Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

Event-Related Potential Study of Executive Dysfunctions in a Speeded Reaction Task in Cocaine Addiction

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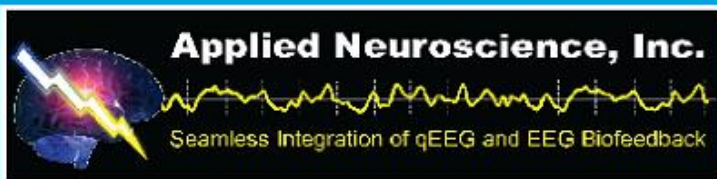Published online: 12 Dec 2008.

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SCIENTIFIC ARTICLES

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ABSTRACT. *Introduction.* This study used a flanker task with NoGo elements to investigate frontal executive function deficits in 19 cocaine abusers. The executive functions of interest in this study were cortical inhibition or ability to withhold motor response, the ability to select an appropriate response among several competing ones, the ability to inhibit inappropriate responses, and the ability to detect error and exercise corrective control.

Method. These processes were evaluated with specific frontal and parietal event-related potentials (ERPs) registered during performance on this speeded reaction time task with conflicting motor response demands. Specifically we used behavioral response measures, stimulus-locked anterior (frontal N200, N450) ERP markers of conflict detection, response inhibition (NoGo-N2 and NoGo-P3), and response-locked error-related negativity that represent different time points of signal classification, motor response conflict detection, response inhibition, and error monitoring processes.

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Results. The results revealed that the higher level executive motor control attributed to the prefrontal cortex is hypoactive in cocaine abusers and therefore is incapable to effectively resolve response conflicts arising between the competing motor response alternatives. It was also demonstrated that the mesial frontal structures, such as the anterior cingulate cortex, implicated in motor response conflict detection and error monitoring functions were also compromised in addicts.

Conclusion. It is reasonable to propose that a "hypofunctional" prefrontal and midfrontal processing results in a diminished ability to effectively override strong habitual automated response tendencies controlled by the lower level neural mechanisms triggered by the external stimuli. The results propose a neurobiological basis for the understanding why cocaine abusers are facing difficulties in controlling their drug-seeking and drug-taking behaviors and why their drug-related habitual behavior is so vulnerable to be triggered by external (e.g., drug-related items and environment) cues.

INTRODUCTION

Patients with substance use disorder (SUD) show cognitive deficiencies affecting normal behavioral functioning. Cognitive functional diagnostic tools are needed to reveal cortical origin of the observed executive impairments and the underlying abnormalities in neural mechanisms in this disorder presented with frontal "top-down" control deficiency symptoms. In general, executive processes are shown to be more negatively affected in cocaine addiction (Goldstein et al., 2001). Current cocaine addiction theories consider this form of SUD as a complex neural and behavioral process where inability to exercise cognitive control to override strong drug-seeking and drug-taking behaviors is considered to be a very important factor (Goldstein & Volkow, 2002; Hester & Garavan, 2004). These theories also emphasize the role of executive dysfunction in cocaine addiction, and the negative psychopharmacological effects of cocaine abuse on brain structures that are involved in the cognitive control of behavior (Lyvers, 2000).

Functional abnormalities of cocaine-dependent patients versus controls have been observed in the orbitofrontal cortex, insula, anterior cingulate cortex (ACC), basal ganglia, and limbic-related regions (Volkow, Fowler, & Wang, 2003, 2004). Another major target for this drug of abuse is the striatum, a subcortical brain region important for the habit formation and storing of fixed behavioral patterns (Koob & Le Moal, 2001). The neural structural deficits within prefrontal and limbic structures contribute to the deficits in behavioral inhibition, which are the characteristics of chronic cocaine users. Chronic abuse of cocaine is associated with structural and functional abnormalities in the brain, particularly in prefrontal and midline mesial frontal structures known to be involved in executive control, and chronic cocaine users consistently display neuropsychological impairments on tests of executive function (Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Franklin et al., 2002; Matochik, London, Eldreth, Cadet, & Bolla, 2003; Miller & Cohen, 2001).

Neurocognitive tests aimed at testing specific domains of cognitive functioning (attention, working memory, set shift, etc.) are usually assessed using neuropsychological test batteries with reaction time and accuracy being the main outcomes. Electrophysiological evaluations that use along with behavioral data also electroencephalographic (EEG) and/or event-related potential (ERP) measures allow more accurate and in-depth analysis of specific cognitive functions, in particular executive functions, known to be compromised in SUD. Among cognitive processes subsumed under the

"executive functions" term, cortical inhibition deserves special attention in cocaine addiction.

Cortical inhibitory state in ERP can be assessed by use of a continuous performance test in which a motor response is required to one signal ("Go") but must be suppressed to others ("NoGo"). In normal individuals the anterior P300 waveform to the Go is larger than to the NoGo condition for this task. In contrast, cocaine addicts have lower P300 overall (Biggins. MacKay, Clark, & Fein, 1997; Fein, Biggins, & MacKay, 1996; Kouri, Lukas, & Mendelson, 1996; Polich, Pollock, & Bloom, 1994), and they may do not show any increase in the anterior P300 to the Go condition. The frontal activation is larger in the NoGo than in the Go condition and is presumed to reflect the inhibition that is required for response suppression. In cocaine addicts the frontal activation during the NoGo task is lower than in normal individuals, an indication that frontal lobe control of response inhibition is reduced (Hester & Garavan, 2004; Strik, Fallgatter, Brandies, & Pascual-Marqui, 1998). Two major ERP components have been identified as the markers for response inhibition: first, the NoGo-N2, a negative deflection with a fronto-central maximum around 200 to 300 msec, and second, referred to as NoGo-P3, an augmented positive-going peak usually peaking between 300 and 600 msec (Falkenstein, Hoormann, & Hohnsbein, 1999). The ERP markers of response inhibition (hereafter referred to as NoGo-N2 and NoGo-P3) represent different time points of response inhibition process and can be used as sensitive cortical inhibition indices in addiction research.

One important executive function is the ability to select a contextually appropriate response among several competing ones, whereas another important function of executive control is the ability to inhibit contextually inappropriate responses. These processes can be evaluated with specific frontal and parietal ERP waves registered during processing of conflicting response tendencies manipulated by experimental task. Other executive deficits in SUD are observed during performance on speeded reaction time tasks and are manifested in deficiencies related to response error monitoring and motor response conflict detection. These deficits are evaluated by assessment of response-locked fronto-centrally distributed ERP such as error-related negativity (ERN). Other ERP parameters related to response conflict detection and processing can be extracted from such fronto-central ERP components as N200 (Donkers & van Boxtel, 2004) and N450 (West, 2003; West, Bowry, & McConville, 2004) components. Neuroimaging studies (Goldstein & Volkow, 2002; Hester & Garavan, 2004) showed that the higher level executive motor control attributed to the prefrontal cortex (PFC) is hypoactive in SUD and therefore is incapable to effectively resolve response conflicts arising between the conflicting motor response alternatives. It is reasonable to propose that a "hypofunctional" PFC processing results in a diminished ability to effectively override strong habitual automated response tendencies controlled by the lower level neural mechanisms (e.g., premotor areas, basal ganglia).

