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Intact inhibitory control processes in abstinent drug abusers (II): A high-density electrical mapping study in former cocaine and heroin addicts

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ABSTRACT

Response inhibition deficits are well-documented in drug users, and are related to the impulsive tendencies characteristic of the addictive phenotype. Addicts also show significant motivational issues that may accentuate these inhibitory deficits. We investigated the extent to which these inhibitory deficits are present in abstinence. Salience of the task stimuli was also manipulated on the premise that emotionally-valenced inputs might impact inhibitory efficacy by overcoming the blunted responses to everyday environmental inputs characteristic of this population. Participants performed response inhibition tasks consisting of both neutral and emotionally valenced stimuli while high-density event-related potentials (ERPs) were recorded. Electrophysiological responses (N2/P3 components) to successful inhibitions in abstinent abusers ($N = 20$) and non-using participants ($N = 21$) were compared. In contrast to previous work in current users, our abstinent cohort showed no detectable behavioral or electrophysiological differences in their inhibitory responses, and no differences on self-reports of impulsivity, despite their long histories of chronic use (mean = 10.3 years). The current findings are consistent with a recovery of inhibitory control processes as a function of abstinence. Abstinent former users, however, did show a reduced modulation, relative to controls, of their ERPs to valenced input while performing successful inhibitions, although contrary to our hypothesis, the use of valenced inputs had no impact on inhibitory performance. Reduced ERP modulation to emotionally valenced inputs may have implications for relapse in emotional contexts outside the treatment center.

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1. Introduction

It is well-established that currently using drug abusers show consistent and relatively severe difficulties in response inhibition that are associated with reduced integrity of white matter and hypo-activations in some of the major nodes of the brain's response inhibition circuit (Hester and Garavan, 2004; Moeller et al., 2005). These response inhibition deficits are often related to the impulsivity and poor decision making that is characteristic of this population (Brady et al., 1998; Coffey et al., 2003; Everitt et al., 2008; Fillmore et al., 2002; Franken et al., 2007b; Garavan and Hester, 2007; Garavan et al., 2008; Garavan and Stout, 2005; Kaufman et al., 2003; Lane et al., 2007; Li et al., 2008, 2006; Perry and Carroll, 2008; Sokhadze et al., 2008; Verdejo-Garcia et al., 2006;

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Verdejo-Garcia et al., 2007; Wagner, 2001). However, the extent to which these deficits ameliorate as a function of abstinence duration, or what the temporal trajectory of such a functional recovery might be, remains to be understood. A potentially significant contributor to these inhibitory deficits may stem from the anhedonic tendencies that are also a core feature of the addictive phenotype (Erlenmeyer-Kimling et al., 1993; Franken et al., 2007a; Hatzigiakoumis et al., 2011; Janiri et al., 2005). Active drug abusers commonly exhibit reductions in their ability to experience adequate reward from everyday events and items, evidenced by their blunted responses to emotionally evocative stimulation (Aguilar de Arcos et al., 2005; Fox et al., 2011). This emotional blunting is also found in recently abstinent abusers (Dunning et al., 2011; Fox et al., 2007), and it seems a reasonable proposition that this anhedonia may contribute to, or interact with, inhibitory deficits to accentuate the tendency toward drug seeking behaviors. Both of these constructs are believed to be important contributing factors to relapse, since anhedonia correlates strongly with craving intensity (Hatzigiakoumis et al., 2011), and inhibitory deficits are believed to lower the threshold for drug initiation (Whelan et al., 2012).

There were two goals in this study, the first of which was to investigate potential recovery of inhibitory control mechanisms in abstinent cocaine and heroin abusers at varying durations of abstinence, employing high-density electrical mapping techniques and questionnaires relating to impulsivity. This work was conducted as part of a multi-methodological neurophysiological approach to this issue and the reader is referred to the partner paper (Bell et al., in this volume) which reports highly consistent results using functional neuroimaging to assess inhibitory control mechanisms in abstinent cocaine abusers. The second major goal of the current study concerned manipulation of stimulus salience to assess whether the use of emotionally valenced test materials might additionally affect inhibitory efficacy in former drug abusers, on the premise that increasing the evocativeness of the inputs might at least partially overcome the blunted responses to everyday environmental inputs that are characteristic of anhedonic individuals (Katz et al., 2010). Indeed, such an effect has been demonstrated in problem gamblers (van Holst et al., 2012). Problem gamblers performed an inhibition task with stimuli that consisted of neutral valenced images, positively valenced images, or images depicting gambling scenes. While their reaction times on the neutral task were slower than controls' and their number of false alarms comparable, when performing the task with positively valenced images or images depicting gambling scenes, problem gamblers had faster reaction times and made fewer false alarms than controls. This implies that the difficulties with inhibition previously found in addicted populations may not purely be related to executive dysfunction, but may in fact be at least in part related to motivation.

