- and avoidance-related motivational states [312-315]. Thus, power in the alpha band might be used to index variability in frontal cortical activity during reappraisal. This possibility is further highlighted by fronto-parietal interactions within the alpha oscillatory range that are involved in the executive control of complex cognitive functions [123, 316].

In the present study, we hypothesized that frontal activation associated with cognitive reappraisal would be reflected in event-related desynchronization (ERD; i.e., decrease in spectral power) of induced frontal alpha oscillation. To further investigate if both alpha band ERD and LPP modulation are reflective of cognitive reappraisal processes, we further hypothesized that greater frontal alpha ERD would predict larger reductions in LPP amplitude during reappraisal. Moreover, event-related theta (i.e., 4–7 Hz) oscillations, shown to be sensitive to emotion valence and not arousal [317-318], were also examined as an additional measure of processing of affective stimuli.

Unlike conventional analysis methods of ERP and EEG oscillatory activity, this study used the SPM-based analysis approach [SPM8 for MEG/EEG (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm)] that uses general linear model to exploit multiple experimental designs and uses random field theory to circumvent the multiple comparison problem in a mass univariate test [86], which is more commonly used in neuroimaging studies [319]. For a completely data-driven EEG/ERP data analysis, sensor-level topological inferences of SPM can be used to find significant effects in time × frequency or time × channels search spaces, whose *p*-values are appropriately adjusted for multiple comparisons [320].

METHODS

Participants

Forty-nine undergraduate students (23 male, 26 female) participated in the study. Three participants were excluded due to poor quality EEG recordings, and therefore 46 participants (23 male, 23 female) were included in the final EEG analyses. The study was approved by the Stony Brook University Institutional Review Board (IRB) and all participants gave informed consent and received course credit.

Stimulus Materials

Fifty unpleasant pictures (e.g., car crashes, angry dogs) and 50 neutral pictures (neutral landscapes, household objects) were selected from the International Affective Picture System[1] (IAPS; Lang, Bradley & Cuthbert, 2005). Normative ratings indicated that the unpleasant pictures were less pleasant (valence $M = 2.51$, $SD = .78$) and more emotionally arousing ($M = 5.78$, $SD = .68$) than the neutral pictures ($M = 5.02$, $SD = .44$ and $M = 3.44$, $SD = .41$), respectively (higher numbers indicate more pleasant and higher arousal ratings). Each picture was displayed in color and filled the computer screen (which measured 48.26 cm, diagonally). Participants were seated approximately 60 cm from the screen and the images occupied about 40° of visual angle horizontally and vertically. Partway through picture presentation, participants heard the word, "normal" or "reduce" played through earphones.

Procedure

Participants were told that they would be viewing unpleasant and neutral pictures, and that during picture presentation, they would hear one of two words. If they heard the word 'normal', participants were told that they should continue viewing the picture as they normally would. If they heard the word, 'reduce', participants were told that they should reduce their emotional response to the picture *by making the picture seem less emotional*. Participants were told that they should do this by changing the *meaning* of a picture, or their *perspective* on the depicted characters and events. For example, participants could tell themselves that a photo of a gruesome war scene was taken from a movie, or that the people depicted in a house-fire would survive. The experimenter provided examples by presenting IAPS pictures and re-interpreting picture meaning for

the participant. Special attention was paid to the neutral pictures – specifically, the experimenter explained that it might be difficult for participants to reduce their response to a picture that was already relatively un-arousing, however that they should try to do so nonetheless. Again, the experimenter gave examples using neutral IAPS pictures (e.g., a building in a picture was boring and nothing interesting would ever happen there).

Next, participants performed six practice trials to familiarize themselves with the paradigm. After each of the 'reduce' trials, the experimenter asked participants to indicate how they had reduced their emotional response to the picture, thus providing an opportunity for the experimenter to determine that participants had understood the directions and were completing the task as instructed (i.e., using cognitive reappraisal as opposed to another emotion regulation strategy).

Trials were blocked by picture type and there were 4 blocks - 2 neutral and 2 unpleasant. Block order was determined randomly for each participant. Prior to each picture-type block, participants were informed about the types of pictures they would be seeing in the upcoming block (e.g., the screen read, "In the next block, you will only see unpleasant pictures.").

Each trial began with a white fixation cross that was presented in the center of a black background for 1,000 ms. Following this, participants viewed an unpleasant or neutral picture; 1,500 ms after picture onset, participants received the auditory instruction informing them to continue viewing the picture as they normally would ("normal") or to reduce their emotional response to the picture using cognitive reappraisal ("reduce"). The picture remained onscreen for 5,500 ms beyond the instruction; thus total picture presentation time was 7,000 ms [2]. Participants were asked to reduce their emotional response to exactly half of the unpleasant and half of the neutral pictures in each block, and the order of 'regulated' and 'normal' trials was random within each block. Across the entire experiment, there were 25 trials of each type: unpleasant normal, unpleasant regulated, neutral normal, and neutral regulated. Each participant viewed all pictures, and picture assignment to the 'regulated' or 'normal' conditions was determined pseudorandomly within the constraints noted above. Participants received a break after each picture-type block and the inter-trial interval was 1,000 ms, during which time participants viewed a white fixation cross centered on a black background.