Objectives and Aims of the Study

The objective of this exploratory study was to investigate the timing and character of the interaction between the cortical areas-of-interest, specifically the PFC, ACC, and premotor areas and posterior attention systems in the cognitive tests with demanding motor response task. This study used a speeded forced choice task (Eriksens' flanker test) with response inhibition (NoGo) trials to infer dysfunctions of executive control analyzing overt behavioral responses (e.g., reaction time and errors) and dense-array ERP. The study used stimulus-locked ERPs to distinguish the neural processes related to stimulus identification and categorization, response selection, inhibition of inappropriate conflicting responses, and execution of correct responses. Specific ERP, such as the response-locked ERN was used to index output response monitoring. The same test was conducted in two groups of participants: (a) a group of patients with cocaine abuse/dependence ($N = 19$), and (b) age- and gender-matched group of healthy controls

($N = 15$). Each participant enrolled in the study participated in a flanker experiment described in the Method section.

One of the aims was to examine behavioral and ERP measures of the processes related to a direct inhibition of responses in a response inhibition (NoGo condition) trials of the task in patients with cocaine addiction and controls. To determine which neural processes are dysfunctional in this form of SUD, we compared behavioral and ERPs measures between patients with cocaine addiction and healthy controls. We predicted that the patient groups (compared to controls) will exhibit less inhibitory efficiency than controls in the NoGo trials of this task. Patient group differences in inhibition efficiency were predicted to be reflected in a lower amplitude of the fronto-central ERP indices of the inhibition (so-called anterior NoGo-N2 and NoGo-P3), because attenuated ERP indices of inhibition will be reflecting deficient PFC inhibitory activity.

Another aim was to determine the differences in ERP indices of visual signal processing and action monitoring in a forced choice Eriksens' flanker task (as the most commonly used speeded task with a higher rate of behavioral errors) in patients with cocaine addiction and healthy controls. In this experiment, we specifically used the fronto-central N200 and N450 components of stimulus-locked ERPs and the response-locked ERN as measures of response conflict and action monitoring in this speeded reaction time (RT) task with interferences. Therefore, we used the fronto-central N200, N450, and ERN as indices of response conflict and monitoring system functioning. From the numerous studies (Donkers & van Boxtel, 2004; West, 2003; West et al., 2004) it is known that dipole sources of these frontal ERPs (N200, N450, ERN) are localized to different subdivisions of the ACC.

The study was based on a model of movement preparation, execution, and response conflict monitoring processes in which prefrontal, medial frontal, parietal, and primary motor areas are differentially impaired in patients with cocaine abuse. In this speeded forced-choice experiment with motor response execution and inhibition demands we used dense-array ERP and behavioral response measures to test the hypothesis that higher order motor control and cognitive functions are impaired in cocaine abusers. The goal of this chronopsychophysiological methodological approach was to determine if executive motor control impairments in SUD are the result of an abnormal interaction between the prefrontal (PFC), mesial frontal (ACC), premotor, and motor cortices accompanied by a diminished executive cortical control over movements in a speeded motor task with flanker distracters.

The study used the temporal resolution of event-related brain potential recording techniques to detect sequential activation of functionally connected cortical areas involved in movement preparation and inhibition and to identify functional abnormalities leading to executive movement impairment and cognitive deficits in cocaine addiction.

Methodological Background

ERP measures of signal processing, response selection, and error monitoring. P300. The most widely studied cognitive ERP component is P300 (P3), a wave of positive polarity that peaks within 300 to 500 sec (Polich & Kok, 1995; Pritchard, 1981). P300 amplitude is inversely related to stimulus probability and directly related to the information-processing engaged by the stimulus (Johnson, 1986; Pritchard, 1981). P300 varies in latency as well as amplitude. P300 latency has proven to be a useful adjunct to RT in studies of mental chronometry, as it tends to be more reflective of manipulations of stimulus-evaluation time than the time consumed by subsequent response-related processes (Pritchard, Houlihan, & Robinson, 1999; Verleger, 1997). Thus, for example, if a certain experimental manipulation shortens RT but does not affect P300 latency, then it can be concluded that the manipulation acts to shorten RT by primarily affecting response-related processes rather than processes related to stimulus evaluation.

N200. The negative ERP component (N200), located over centro-parietal and posterior scalp locations occurs between about 190 and 320 msec poststimulus (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993). This ERP component is associated with stimulus categorization, perceptual closure, and attention focusing, therefore signaling that a completed perceptual representation has been formed (Potts, Patel, & Azzam, 2004; Wijers, Mulder, Gunter, & Smid, 1996). The anterior fronto-central N200 component is thought to be related to conflict monitoring (Donkers & van Boxtel, 2004) in tasks with interferences (Stroop test). In a Go–NoGo task, this component is often interpreted as reflecting inhibitory executive functions (Heil, Osman, Wiegelmann, Rolke, & Hennighausen, 2000; Kopp, Rist, & Mattler, 1996). Van Veen and Carter (2002) used the Eriksen flanker task (Eriksen & Eriksen, 1974), in which participants have to respond to a centrally presented target while trying to ignore simultaneously presented flanker stimuli. Such a task activates the ACC that has been shown to respond to conflict between simultaneously active, incompatible response tendencies. The fronto-central N200 was used in this study as an index of the ACC activity.

ERN and ERP indices of response selection and conflict monitoring. In speeded RT tasks (e.g., Stroop or flanker tests) immediately after errors (50–150 msec), a negative component appears over the fronto-central areas, the ERN (Herrmann, Remmler, Ehlis, Heindrich, & Fallgatter, 2004). The ERN has been attributed to cognitive operations of detecting errors or response conflict (Gehring & Knight, 2000). Dipole modeling has localized ERN sources to the ACC (Gehring & Knight, 2000; Herrmann et al., 2004; Van Veen & Carter, 2002; West, 2003). In psychiatric studies, a decreased ERN is typically related to increased severity of psychomotor poverty symptoms (Bates, Liddle, Kiehl, & Ngan, 2004). On the contrary, the ERN is found enhanced in anxiety, posttraumatic stress disorder (PTSD), obsessive–compulsive disorder,

and phobia (Hajcak, McDonald, & Simons, 2003; Rauch et al., 1996).

The ERN is generally accepted as a neural index of response-monitoring processes. The ERP studies of the neural correlates of conflict processing using Stroop and similar interference tasks have revealed the frontal N450 (400–500 msec) negative wave that was associated with conflict detection and thought to originate from the activity in the ACC (Markela-Lerenc et al., 2004; West, 2003; West et al., 2004). The N450 is modulated by the degree of conflict, being higher when conflict is high (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Van Veen & Carter, 2002; West et al., 2004). The generators of the N450 and the ERN reflect activity of the ACC and serve as neural correlates of conflict processing and response monitoring processes.