A useful task to investigate inhibitory capability is the Go/No-Go task. In this task, participants are required to push a button in response to a regularly presented succession of stimuli (Go). When a stimulus repeats, participants must inhibit the pre-potent urge to push the button to the second instance (No-Go). When a successful inhibition is made on a No-Go trial, two components of the event related potential (ERP) show characteristic increases in amplitude relative to the responses elicited by the Go trials (Eimer, 1993; Katz et al., 2010; Kiefer et al., 1998; Pfefferbaum et al., 1985). These are a fronto-centrally generated negativity (the N2) arising between 200–400 ms and a later positive potential (the P3), arising between 400–600 ms (Smith et al., 2008). Previous work investigating the amplitudes of the N2 and P3 components under different distributions of Go and No-Go trials has suggested that the N2 reflects conflict monitoring capabilities, while the P3 is a more direct reflection of inhibition (Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010; Nieuwenhuis et al., 2005; Smith et al., 2008). The amplitude of the N2 may also be sensitive to inhibitory capability, as evidenced by an N2 amplitude difference between participants who made high numbers of false alarms vs those who made few such mistakes (Falkenstein et al., 1999). Major generators of the No-Go N2 have been localized to the anterior cingulate cortex and to right lateral orbitofrontal regions, with P3 generators mostly localized to left lateral orbitofrontal areas (Bokura et al., 2001). Areas associated with conflict and response inhibition include the anterior cingulate cortex and the dorsolateral prefrontal cortex (Dias et al., 2003; Dias et al., 2006). Individuals who scored higher on a scale of absentmindedness (the Cognitive Failures Questionnaire) showed higher amplitude N2 and P3 waveforms, perhaps owing to more effortful inhibition processes (Roche et al., 2005), and this is evidenced further by the finding that higher inhibitory load in a Go/No-Go task differentially affects amplitude and latency of the N2 and P3 (Thomas et al., 2009).

Evocative stimuli may also increase inhibitory load. Indeed, behavioral and neuroimaging work has demonstrated that withholding responses to pleasurable stimuli results in lower accuracy (Hare et al., 2005), and activates prefrontal as well as discrete cingulate brain regions when compared to neutral stimuli (Elliott et al., 2000; Goldstein et al., 2007; Shafritz et al., 2006). ERP measures of inhibitory control also reveal effects of stimulus salience, with emotionally valenced words driving higher amplitude N2 and P3 components during successful inhibitions (Chiu et al., 2008), valenced images driving altered No-Go P3s and reaction times (Albert et al., 2010; Wang et al., 2011), and valenced images of high or low intensity determining the degree of N2 and P3 amplitude increase (Yuan et al., 2012).

Toward the dual goals of investigating the extent of recovery of inhibitory control and examining the effect of evocative stimuli, abstinent abusers' inhibitory capabilities were tested using both neutral and emotionally valenced stimuli during a Go/No-Go task in conjunction with the administration of questionnaires relating to impulsivity. There were two main hypotheses: The first was that abstinent cocaine abusers would report less impulsivity, show a degree of recovery of their inhibitory control in the neutral condition, and that the extent of this recovery would be dependent on the duration of abstinence. The second hypothesis, stemming from the idea that evocative stimuli would ameliorate impaired motivation in abstinent drug abusers, was that abstinent cocaine abusers would demonstrate an increased susceptibility to the effect of emotional valence. This was expected to lead to greater relative amplification of N2 and P3 inhibitory responses in former addicts during valenced conditions relative to neutral.