EEG recording and Data Reduction

Continuous EEG was recorded using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Sixty-four electrode sites were used, based on the 10/20 system, as well as one electrode on each of the left and right mastoids. Four facial electrodes recorded the electrooculogram (EOG) generated from eyeblinks and eye movements: vertical eye movements and blinks were measured with two electrodes placed ~1 cm above and below the right eye; horizontal eye movements were measured with two electrodes placed ~1 cm beyond the outer edge of each eye. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio. The data were digitized at 24 bit resolution with a sampling rate of 512 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 102.4 Hz. Each active electrode was measured online with respect to a common mode sense active electrode producing a monopolar (non-differential) channel.

Off-line pre-processing were performed using SPM8 and custom MATLAB (The MathWorks, Natick, MA) scripts. Data were filtered with low and high cutoffs of 0.01 and 30 Hz, respectively and were then re-referenced to the averaged electrical activity from all 64 scalp sites. Due to the onset of two events in each trial, i.e., the picture, followed by the auditory instruction, two separate analyses were conducted. First, ERPs were analyzed in response to picture onset; to this end, the EEG was segmented for each condition (unpleasant normal, unpleasant regulated, neutral normal, and neutral regulated) beginning 200 ms prior to the picture onset and continuing for 1500 ms (i.e., until the presentation of the reappraisal instruction). Second, for the analysis of the electrophysiological response to reappraisal, the EEG was segmented beginning 200 ms prior to the instruction onset and continuing for 5000 ms (i.e., until the end of the picture presentation). For each trial, the baseline was defined as the 200 ms prior to the event (picture or instruction onset).

Eye blink and ocular corrections were performed using the partial signal space projection (pSSP) method proposed by Nolte and Hämäläinen [321]: the contribution of estimated spatial structure of eye-blink artifact was removed only from the artifact-ridden epochs, leaving as much information as possible in the data [321]. Artifact rejection procedure identified a voltage step of more than 75 μV between sample points and a

peak-to-peak voltage difference of 150 μV within an epoch. Additional artifacts were identified through visual inspection and the contaminated epochs were subsequently rejected.

Robust averaging was used to create artifact-free ERPs [322], whereas time-frequency (TF) representations of spectral power over a 4 – 13 Hz frequency range were obtained by applying a Morlet wavelet transform from 150 ms before the onset of auditory instruction to 4500 ms after the auditory instruction. This "windowing" of the original epoch was performed to avoid edge-effects; distortions in the time-frequency transformation at the edges of an epoch [323]. To compute induced (non-phase-locked) spectral power, the average waveform was subtracted from each individual trial before applying the TF transform to the single trial data, which were then averaged to yield induced oscillatory power. Resulting spectral power over time was expressed as percentage amplitude changes relative to a prestimulus baseline period, to standardize power levels across frequencies. TF maps were averaged separately across theta (4 – 7 Hz) and alpha (8 – 13 Hz) frequency bands to produce a time-varying modulation of these spectral bands at each electrode. Changes in standardized induced power over time were referred to as event-related desynchronization/synchronization (ERD/ERS) [324], denoting relative power decreases or increases, respectively.

Statistical Analysis

Statistical analyses for all electrophysiological data (ERPs and TF responses) were carried out using SPM8. Unlike the traditional ERP analysis method, SPM allows for statistical comparisons across all time points and channels simultaneously and objectively identifies spatiotemporal regions with significant effects. Data from each subject were transformed into a 3-D spatiotemporal characterization [space (*X* and *Y* dimensions) and time (*Z* dimension) volumes], such that each 3-D data point (or voxel) contained amplitude information at an electrode at each time-point. A 10 mm × 10 mm × 20 ms smoothing was applied to blur out spatiotemporally focal effects [325-326]. These smoothed maps were then compared between conditions using a 2 (picture type: unpleasant, neutral) × 2 (regulation: normal, regulated) repeated measures analysis of variance (ANOVA). The significance level was set at $p<.05$ after family-wise error (FWE) correction for multiple comparison [327]. Clusters (or spatiotemporal regions) were

considered significant only if they contained at least 100 contiguous voxels. This analysis method has previously been used by other studies as well [328-330].

In response to picture onset, we expected significant differences only for the picture type main effect because the instruction had not yet been presented. However, we expected significant picture and regulation main effects in the post-instruction period. Due to our *a priori* hypothesis regarding the electrocortical modulation as a function of emotion regulation, significant regulation main effects were further explored using *post-hoc* planned *t*-tests.

RESULTS

The minimum number of retained trials was 18 trials per condition. Results that are relevant to our *a priori* hypotheses are mentioned here, while all statistically significant results are outlined in Table 8.1.