Experimental test and procedures to test cortical inhibition. Behavioral measures in response inhibition tasks. In laboratory settings, response inhibition is traditionally tested using stop-signal and Go–NoGo task paradigms (Verbruggen, Liefooghe, & Vandierendonck, 2004). The participant is instructed to perform a task of pressing a button in response to a specific stimulus (Go) and to inhibit a button pressing in response to another (NoGo), or to inhibit response when a stop-signal sign flashes. The NoGo task is functionally equivalent to a stop-signal task in which the respond and stop-signals are presented simultaneously (Band, van der Molen, & Logan, 2003; Logan, 1994). For Go–NoGo tasks, the behavioral index of inhibitory control is the number of errors on NoGo trials. Deficiency of inhibitory control is inferred on the basis of the pattern of errors. Omission errors are interpreted as reflecting deficits in ability to process target and initiate motor act, due to either deficient attention or failed motor preparedness. Commission errors are interpreted as reflecting direct response inhibition deficits in NoGo trials.

ERP measures of response inhibition. ERPs reflect sensory, cognitive, and motor processes and are useful to find correlates of inhibition mechanisms in the classical

Go–NoGo tasks. As previously mentioned, there are several ERP components considered correlates of the motor inhibitory processes in NoGo trials. The studies using visual NoGo tasks reported two effects in NoGo- versus Go-ERPs: a negative wave at midline frontal sites with a latency of 150 to 400 msec, the NoGo-N2, and a positive wave with maximum at the midline fronto-central area with a latency of 300 to 500 msec, the NoGo-P3 (Falkenstein et al., 1999). The NoGo-N2 is thought to reflect a frontal inhibition mechanism, which is active on NoGo trials (Bekker, Kenemans, & Verbaten, 2004; Falkenstein, Hoormann, & Hohnsbein, 2002; Roberts, Rau, Lutzenberger, & Birbaumer, 1994; Strik et al., 1998). The generators of the visual NoGo-N2 have been localized to inferior-lateral prefrontal cortex (Falkenstein et al., 1999, 2002). According to Falkenstein et al. (2002), NoGo-P3 could reflect a closure of a preceding inhibition process, whereas inhibition itself is reflected in the NoGo-N2. On the assumption that NoGo trials and zero delay stop-signal are functionally equivalent, successful inhibition in stop-signal trials should exhibit the frontal N200 and P300 similar to the NoGo-N2 and NoGo-P3 potentials reflecting inhibition localized to the PFC (Kok, Ramautar, de Ruiter, Band, & Ridderinkhof, 2004). Although most investigators agree that the NoGo-N2 and -P3 components are related to frontal inhibition seen during NoGo paradigms (reviewed in Falkenstein et al., 1999, 2002; yet others have shown that the anterior P300 is not only due to response inhibition; Salisbury, Griggs, Shenton, & McCarly, 2004). In a NoGo task, frontal NoGo-N2 and NoGo-P3 are generally considered to be ERP correlates of the frontal inhibitory process.

Experimental task to test response conflict and action monitoring: Flanker task. The flanker test is a type of selective attention task that requires perceptual or cognitive suppression of competing information (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985; Eriksen & Eriksen, 1979). This test is similar to Stroop and Go–NoGo tests of executive functions, except information is spatially distinct (Nigg, 2005). For example,

the individual views a target area in the center of a computer screen, with an instruction to press the corresponding key depending on whether an R or L appears in the center. Immediately adjacent to the center letter are two "flanking" distracter letters that are to be ignored. The flankers can be incompatible (LLRLL) or neutral (e.g., RRRRR). It takes longer to respond to incongruent than to congruent trials because in the first instance the flanker is a possible response that must be suppressed. Even though participants are instructed to ignore the distracters, the presence of incongruent flankers in the stimulus array is associated with longer RTs and higher error rates. This speeded forced choice RT task requires motor responses to congruent and incongruent stimuli, is known to evoke response conflict (e.g., Coles et al., 1985; Kopp et al., 1996), and is often used to assess response error monitoring function. Decrement in performance in the flanker task is thought to result from activation of the conflicting response by the incongruent flankers (Coles et al., 1985).

Model of the prefrontal-cingulate interaction in motor response control. The activation of the PFC and the ACC occurs in diverse demanding cognitive tasks, including tasks requiring motor response inhibition (Gehring, Himle, & Nilesenson, 2000; Gehring & Knight, 2000). Several studies outlined that the ACC deals with relatively simple conflict monitoring (Botvinick, Nystrom, Carter, & Cohen, 1999; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Bush et al., 2002; Carter et al., 1998; Devinsky, Morrell, & Vogt, 1995), whereas the PFC deals with more complex aspects including selection of actions (Corr, 2002; Faw, 2003). The PFC is not critical for performing simple, automatic movements. Such motor acts are controlled by the lower level premotor areas. By contrast, the PFC is important when top-down processing is required, and when mapping between sensory inputs, action plans, and memory must be integrated and coordinated (Miller & Cohen, 2001). Whereas the automatic aspects of motor behavior and learned responses may have been relegated to lower

structures, the more schematic representations of action, as well as the general rules of motor tasks, remain represented in prefrontal networks (Damasio, 1996; Elliott, 2003; Fuster, 2001). It is suggested that the ACC is involved in detecting conflict and that the PFC is involved in resolving it (Aron, Robbins, & Poldrack, 2004; Gehring & Knight, 2000). There is a model in which the PFC detects the need for executive control and signals the ACC to perform the control function (Markela-Lerenc et al., 2004; Turken & Swick, 1999). Another model postulates the reverse arrangement, in which the ACC detects the problems and communicates with the PFC structures that implement the executive control (Gehring et al., 2000). A more complex model (Gehring & Knight, 2000) points out that the ACC monitors for errors and conflicts but depends on the PFC for processing necessary to implement error correction or conflict resolution. The PFC maintains action representation necessary for decision making. Without such decision the ACC is unable to distinguish correct from incorrect responses. The model suggests that a system other than the ACC or the PFC (e.g., basal ganglia) implements corrective action, but it operates under the strong modulatory frontal influences.

The neuroanatomical basis of executive function appears to be the PFC. Coordinated activation of the PFC and the ACC serve diverse executive functions, including those directly involved in motor control through the access to the premotor areas.

This study was guided by the following hypothetical assumptions:

1. The PFC is essential in maintaining task-relevant motor action representation in cognitive tasks.
2. The ACC is essential to detect response-related conflict and errors during cognitive tasks and, once a conflict occurrence is detected, signals the PFC for resolution.
3. The left dorsolateral PFC (DLPFC) is critical for the resolution of conflict by selecting an appropriate response according to task demands, whereas the right inferior PFC is involved in inhibition of the inappropriate responses.
4. The PFC controls motor action planning in the fronto-striatal loops and modulates movement preparation in the supplementary motor areas (SMA), premotor area (MI), and basal ganglia.
5. The premotor cortical structures and basal ganglia control and program motor function in the absence of response conflict, when the prefrontal executive control is not recruited.

Our hypothesis posits that the hypofunctional prefrontal processes in cocaine addiction can result in the inability to effectively override habitual response and implement a corrective modulation of the premotor structures. This model assumes that cocaine-addicted participants will perform worse when engagement of PFC is required for effective corrective action after errors. On the other hand, globally lower functionality of mesial frontal structures implicated in response conflict detection and error signaling (i.e., ACC and pre-SMA) in cocaine addition will result in lower ability to detect conflicting response tendencies and committed response errors, therefore providing less efficient feedback needed for executive prefrontal involvement for response conflict resolution and error corrections.