2. Methods

2.1. Participants

Participants with no drug use history were recruited from the volunteer pool at the Nathan S. Kline Institute for Psychiatric Research. Former drug users were recruited from the Russel E. Blaisdell Addiction treatment center and the Open Arms halfway house in Rockland County, New York. The Russel E. Blaisdell treatment center is an inpatient facility, and the Open Arms halfway house randomly performs urine toxicology screenings twice a week, which ensured that all participants were continuously abstinent and free of acute effects of drugs while performing the study. All potential participants were given the Structured Clinical Interview for the DSM-IV. All abstinent participants received a primary Axis I diagnosis of Substance Dependence. Abstinence was also confirmed by a New York State accredited substance abuse counselor that the patient met with on a weekly basis. Exclusion criteria for abstinent abusers and controls were as follows: 1) Any DSM IV, Axis 1 diagnosis (excluding dependence or a past diagnosis of depression caused by drug use for the abstinent abusers) based on the Structured Clinical Interview for the DSM IV (SCID); 2) Head trauma resulting in loss of consciousness for longer than 30 min; 3) Presence of any past or current brain pathology; 4) A diagnosis of HIV; 5) Age

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above 55 years and below 19 years. Because of the high rates of comorbidity of alcohol and drug abuse among the patient population, abstinent abusers were not excluded if they had abused other drugs or alcohol prior to the onset of their abstinence. None of the abstinent abusers were currently using any amount of alcohol or drugs. Years of drug use were recorded during the initial SCID interviews. Controls were excluded if they had any major Axis 1 disorder or alcohol/drug dependence diagnosis based on a SCID for the DSM IV. Participants were paid $100 for their participation and any travel expenses were covered. All participants signed an informed consent document administered by HIPAA-certified staff. All procedures were approved by the Institutional Review Board of the Nathan S. Kline Institute for Psychiatric Research and City College of the City University of New York. The study conformed to the principles outlined in the Declaration of Helsinki.

EEG recordings for the neutral Go/No-Go task were completed on 21 abstinent abusers and an equal number of healthy controls with no drug use history. The groups were matched on age, education, sex, and handedness. One abstinent abuser had to be dropped due to data quality issues. Two abstinent participants also completed the fMRI version of the task in Bell et al. (in this volume).

A subset of 18 users and 18 controls who participated in the neutral task (task 1) also successfully completed the emotional Go/No-Go task (task 2). Two controls had to be dropped from this task due to data quality issues, and one abstinent user had to be dropped due to excessive artifacts.

All abstinent participants reported cocaine or heroin as their primary drug of choice, and all participants reported being once-chronic users of cocaine, with seven reporting use of both heroin and cocaine. The duration of abstinence for the abstinent abusers was between 1 month and 2 years with an average of 15 months. This number was gleaned from both the participant's report and from counselors at the addiction treatment centers. The average age was 39, with a range between 21 and 55 years. We also assayed severity of the participant's drug use, during their most intense period of use, with the Kreek–McHugh–Schluger–Kellog (KMSK) Scale (Kellogg, 2003). The focus was on cocaine and heroin abusers, though participants had used other drugs in the past. Table 1 illustrates the demographics and the drug use histories of the abstinent user pool in both the neutral and emotional tasks for all participants who completed recordings.

2.2. Tasks

Participants were asked to complete two separate tasks.

2.2.1. Task 1: neutral Go/No-Go

Participants performed a Go/No-Go task, responding quickly and accurately to every stimulus presentation, while withholding responses to the second instance of any stimulus repeated twice in a row. The probability of Go and No-Go trials was .85 and .15 respectively. We used pictures from the International Affective Picture System (IAPS; Lang and Cuthbert, 1997), a set of normative photographs that includes content across a wide range of semantic categories (http://csea.phhp.ufl.edu/Media.html#topmedia). In this task, emotionally neutral stimuli were presented in a pseudorandom sequence depicting people, landscapes, abstract patterns and objects (valence: 5.2; arousal: 3.5). Images were presented centrally every 1000 ms for 800 ms with an inter-stimulus-interval of 200 ms. Images subtended 8.6° horizontally by 6.5° vertically. This is identical to the task used in the partner paper by Bell et al. (in this volume). Five blocks of the neutral response inhibition task were run, and participants were allowed to take a break whenever they liked. Each block lasted 3.5 min and consisted of 180 trials, for a total of 900 trials per participant, 135 of which were inhibition trials. 158 neutral pictures were shown randomly over 900 trials, implying that no picture was seen more than 5 times for the entire run of task 1. Given the timing of the task and the inclusion of short breaks, this implies that no picture was shown more than once every four to five minutes on average. Participant inclusion required at least 80% of trials be accepted after artifact rejection. Thus, mean trial numbers in this task ranged from 112 to 131 inhibitions. Task 1 always preceded task 2. The order of the tasks was explicitly not counterbalanced because of the desire to first assess inhibitory mechanisms in the absence of any generalized effect that might result from viewing the emotional pictures in phase two of the experiment.