Picture Induced ERPs

Compared to neutral pictures, unpleasant pictures elicited significantly larger LPPs from 692 – 828 ms following stimulus onset [$F(1,135) = 47.28$, $p_{FWE} < 0.001$] at a centro-parietal (CPz, CP1, CP2 and Pz) cluster (**Fig. 8.1**). The effect of regulation condition and the interaction between regulation condition and picture type did not reach significance, as was expected ($p_{FWE} > 0.05$).

Regulation Induced ERPs

Figure 8.2 presents the grand-averaged waveforms at representative midline recording sites. There was a main effect of picture type such that unpleasant compared to neutral pictures elicited larger amplitudes (across regulation condition) at electrodes: peaking at FPz, FP2 and F8 from 374 – 588 ms, at P4, P6 and CP4 from 606 – 732 ms, and at P4 from 1422 – 1532 ms [$F(1,135) > 36.2$, $p_{FWE} \leq 0.001$] following instruction onset (**Fig. 8.3A**). In addition there was an effect of regulation condition such that pictures in the regulated (reduced) compared to the normal condition elicited smaller amplitudes at F1, Fz, F2 from 428 – 464 ms [$F(1,135) = 34.9$, $p_{FWE} = 0.002$] following instruction onset. Follow-up comparison showed significantly higher amplitudes in response to normally viewed unpleasant pictures compared to those which were reduced at POz from 1218 – 1256 ms, and at AFz from 1200 – 1300 ms [$F(1,135) > 28.4$, $p_{FWE} < 0.03$] (**Fig 8.3B**). For

neutral pictures, none of the spatiotemporal clusters reached significance ($p_{FWE} > 0.05$). Reduced compared to normally viewed pictures also elicited smaller amplitudes at a cluster comprised of Cz and C1 from 284 – 336 ms following instruction onset [$F(1,135) = 125.9$, $p_{FWE} < 0.001$], also significant for both picture types when analyzed separately with planned comparisons (**Fig. 8.3B,C**).

Regulation Induced TF Results

For induced alpha frequency band, there was a main effect of regulation condition, peaking at F7 from 2304 – 2386 ms and 3752 – 3812 ms, and at T7 from 2736 – 2770 ms [$F(1,135) > 26.3$, $p_{FWE} < 0.02$], while picture type main effect and interaction effects did not reach significance ($p_{FWE} > 0.05$). Follow-up comparisons for regulation effect showed that it was in fact driven by the reappraisal of unpleasant pictures, such that there was a significant alpha band ERD in response to reduced pictures compared to those which were viewed normally at F7 from 2624 – 2722 ms and at T7 from 2306 – 2338 ms [$F(1,135) > 27.5$, $p_{FWE} < 0.008$] (**Fig. 8.4A**).

For induced theta frequency band, there was a picture type main effect, peaking at FP1 from 2008 – 2054 ms and 3110 – 3162 ms, at Cz and Pz from 3130 – 3150 ms, and at CP6 from 1984 – 2032 ms [$F(1,135) > 28.5$, $p_{FWE} < 0.004$]. The regulation main effect reached significance at F7 from 2526 – 2624 ms [$F(1,135) = 27.9$, $p_{FWE} = 0.004$], while the interaction effects did not reach significance ($p_{FWE} > 0.05$). Follow-up comparison showed that the regulation main effect was again driven by the reappraisal of unpleasant pictures, such that there was a significant theta band ERS in response to normally viewed unpleasant pictures compared to those which were reduced at F7 from 2526 – 2624 ms [$F(1,135) = 30.3$, $p_{FWE} = 0.002$] (**Fig 8.4B**).

Correlations

To study the association between the LPP and alpha and theta band activity in response to picture-onset, significantly different spatiotemporal clusters of the LPP (anterior and posterior-occipital), alpha ERD/ERS (left frontal), and theta ERD/ERS (left frontal) responses were extracted [averaged at the peak electrode(s) across the significantly different time window] and were intercorrelated. These correlations revealed a significant positive association between the anterior LPP amplitude and alpha band ERD [$r(44) =$

0.36, p = 0.015) showing that lower the LPP amplitude in response to reduced unpleasant pictures is associated with higher alpha band ERD in the same condition. Moreover, there was also a positive correlation between the relative (normally viewed minus reduced) anterior LPP amplitude and respective alpha band ERD ($r(44) = 0.32$, p = 0.03) (**Fig. 8.5**) showing that higher reappraisal-mediated differences in the LPP amplitude are associated with higher respective differences in the alpha band ERD.

DISCUSSION

The present study explores electrophysiological data to investigate cortical activation in response to cognitive reappraisal of unpleasant stimuli. In line with previous work, unpleasant pictures elicited a more positive LPP as compared to neutral pictures [302, 304, 307, 331], and this was reduced following instructions to reappraise [115, 297, 305, 332]. In the current study, however, we also established a distinct frontal correlate of reappraisal-related cortical activation: reappraisal of unpleasant stimuli was associated with left frontal alpha band ERD, a direct measure of cortical activation. We further established that this frontal alpha activity was also associated with reappraisal-related modulation of LPP, such that higher the alpha band ERD, the larger is the LPP modulation during reappraisal.