Testing the model by comparing behavior and ERP indices of inhibition in SUD patients and controls. To test these hypotheses we examined behavioral output and spatio-temporal pattern of brain activation during speeded choice RT task with response inhibition trials using dense-array scalp EEG recordings and analysis of ERP components. To determine which neural processes are dysfunctional in SUD, we compared behavioral performance and ERP measures between cocaine addicted patients and controls. We assumed that the effects related to inhibition (NoGo-N2, NoGo-P3) have generators in the PFC, whereas effects related to error and correct response

monitoring (ERN) and motor response conflict (frontal N200 and N450) have generators in the ACC on the base of numerous studies that used dipole source localization techniques for these ERP measures (Falkenstein et al., 1999, 2002; Kok et al., 2004; Nieuwenhuis et al., 2003; Van Veen & Carter, 2002; West et al., 2004).

The Go–NoGo part of the experiment tested the prefrontal deficits in direct inhibition of motor response in the trials with NoGo task. We predicted that patients compared with controls will commit disproportionately more commission errors in these NoGo trials. We predicted that the patients will show less inhibitory efficiency than controls and will exhibit behavioral and ERP deficits in withholding responses. Patient differences in inhibition efficiency were expected to be reflected in a lower amplitude of the fronto-central NoGo-N2 and NoGo-P3. We also used the ERN as response monitoring index to test the hypothesis that behavioral error monitoring system is underresponsive to occurring errors in SUD patients during inhibition of motor responses, and thus contributes to the executive functioning deficits observed in cocaine addiction. We predicted that if the executive action monitoring is hypofunctional in cocaine addiction, then the failure to inhibit response after NoGo target stimulus will not lead to an enhanced ERN.

The second (flanker experiment with congruent and incongruent flankers) integral part of the experiment tested the hypothesis that in patients with cocaine addiction, as compared to healthy controls, the frontal conflict monitoring system has lower capacity to detect and respond to response interferences, whereas action monitoring is underresponsive to errors. The experiment utilized a flanker task, in which interfering flanking letters are used to induce errors to a critical central letter indicating response side (left vs. right key press). Patients with cocaine abuse were predicted to have an attenuated amplitude and a prolonged latency of the anterior N200 and N450 ERP components in an incongruent flanker condition indicating a low reactivity to

potential response conflict and a smaller ERN on error trials compared to controls. We predicted globally slower RTs but less pronounced behavioral and ERP interference effects in congruent trials in patients with cocaine addiction compared to controls because less response conflict and interference occur in such congruent trials and PCF involvement is not crucial.

METHODS

Participants

Recruitment and screening procedures. Male and female patients of any race older than 18 meeting inclusion and not exclusion criteria were eligible for this study. The protocol of the study and recruitment advertisements were approved by the local Institutional Review Board (IRB). The advertisements were posted at the local hospital and drug and alcohol rehabilitation center. Inclusion criteria were meeting *Diagnostic and Statistical Manual for Mental Disorders* (4th ed., text rev.; American Psychiatric Association, 2000) criteria for cocaine abuse/dependence. In addition, eligible participants must be judged to be in generally good physical health except for possible acute or chronic drug-related problems and willing and able to participate in cognitive lab tests. Exclusion criteria were (a) current diagnosis of other Axis I psychiatric disorder, other than cocaine dependence and PTSD (as most cocaine abusers in our population have high PTSD scores); (b) current psychiatric symptoms requiring medication; (c) severe medical or psychiatric impairments that preclude from the cooperation with the study protocol; (d) substance withdrawal symptoms requiring immediate medical attention; (e) inability to read, write, or speak English; and (f) neurological disorders that may affect EEG recording (e.g., epilepsy). Major patient recruitment sites were Ambulatory Clinic of University of Louisville Hospital, Jefferson County Drug and Alcohol Treatment Center (JADAC; located in one block from the lab). The patients were referred to Drs. Stewart and Hollifield for psychiatric

assessment and determination of eligibility to enroll in this study. Each individual with SUD was evaluated and screened by Dr. Stewart (board certified addiction specialist) to confirm cocaine abuse or cocaine dependence diagnosis. The patients with cocaine dependence diagnosis history were referred as well from the other psychiatric units in Louisville metro area.

Psychiatric status questionnaires, drug use, and psychosocial functioning screening. The Structured Clinical Interview for *DSM–IV* (First, Spitzer, Gibbon, & Williams, 2001) was used for Axis I diagnoses. PTSD was assessed using The Posttraumatic Symptom Scale–Self-Report (Foa et al., 1989) questionnaire. The Hopkins Symptom Checklist–25 (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974) was used to measure symptoms of anxiety and depression. Handedness of patients was assessed using the Edinburgh inventory (Oldfield, 1971). Scores from the Addiction Severity Index were used to measure problem severity in the areas of medical, employment, drug abuse, legal, family/social, and psychiatric difficulties (McLellan, Luborsky, Woody, & O'Brien, 1980). Cocaine Negative Consequences Checklist (Michalec et al., 1996) was used to assess short- and long-term adverse effects resulting from cocaine use. Psychosocial adjustment will be assessed using the Social Adjustment Scale (Weissman & Bothwell, 1976). These psychiatric assessments were important part of our outpatient participants' clinical evaluations at the intake stage, as most of them expressed willingness to enroll in an integrated behavioral treatment trial based on neurofeedback and motivational interviewing.

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

Control participants were recruited by the advertisement posted at different University of Louisville Health Science Center locations.

Participants in the study. Nineteen cocaine abusing/dependent participants (7 female, *M* age $= 42.1 \pm 5.5$, range $= 32$–56 years, 40% Afro Americans; SUD group) and 15 non-drug-using control participants (8 female, *M* age $= 37.0 \pm 9.4$, range $= 29$–64 years; CNT group) were in this study. Sixteen participants in the SUD group tested positive for cocaine; 8 of them also tested positive for marijuana use. Three participants in the SUD group who did not tested positive were recovering addicts who enrolled in this study after the inpatient JADAC rehabilitation course with abstinence period of less than 60 days. Therefore the majority of our outpatient population was current cocaine users. The most preferred form of administration of the drug was smoking crack cocaine. One SUD participant in this study used cocaine intravenously. Sixteen of the cocaine addicts reported also regular use of nicotine/ smoking. None of the participants in the SUD group were in any treatment program other than attending Narcotics Anonymous or Alcoholic Anonymous meetings. All of the participants except 2 patients from the SUD group and 1 from the CNT group were right-handed. All control participants reported no current or past history of neurological or psychiatric disorders or dependence on any substances other than nicotine or caffeine. Participants were fully informed about the nature of this research and signed an informed consent form approved by the IRB of the University of Louisville (Protocol #240.06). For the specimen collection (urine drug screen), participants signed a separate consent form also approved by the IRB within the same study protocol.