Our ERP results in emotion reappraisal (i.e., significantly reduced LPP amplitude in response to reappraised stimuli compared to those viewed normally) also corroborate with earlier reports of LPP amplitude modulation demonstrating effectiveness of reappraisal as an emotion regulation technique [53, 115, 117, 308, 332], and highlight a top-down processing of evaluation of the affective stimuli [333]. Of note is the polarity reversal between the anterior and parieto-occipital LPP differences as a function of emotion regulation (**Fig. 8.2**), such that at the anterior electrode sites, LPP in response to reappraised stimuli seem "larger" than those in response to attended stimuli, while this pattern is revered at the parietal electrode sites. This polarity reversal is primarily due to the use of average-referencing technique (EEG data referenced to the averaged EEG activity from all electrodes) for data processing [334-335], which has been used by earlier studies investigating affective neural processing [297, 336-337].

However, the novelty of current results is in the finding of induced frontal alpha band ERD as a function of emotion reappraisal of unpleasant stimuli, and its relation to

LPP modulation. Frontal alpha band oscillation has typically been defined to serve an inhibition function [122, 309-311] and, its desynchronization has been linked to PFC activity during working memory and attentional processes [122, 309, 338]. Specifically, in context of reappraisal, implementing regulatory control and goal-directed monitoring appear to rely on the lateral PFC [23, 121, 300, 339]. Therefore, during emotional reappraisal, induced frontal alpha band ERD might be a useful electrocortical marker of PFC activation. It should be noted that frontal alpha ERD in response to emotional reappraisal was most significant at the left fronto-temporal electrodes (**Fig. 8.4B**). Therefore, although, it is widely accepted that scalp location of an electrocortical response may not necessarily represent the underlying neural substrates [340], it is quite remarkable that fMRI studies have also demonstrated greater activation in left PFC when cognitive emotion reappraisal is used to down-regulate negative emotion [118-119]. It is possible that this frontal asymmetry reflects the fact that reappraisal is a verbally-mediated process [341]. Alternatively, left frontal alpha ERD is also consistent with the notion that relative increases in the left hemisphere (i.e., alpha ERD) are associated with positive emotional stimuli [342-343], and approach-related motivational states [315, 344]. Thus, the increased left frontal activation during reappraisal may relate to either the verbal nature of reappraisal, or variability attributed to motivational states. Future studies might further evaluate these possibilities by examining frontal alpha ERD in emotion regulation tasks that no not require verbally-mediated changes in stimulus meaning [i.e., distancing [345-346]]. Moreover, we also showed that the LPP suppression was positively correlated with induced frontal alpha ERD during emotional reappraisal, such that higher suppression of LPP amplitude was directly proportional to higher ERD of induced frontal alpha oscillation.

Taken together, the LPP modulation, alpha ERD and their intercorrelation in response to emotion regulation suggests that time and time-frequency domain measures of scalp recorded EEG can be exploited together to study mental chronometry of cognitive processes underlying emotion reappraisal. Specifically, we showed that the LPP effect, a measure of emotional arousal [70, 302], appears about 1400 ms before alpha ERD effect, a marker of activation of mechanisms regulating executive control [123, 309], which reflects that during cognitive reappraisal, reduced emotional arousal precedes cognitive control. Therefore, current results provide electrocortical evidence in support of (and

extend) the theory that posits that the emotion-modulatory effects of reappraisal stem from the interaction between emotional appraisal processes implemented in multiple emotion-related structures, including the amygdala [119, 341], *followed by* initiation of cognitive control processes implemented in prefrontal and cingulate regions [339, 347].

In the current study we also showed theta band ERD in response to emotion regulation, which is consistent with earlier reports of theta being related to affective arousal and emotional processing [311, 348-350]. The left lateralization of theta ERD is also consistent with prior studies comparing responses to high and moderate versus low arousal IAPS pictures [351] and angry versus neutral faces [350]. Moreover, lack of association between theta ERD and LPP modulation in response to cognitive reappraisal may also complements the specificity of frontal alpha ERD as a marker of frontal cortical activation subsequent to LPP modulation during cognitive reappraisal.

In addition to these findings, a significant P300 difference between the picture types at left fronto-temporal regions emerged in the current study. Although there have been plethora of studies reporting enhanced P300 amplitude for emotional (pleasant and unpleasant) compared to neutral picture stimuli [352-358], only a few studies have reported lateralized P300 differences in response to emotion processing [359-360]. However, majority of P300 studies quantify peak amplitudes only at midline electrodes [57, 361-362]. Therefore, given the inconsistencies in the literature, this finding should be interpreted with caution, and awaits further evidence from more data-driven and less *a priori* analysis approaches.

Finally, a major limitation of the current study was the absence of self-report measures of emotional arousal. Although, these measures were not obtained in the current study, several previous studies using similar emotion reappraisal procedure have shown decrease in self-reported arousal and valence ratings of unpleasant pictures. Therefore, investigating these associations can be an important area for a future study. Furthermore, it may be useful to use both ERP and ERD measures to examine emotion regulation as a function of individual differences in the tendency to utilize reappraisal. Another future study may investigate psychopathologies that are plagued by deficits in emotion regulation, motivation and cognitive control.

In sum, the present study demonstrated the first evidence of induced frontal alpha band ERD as a distinct electrocortical correlate of reappraisal-related cortical activation.

The association of this frontal alpha modulation and LPP reduction in response to reappraisal instructions further highlights interaction between frontal activation and emotional arousal. These data are largely consistent with existing functional neuroimaging studies which highlight the role of the PFC is emotion regulation, and suggest that frontal alpha ERD could be an interesting metric for interactions between emotion and cognition that rely on the PFC.

Footnotes

1. Unpleasant IAPS pictures were: 1201, 1302, 1525, 1930, 2053, 2095, 2120, 2130, 2141, 2205, 2352.2, 2455, 2661, 2683, 2688, 2691, 2700, 2703, 2710, 2716, 2717, 2750, 2810, 2811, 3005.1, 3015, 3016, 3017, 3030, 3053, 3063, 3168, 3181, 3220, 3225, 3266, 3301, 3530, 6020, 6190, 6212, 6315, 6415, 6570.1, 6831, 9252, 9420, 9430, 9570, 9635.1; neutral IAPS pictures were: 2102, 2191, 2200, 2215, 2272, 2280, 2305, 2383, 2385, 2393, 2441, 2446, 2512, 2514, 2516, 2518, 2575, 2579, 2580, 2593, 2595, 2745.1, 2980, 5510, 5530, 5531, 5535, 7030, 7036, 7037, 7038, 7039, 7043, 7050, 7054, 7056, 7180, 7211, 7234, 7236, 7493, 7500, 7546, 7547, 7590, 7700, 7705, 7710, 7920, 9913.
2. On approximately one-third of trials in each condition (randomly selected), participants received a startle probe immediately following picture offset; these data are not reported here.

Table 8.1: Statistically significant spatiotemporal temporal for all the aforementioned SPM-based comparisons.

Comparisons	Statistic ($F_{1,135}$)	P_{FWE}-value	Time Window (ms)	Electrode Site	ERP component
In Response to Picture Onset					
ERP Analysis					
Picture type main effect	48.50	<0.001	436 – 550	F7, FC5, T7	P300
	47.29	<0.001	692 – 828	CPz, CP1, CP2, Pz	LPP
In Response to Instruction Onset					
ERP Analysis					
Picture type main effect	66.45	<0.001	374 – 588	Fpz, Fp2, F8	LPP
	52.93	0.001	54 – 112	P7	N100
	38.38	0.001	606 – 732	P4, P6, CP4	LPP
	36.27	0.001	1422 – 1532	P4	LPP
Regulation main effect	125.92	<0.001	284 – 336	Cz, C1	P300
	109.94	<0.001	200 – 210	FC1, FCz, FC2	P200
	52.82	<0.001	295 – 305	O1, Oz, O2	P300
	34.94	0.002	428 – 464	F1, Fz, F2	LPP
Planned Comparison					
Unpleasant pictures	55.95	<0.001	198 – 232	Cz	N200
	51.24	<0.001	296 – 322	Cz	P300
	35.68	0.001	200 – 224	PO7, P7	N200
	29.02	0.017	1218 – 1256	POz	LPP
	28.42	0.021	1200 – 1300	AFz	LPP

Neutral pictures	49.98	<0.001	306 – 322	Cz	P300
	36.84	0.001	192 – 234	PO7, P7	N200
Induced TF Analysis (Alpha)					
Regulation main effect	31.72	0.002	2304 – 2386	F7	-
	26.33	0.012	2736 – 2770	T7	-
	23.42	0.035	3752 – 3812	F7	-
Planned Comparison					
Unpleasant pictures	29.12	0.004	2624 – 2722	F7	-
	27.57	0.007	2306 – 2338	T7	-
Induced TF Analysis (Theta)					
Picture Type main effect	40.69	<0.001	3110 – 3162	Fp1	-
	33.22	0.001	3130 – 3150	Cz, Pz	-
	31.60	0.001	2008 – 2054	Fp1	-
	28.53	0.003	1984 – 2032	CP6	-
Regulation main effect	27.87	0.004	2526 – 2624	F7	-
Planned Comparison					
Unpleasant pictures	30.29	0.002	2526 – 2624	P7	-