Instrumentation

EEG Data acquisition and signal processing. All EEG data are acquired with a 128 channel Electrical Geodesics Inc. (Eugene, OR) system (v. 200) consisting of Sensor

Net electrodes, Net Amps, and Net Station software (v. 4.0.1) running on a Macintosh G4 computer. EEG data are sampled at 500 Hz, 0.1–100 Hz analog filtered, referenced to the vertex. The Sensor Net is a lightweight elastic thread structure containing silver/silver chloride electrodes housed in a synthetic sponge on a pedestal. The sponges are soaked in a potassium chloride solution to render them conductive. EEG data are recorded continuously. Stimulus-locked EEG data are segmented offline into 1000 msec epochs spanning 200 msec prestimulus to 800 msec poststimulus around the critical stimulus events—for example, Go and NoGo stimuli. For the response-locked ERN data are segmented from 500 msec pre- and 500 msec postresponse. Data are digitally screened for artifact (eye blinks or movements, etc.), and following additional visual, contaminated trials removed using both built-in artifact rejection tools. If data contain a significant number of trials contaminated with lateral eye movements, eye movement artifact correction algorithm will be applied. Remaining data are sorted by condition and averaged to create the ERPs. Prior to averaging ERP data are digitally filtered at 20 Hz lowpass to remove residual high-frequency noise. Averaged ERP data are baseline corrected over a 200 msec baseline period relative to segment start, and re-referenced into an average reference frame (Dien, 1998). The participant ERPs are averaged together to produce the grandaverage waveform across participants.

Stimulus presentation and behavioral response collection. All stimulus presentation and behavioral response collection is controlled by a Dell computer running E-prime software (Psychology Software Tools, PA). Visual stimuli are presented on a 15-in. flat-panel display. Manual responses are collected with a four-button keypad. In all experiments, participants are seated in an adjustable chair with their chin in a chinrest. The chinrest is placed so that participant's eyes are 50 cm from the center of the flat panel screen. Participants are instructed to remain as still as possible with their eyes on the fixation mark. Participants are requested to refrain from blinking during trials. Breaks are provided every 3 to 4 min so that participants can rest their eyes.

Stimuli and timing: Eriksens' flanker test with NoGo trials. This study uses a flanker task, in which one critical center letter is flanked to the right and left by distracter letters (Eriksen & Eriksen, 1974; Eriksen & Eriksen, 1979). In some cases, the flankers match the central letter (congruous, no interference) and sometimes they match the other letter (incongruous, interference). Participants respond with a two-choice, forced-alternative, pressing a left-hand key to one central letter, a right-hand key to the other. The letters are R and L. Congruent trials look as "LLLLL" or "RRRRR," whereas incongruent as "LLRLL" or "RRLRR." In another block representing a modification of the initial flanker task by adding NoGo-trials, participants should not respond to a central target stimulus in a form of N-letter regardless of which letter is flanked on each side (e.g., "RRNRR" and/or "LLNLL" string requires no response). The stimulus is presented at the screen for only 100 msec. There are 960 trials in this test. Probability of NoGo trials (NNNNN, LLNLL, RRNRR) is 20% (half of them are congruent), whereas probabilities of Go trials is 80% (half of them congruent). There are eight blocks (120 trials/block) in this task. This flanker test takes 45 min to complete. Figure 1 illustrates stimulus material in this version of flanker task.

FIGURE 1. Stimuli material used in this modification of Eriksens' flanker test with NoGo trials. *Note.* The letters are white on a black background at the screen of monitor.

Eriksens' Flanker Test with NoGo trials
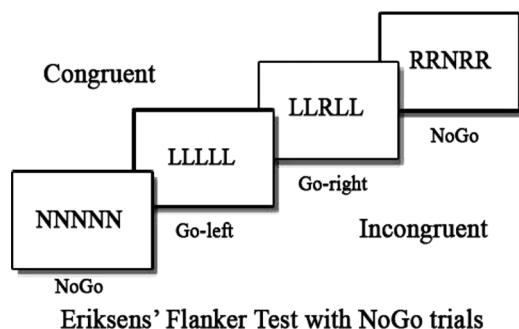
Dependent Measures and Data Analysis

Behavioral measures. Behavioral measures are mean reaction time, accuracy (percentage of correct responses), number of commission (pressing key to a NoGo stimulus or pressing wrong key), and omission errors (missed response to a Go stimulus).

Electrophysiological (ERP). This is adaptive mean amplitude and latency of ERP peak (e.g., N200, P300) within a temporal window across a region-of-interest (ROI) channel group. Each ROI contains at least four electrodes. For the flanker experiments list of ERP dependent variables includes amplitude and latency of the anterior (fronto-central) N200 (300–400 msec), anterior N450 (400–500 msec), posterior N200 (N2b, 240–320 msec), anterior (frontal P300) and posterior P300 (P3b, 350–600 msec) in successful and unsuccessful Go and NoGo trials, and correct and error choice (flanker) trials, and the frontal ERN (50–200 msec postresponse) in error trials only. Difference waves are calculated for NoGo-N2 and NoGo-P3 (e.g. NoGo-N2-minus-Go-N2) in NoGo flanker trials. Response-locked ERN is recorded in trials with commission errors only. Topography of the ROIs and time windows for each ERP component is adjusted after visual inspection of the averaged waveforms.

Data analysis. Statistical analyses are performed on the participant-averaged behavioral and ERP data with the participant averages being the observations. The primary analysis model is the repeated measures analysis of variance (ANOVA), with dependent EEG variables being all ERP and ERN component's amplitude at selected time windows. Data for each EEG-based dependent variable are analyzed using repeated measures ANOVA (SPSS 14.0). Within-subject factors are *stimulus* (Go-target, NoGo), *congruence* (congruent, incongruent), and *error* (commission, omission) type for the ERN. The between-subject factors is *group* (SUD, controls). The waveform and topographic plots and the dipole analyses are performed on the grandaverage data. Topographic maps are created using spherical spine interpolation. A priori hypotheses are tested with single-tailed student's t tests for groups with unequal variance. In all ANOVAs, Greenhouse–Geisser corrected p values are employed where appropriate.

RESULTS

Behavioral Responses

Reaction times in both congruent and incongruent Go trials were globally slower in SUD group ($M \pm SD = 435.5 \pm 54.2$ in SUD vs. 381.0 ± 66.0 msec in CNT group; one-way ANOVA, $F = 5.13$, $p = .033$) and was more pronounced in congruent Go trials (429.0 ± 67.4 vs. 362.5 ± 65.6 msec, $F = 6.09$, $p = .021$). Patients in SUD group did more commission and omission errors in congruent trials compared to controls (11.3 ± 11.0 vs. $2.39 \pm 2.23\%$, $F = 6.92$, $p = .16$), but difference was not significant for incongruent Go trials.