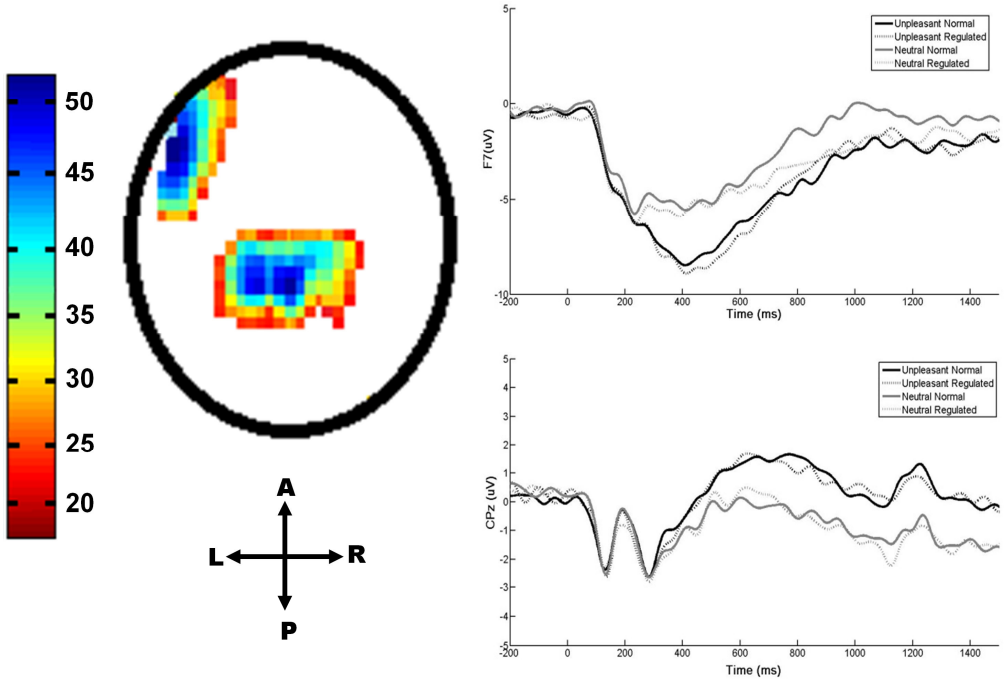

Figure 8.1: Scalp distribution of the difference between unpleasant and neutral pictures for ERP clusters that varied by picture type (left). The left fronto-temporal cluster was larger for unpleasant compared to neutral pictures 430 – 550 ms following picture onset, and the centro-parietal cluster was larger for unpleasant compared to neutral 690 – 820 ms following picture onset. Grand-averaged waveforms for each condition are depicted at representative electrodes from each cluster (right). The color-bar reflects the *F*-value of the comparison.

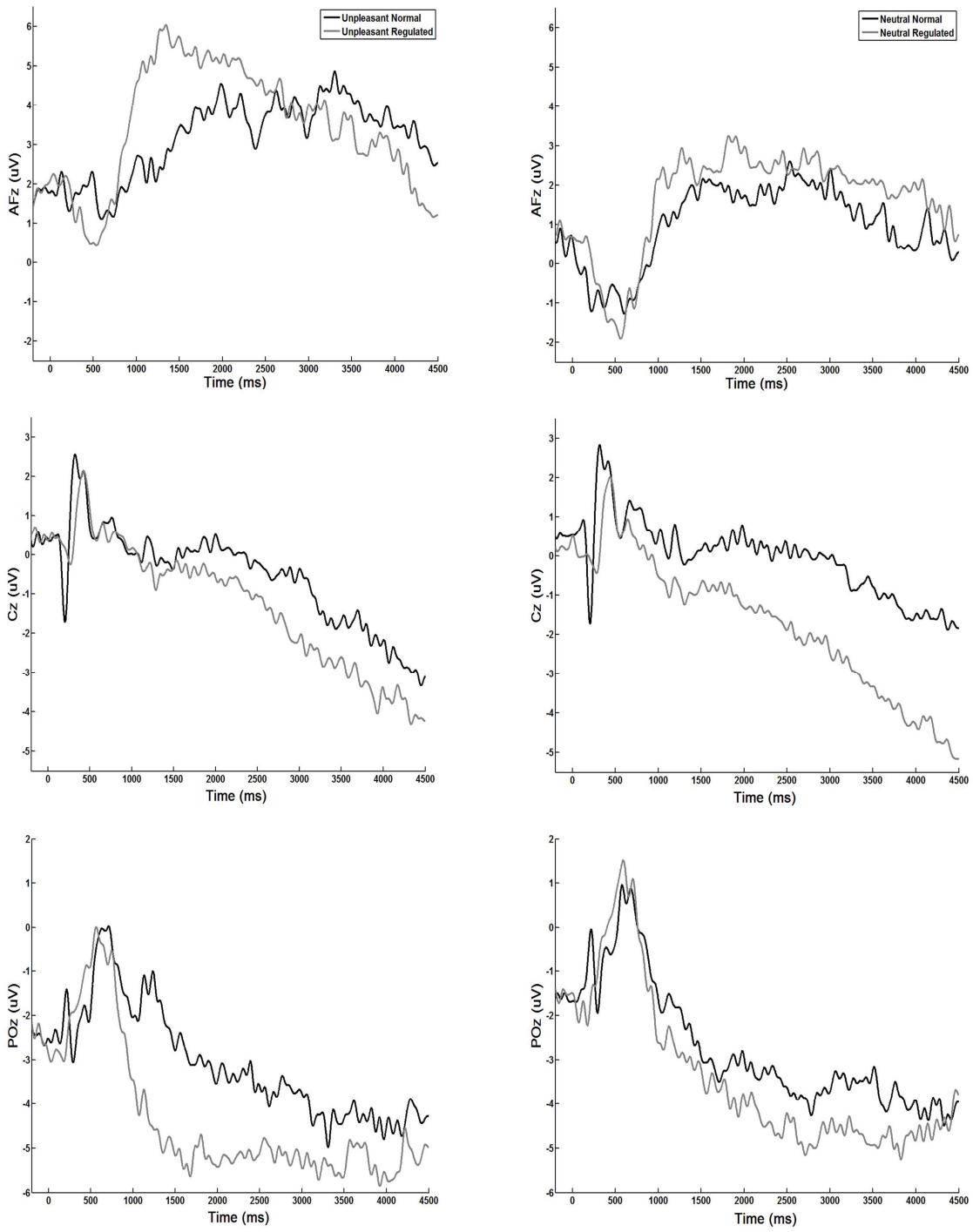

Figure 8.2: Grand-averaged ERP waveforms (in μV) for unpleasant (left) and neutral (right) pictures, presented in the 'normal' and 'regulated' conditions (auditory instruction onset at 0 ms).

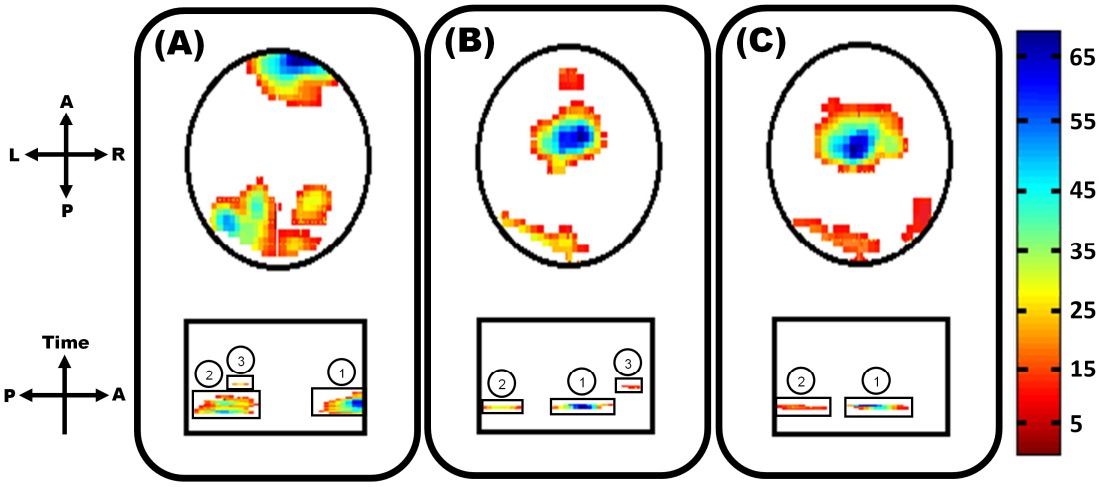

Figure 8.3: Planned comparison showing significant differences with scalp (top) and space-time (bottom) representations. **(A)** Differences between unpleasant and neutral pictures normally show significant regions at (1) Anterio-Frontal LPP, (2) Centro-parietal LPP, and (3) Parietal LPP. **(B)** Differences between unpleasant pictures viewing normally and those which were regulated show significant regions at (1) Central N200 and P300, (2) Parietal N200, and (3) Anterio-Frontal LPP. **(C)** Differences between neutral pictures viewing normally and those which were regulated showed significant regions at (1) Central P300, and (2) Parietal N200.