Centro-Parietal ERP Components

N2b. The amplitude of N2b (averaged across four centro-parietal EEG recording sites; $N = 19$ in the SUD group and $N = 15$ in the CNT group) was lower (i.e., less negative) in the SUD group compared to controls in congruent and incongruent Go (-0.27 ± 0.98 vs. -1.06 ± 0.91 μV, $F = 4.89$, $p = .035$) and NoGo trials (-0.28 ± 0.98 vs. -1.85 ± 0.94 μV, $F = 5.45$, $p = .026$). The latency of N2b component was delayed in the SUD group compared to controls both in Go (268.1 ± 33.9 vs. 235.3 ± 39.7 msec, $F = 6.67$, $p = .015$) and NoGo (262.6 ± 32.3 vs. 232.6 ± 38.1 msec, $F = 6.16$, $p = .018$) conditions. There were no any other interactions effects for amplitude and latency of the N2b.

P3b. The amplitude of P3b was lower in the SUD group compared to controls both to congruent and incongruent Go stimuli (2.22 ± 1.62 vs. 4.00 ± 2.75 μV, $F = 5.18$, $p = .03$) but only to incongruent NoGo

stimuli (1.80 ± 1.39 vs. $3.28 \pm 2.44\,\mu V$, $F = 4.68$, $p = .039$). The latency of P3b was not statistically different in SUD compared to the CNT group (across all Go stimuli, 473.2 vs. 466.7 msec, *ns*) but showed a significant Congruence (congruent, incongruent) × Group (SUD, CNT) effect ($F = 5.12$, $p = .031$). This interaction can be described as a shorter P3b latency to incongruent stimuli, whereas longer latency to congruent stimuli in addicts compared to controls.

Frontal ERP Components

N200 (N2a). The amplitude of this component did not show any group differences, but the latency of N2a was globally longer in cocaine addiction group in all conditions (congruent and incongruent Go, 281 vs. 239 msec, $F = 6.96$, $p = .013$; congruent and incongruent NoGo, 276 vs. 238 msec, $F = 7.35$, $p = .011$). This might be indicative of slower processing of response conflict in SUD group.

N450. We could not find any amplitude or latency group differences for N450 component (see Figure 2). I have added in-text call-outs for Figures 2 through 6. Please ensure they are listed in the proper place.

Anterior difference waves. For the assessment of cortical inhibition we analyzed difference waves (NoGo-minus-Go) both for N200 (NoGo-N2) and P300 (NoGo-P3) window ranges.

Frontal N200 differences wave (NoGo-N2). A one-way ANOVA showed significant differences between the SUD and CNT groups only in congruent NoGo-N2 waves. Amplitude of the difference wave was lower in the SUD group compared to controls (0.32 ± 0.85 vs. $-0.65 \pm 1.56\,\mu V$, $F = 4.90$, $p = .035$). Furthermore, we found a marginal Congruence × Group interaction ($F = 4.22$, $p = .05$), which can be described as a significantly more pronounced frontal NoGo-N2 difference wave in incongruent trials in controls, without any between-group differences for congruent trials. Considering that NoGo-N2 was used as a cortical inhibition index, it may point that higher efforts to inhibit response to more difficult incongruent trials were exposed by CNT group participants, even though main effect of congruence on this parameter was not reaching significance level. This effect was observed at the FCz site and at the ROI, which included five neighboring fronto-central channels (see Figure 3).

FIGURE 2. Frontal and fronto-central region-of-interest (F2, FCz, and EGI channel 5 located between them, 0.5 cm left from FC2) grandaverage event-related potential waveforms during congruent and incongruent Go trials in controls ($N = 15$) and cocaine addicts ($N = 19$). *Note.* The controls group as compared to cocaine addicts shows more pronounced frontal negativity differences between congruent and incongruent Go trials.
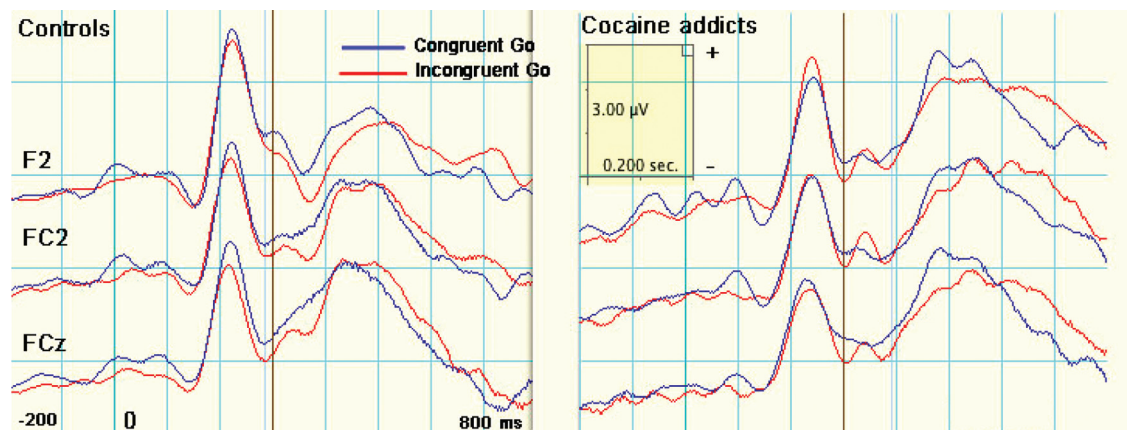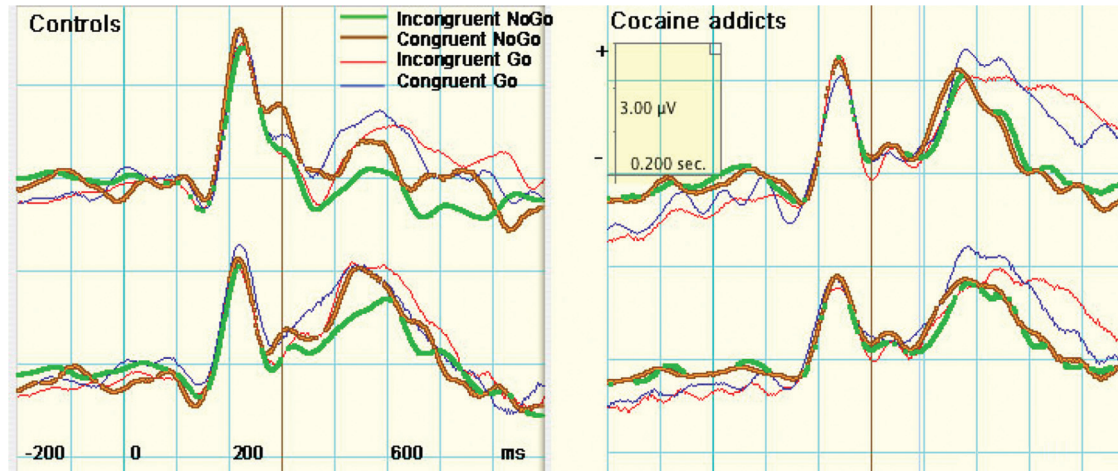
FIGURE 3. Frontal and fronto-central (F2 and FCz) grandaverage event-related potential waveforms during all Go and NoGo conditions. *Note.* The group of cocaine addicts compared to controls shows less frontal negativity (N200, N450) differences between congruent and incongruent NoGo trials.