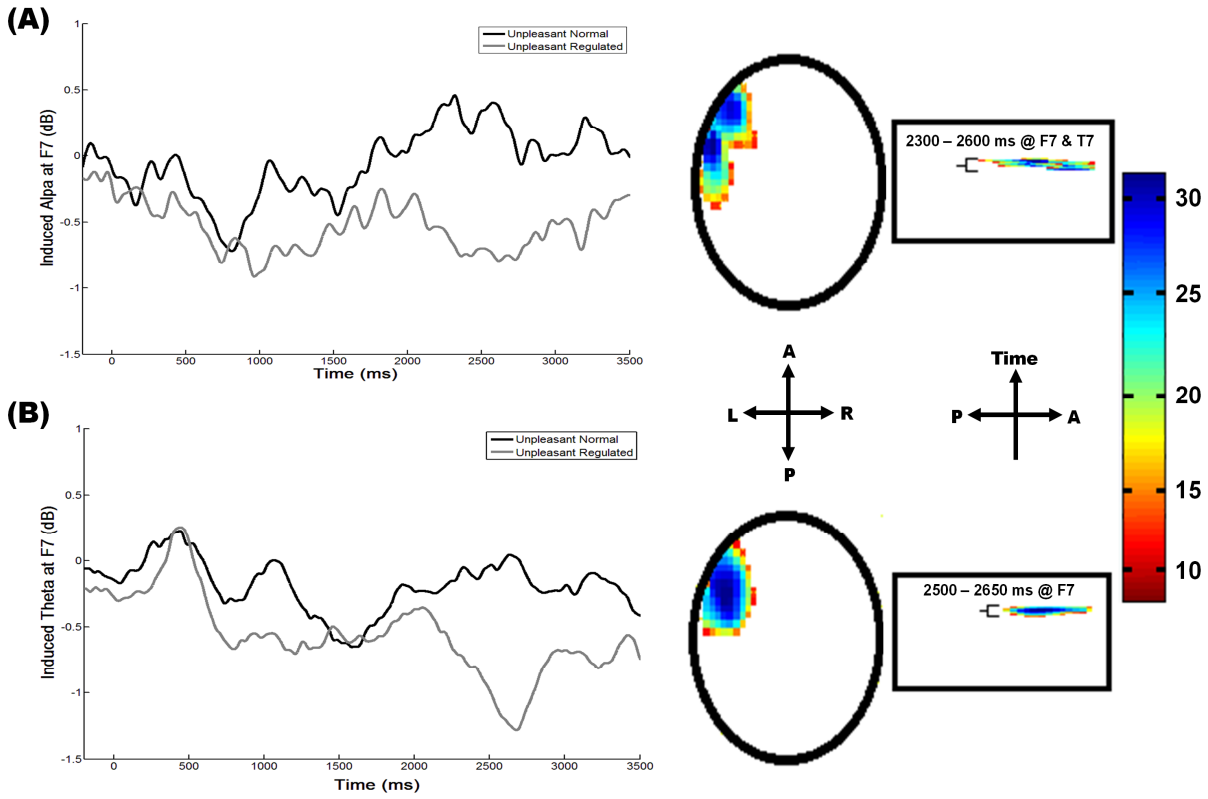

Figure 8.4: (A) Induced alpha band spectral power at F7 scalp electrode for unpleasant pictures viewed normally and those which were regulated (left). Significant differences between the two conditions are shown on the scalp (center) and space-time (right) maps showing significantly higher alpha around F7 and T7 electrode sites in the condition in which unpleasant pictures were normally viewed. (**B**) Induced theta band spectral power at F7 scalp electrode for unpleasant pictures viewed normally and those which were regulated (left). Significant differences between the two conditions are shown on the scalp (center) and space-time (right) maps showing significantly higher theta around F7 electrode site in the condition in which unpleasant pictures were normally viewed.

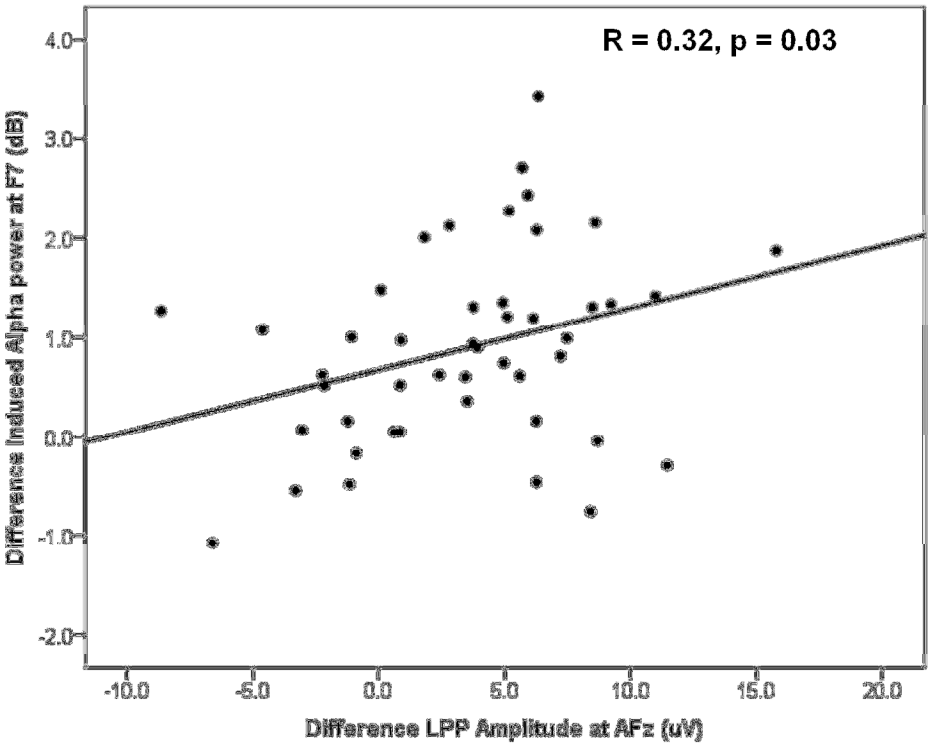

Figure 8.5: Correlation between differential induced alpha power and respective LPP modulation in response to the regulation of unpleasant pictures.

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