Anterior frontal NoGo-P3 difference wave. This frontal difference wave showed between group difference being higher in controls compared to the SUD group (1.38 ± 1.30 vs. $0.41 \pm 1.10 \,\mu$V, $F = 4.36$, $p = .047$). There were no group interactions with congruence for this frontal difference wave (see Figures 4 and 5).

ERN

This stimulus-locked parameter was calculated only for those participants who committed more than 12 commission errors. Only 6 participants from the CNT group and 6 from the SUD group met this criteria. The amplitude of ERN during commission errors was significantly more negative in controls compared to addicts (-5.71 ± 2.76 vs. $-2.20 \pm 1.52 \,\mu$V, $F = 7.42$, $p = .021$), which shows higher effectiveness of error detection and error monitoring in control participants. The latency of ERN did not show any group differences (see Figure 6).

DISCUSSION

Our results show poorer performance on the speeded flanker task with response inhibition demands in cocaine addicts compared to controls. Cocaine abusers had significantly slower RT and higher error rate globally, but behavioral responses showed more differences in congruent rather than incongruent Go trials. More omission than commission errors were committed by addicts, which did not support our initial expectation of higher rate of commission errors in this group.

Posterior (centro-parietal) measures of attention (N2b, P3b) also showed lower magnitude of response both to congruent and incongruent Go and NoGo trials in addicts compared to controls. Another interesting and unexpected finding was longer latency of P3b to congruent stimuli rather than incongruent ones in addicts. However, P3b decrements are found in most of SUD and alcoholism, not only cocaine use disorder (Bauer & Hesselbrok, 2001; Carlson, Iacono, & McGue, 2002; O'Connor, Bauer, Tasman, & Hesselbrock, 1994; Polich et al., 1994; Porjesz & Begleiter, 1998). The P3b attenuation effect is also typical for many psychiatric disorders that often are comorbid with SUD, such as conduct disorder, attention deficit/hyperactivity disorder, PTSD, bipolar disorder, schizophrenia, and so on (Bauer, 1997; Bauer & Hesselbrock, 1999,

FIGURE 4. Typical frontal P300 "anteriorization" effect observed in the group of control participants ($N = 15$) in this study. *Note.* During both congruent and incongruent NoGo trials the P300 component is better visible at more anterior parts of the topographic maps. The amplitude of this positive component is larger and is expressed more during conflicting incongruent NoGo trials at time window peaking around 400 msec poststimulus. The red color reflects higher amplitude of the wave.
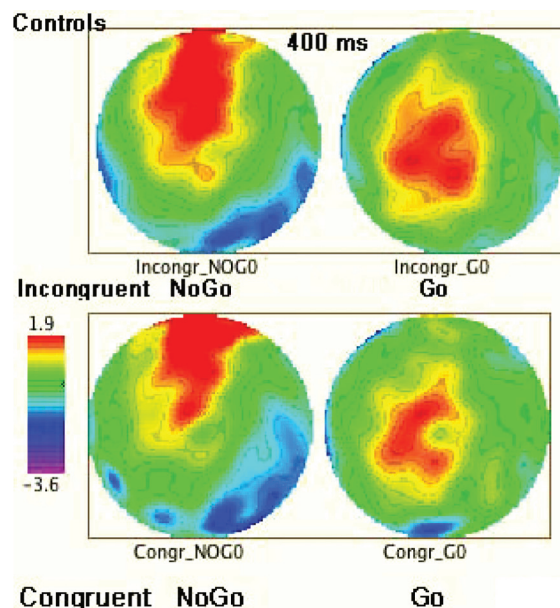
2001; Friedman & Squires-Wheeler, 1994; O'Connor et al., 1994). Reduced P3b might be reflecting as well a predisposition ("risk factor") for development of substance use disorder in general, rather than direct consequence of drug abuse.

In this regard, it was more valuable to detect frontal NoGo-N2 and NoGo-P3 amplitude and latency differences between cocaine addicts and controls, because reduced anterior ERP components during response withholding could be related to prefrontal brain dysfunction and point that a deficit in frontal inhibitory control is an underlying mechanism shared by different psychiatric conditions (Bauer & Hesselbrock, 1999; Clark, Parker, & Lynch, 1999; Tarter et al., 2003). Once again, in a similar manner as for behavioral responses and posterior ERPs measures, our cocaine-addicted participants showed significantly less pronounced frontal NoGo-N2 difference wave in incongruent NoGo trials rather than controls. Considering that the NoGo-N2 was used as a cortical

inhibition index in this study, we can suggest that more efforts to inhibit response on relatively more conflicting incongruent trials were exercised by the control participants but not by the addicts. Error-related negativity was significantly larger in controls compared to cocaine addicts during commission errors and met our prediction of underreactivity to committed errors in cocaine addicts.

Unfortunately, we could not detect any significant differences either in amplitude or latency of the frontal component N450, which is also thought to be originating from the ACC during tasks with conflicting response demands (e.g., flanker or Stroop test). One of the explanations for this could be sought in the methodology of the component scoring used in our study. The N450 component is exhibited as a negative deflection immediately after the peak of P300 or on a descending front of P300. Considering that the SUD group showed globally attenuated P300, a different approach to baseline

FIGURE 5. Group of cocaine addicts ($N=19$) compared to control group ($N=15$) shows less differentiated congruent versus incongruent NoGo anterior frontal P300 amplitude on topographic maps (400 msec poststimulus), and globally lower amplitude of the component during motor response withholding.
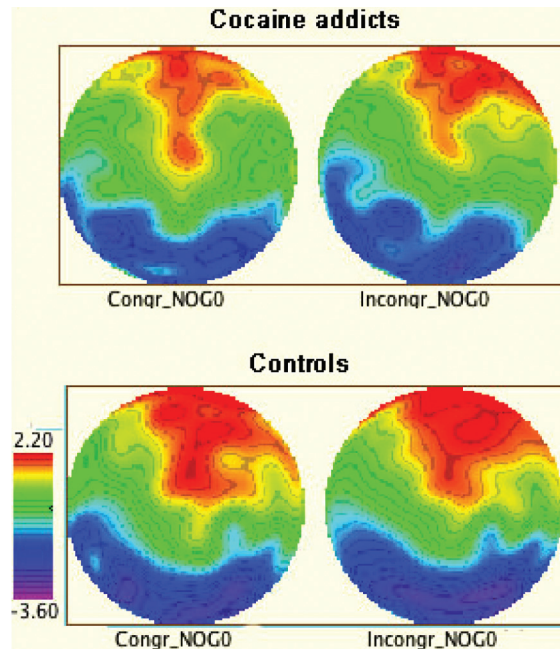

FIGURE 6. Error-related negativity (ERN) during commission errors in controls ($N=6$) and cocaine addicts ($N=6$). *Note.* The amplitude of ERN is larger in controls than addicts even through the latency did not show significant differences. The window selected for these fronto-central region-of-interest containing four electro-encephalographic recording sites (AFz, Fz, and two EGI channels located close to F1 and F2) is highlighted by the light gray color and shows a negative peak between 50 and 150 msec postcommission error.
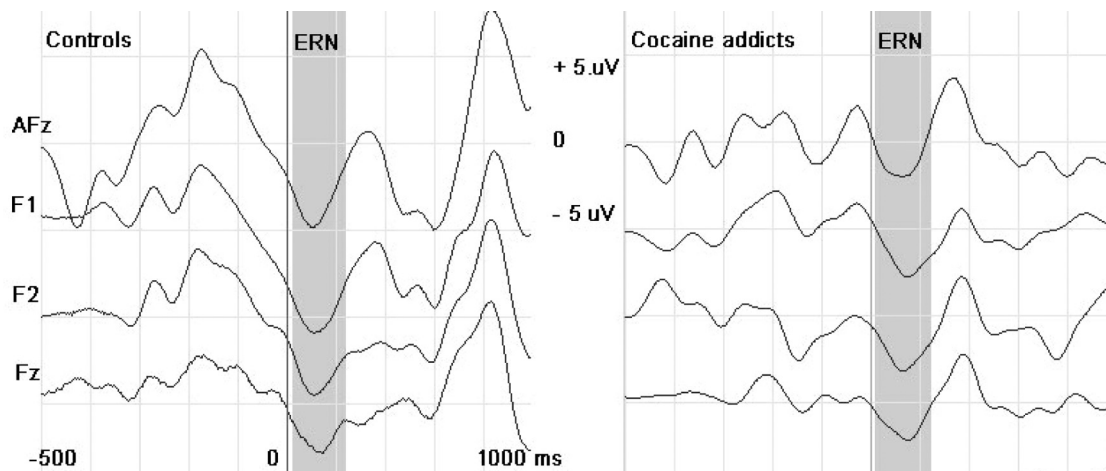
correction method or a different calculation of the N450 parameters (e.g., magnitude or integral of the wave) might happen to be more sensitive to detect group differences, and we plan to recalculate this index using more appropriate scoring techniques.

In general, the results of our study indicate that the difficulties that cocaine-dependent participants experience during flanker task and response inhibition are expressed more when corrective actions should be detected and signaled (but are not) by the medial frontal conflict and error detection system (i.e., ACC) and when more executive (top-down) control engagement should be requested. Underreactive motor response conflict detection and error monitoring system along with the "hypofunctional" prefrontal control might be the main reason for the lower capacity for corrective action need detection and actual implementation of cognitive control necessary for the better performance on this task.

In accordance with the view of hierarchical organization of central motor control, different brain areas are involved in functionally separate mechanisms of advanced movement preparation such as response selection and motor act programming. The frontal lobes control motor acts during performance on reaction task through the planning (e.g., PFC via associated basal ganglia circuits), preparation (pre-SMA, SMA, and their basal ganglia and cerebellum loops), and execution of movements (primary MI and subcortical areas; Brunia, 1999; Brunia & van Boxtel, 2001; Faw, 2003; Fuster, 1997, 1999, 2001; Miller & Cohen, 2001; Thaler, Rolls, & Passingham, 1988).

Anatomically the PFC is known to be connected to the premotor cortex by two main routes. The first one connects PFC with premotor areas via fronto-striatal connections and thalamus. The second route includes direct cortico-cortical connections of the PFC with the mesial premotor areas. Several frontomesial cortical areas are involved in motor control: the anterior pre-SMA, the posterior SMA, and motor areas of the ACC. Externally triggered movements (i.e., those used in our task) are thought to be mainly mediated by the lateral premotor cortex and MI (Jenkins, Jahashahi, Jueptner, Passingham, & Brooks, 2000; Kaiser, Lutzenberger, Preissl, Mosshammer, & Birmbaumer, 2000). These premotor areas seem more involved in selection of movements based on external cues or prompts (Faw, 2003; Passingham, 1995).

Activation of the DLPFC in externally triggered tasks is associated with working memory and other executive top-down control processes (Wiese et al., 2004). The MI area has control over limb movements based on external cues, whereas the SMA is based on internal cues or working memory (Jahanshahi et al., 1995; Passingham, 1995). The DLPFC is contributing to the "movement readiness potential" approximately 1 sec prior to movement, and only then the MI and SMA areas show the "readiness potential" (500 msec prior to action), thus preparing extrapyramidal motor commands, whereas motor cortex sends basic pyramidal commands (Faw, 2003). The left DLPFC is the most important area in the programming strategies, control of executive functions, and motor responses (Miller & Cohen, 2001).

It was suggested that among neural substrates mediating avoidance behavior, the ACC deals with relatively simple expectations of conflict and conflict monitoring (Botvinick et al., 1999; Carter et al., 1998; Devinsky et al., 1995), whereas prefrontal cortex deals with more complex aspects including selection of actions (Faw, 2003). The PFC is not critical for performing simple, automatic movements, such as orienting, which relies on bottom-up processing. In our condition with a congruent (easy, no interferences) flanker stimuli the response is practically automatic, and worse performance by addicts taps at generally more poor psychomotor functioning rather than frontal executive differences. By contrast, the PFC is important when top-down processing is required (Heyder, Suchan, & Daum, 2004). For example, it is needed when a goal-directed behavior must be guided in complex situations when mapping between sensory inputs, action planand memory should be integrated and coordinated (Miller & Cohen, 2001). In a case of incongruent flanker stimuli, normally functioning medial frontal network for motor conflict prediction and interference detection (indexed by N2a and N450), as well as timely and correct identification of an error (ERN) is crucial for triggering this top-down control to adjust motor

response to task demands. Poorly functioning response conflict and error monitoring system in cocaine addicts expressed in a lower frontal N2a and ERN may result in an ignorance (or neglect) both of potential motor conflicts (interference) and committed errors, which may partially explain relatively less errors during incongruent flankers in this group.

Furthermore, even when conflicting response interferences and errors are detected and signaled for executive control, a lowered capacity for the inhibitory prefrontal control over premotor structure tends to fail, thus letting these lower level premotor structures be guided by external signals without significant prefrontal control and corrective override. When working memory load is not too demanding (as it is a case in our study, where the level of errors is relatively low) this unrestricted following initial pattern of response to stimuli and underestimation of potential response conflict may result in a certain advantage for the cocaine addiction group during incongruent trials.

In a real-life environment it is well known that cocaine addicts have difficulties inhibiting their own actions and behaviors aimed at drug seeking and drug taking. The sequelae of lowered frontal executive and inhibitory control over behavioral pattern result in overreactivity of behavioral responses to drug-related external cues and internal craving and drug-related ruminations. It is reasonable to propose that a hypofunctional PFC executive control (probably because of neurotoxicity of cocaine) results in a diminished ability to effectively override strong habitual automated response tendencies controlled by the lower level neural mechanisms (e.g., premotor areas, basal ganglia).

Drug addiction leads to frontal top-down control deficits. Deficient inhibitory control results in an inability to exert corrective actions over strong overlearned habitual responses, thus allowing more automatic external salient stimuli (drug cues and environmental situations) and pathological craving to drive behavior. Individuals predisposed to behavioral disinhibition are more vulnerable to impulsive drug abuse. Reduced prefrontal inhibitory control results as well in a diminished capacity to override stress responses and generally poor stress coping skills typically found in cocaine addicts.

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