Table 1
Demographic and drug use information for abstinent participants and controls.

	Task 1		Task 2	
	Neutral Go/No-Go		Emotional Go/No-Go	
	Abstinent abusers	Controls	Abstinent abusers	Controls
Age	39(±10)	41(±10)	40(±10)	41(±10)
Education	12(±1.8)	12(±2)	13(±1.2)	12(±2)
Sex (M/F)	19/1	20/1	17/0	16/0
Ethnicity (African American/ not African American)	8/12	10/11	7/10	8/8
Drug of choice (Cocaine/ Heroin)	13/7	NA	5/12	NA
Drug use in months (Total)	124(±100)	NA	134(±105)	NA
Alcohol	52(±97)	NA	78(±112)	NA
Marijuana	20(±36)	NA	29(±41)	NA
Cocaine	66(±77)	NA	79(±85)	NA
Heroin	23(±48)	NA	35(±59)	NA
Severity (KMSK Scale)				
Alcohol	11(±5)	NA	10(±5)	NA
Marijuana	8(± 5)	NA	4(± 5)	NA
Cocaine	13(±2)	NA	12(±4)	NA
Heroin	4(±5)	NA	5(± 5)	NA
Abstinence duration in Months	15(±26)	NA	17.7(±26)	NA

2.2.2. Task 2: emotional Go/No-Go

Task design was identical to the neutral Go/No-Go, with the exception that the pseudo-randomly presented stimuli consisted of neutral, negative, and positive pictures from the IAPS (for an identical approach, see De Sanctis et al., 2012), presented in an event-related design. 478 pictures were presented, split into three categories. The 158 neutral pictures, identical to those used in task 1, depicted people, landscapes, abstract patterns and objects (valence: 5.2; arousal: 3.5). The 148 negative pictures depicted attack scenes, mutilated bodies and disgusting objects (valence: 2.56; arousal: 5.6). The 172 positive pictures depicted babies/toddlers, family gatherings, and prestige objects (valence: 7.4; arousal: 4.8). Images were selected such that neutral, positive and negative images did not significantly differ in luminance, contrast and spatial frequency. Emotionally neutral, positive, and negative stimuli were presented randomly with a probability of .45, .275, and .275 respectively. The inclusion of the neutral trials served as a control between the two tasks. There were fourteen experimental blocks for this task, bringing the total experimental run time to 49 min with a total of 2520 trials per participant, 170 of which were neutral valenced inhibitions, 105 of which were positively valenced inhibitions, and 105 of which were negatively valenced inhibitions. The first seven blocks consisted of 79 of the 158 original neutral pictures from task 1, 74 of the 148 novel negative pictures, and 86 of the 172 novel positive pictures. The final seven blocks consisted of the other half of the pictures for each respective valenced set. In total, 478 pictures were shown over 2520 trials. Similar to task 1, given the timing of the task and the inclusion of short breaks, this implies that no picture was shown more than once every six to seven minutes on average.

Participant inclusion required at least 80% of trials be accepted after artifact rejection. Thus, mean trial numbers in this task ranged from 148 to 167 neutral valenced inhibitions, 94–101 negatively valenced inhibitions, and 96–101 positively valenced inhibitions. Participants were permitted to take breaks to prevent fatigue and concentration lapses.

2.3. Questionnaires and procedure

Participants were seated in a comfortable, private room at the Nathan Kline Institute. In order to get a complete picture of their current state of impulsivity, during a pre-test interview, participants were given the following questionnaires relating to their general level of impulsiveness and aggression: Life History of Aggression (Coccaro et al., 1997), Buss-Perry Aggression questionnaire (Buss and Perry, 1992), and Barratt's Impulsiveness Scale (Patton et al., 1995).

For the electrophysiological portion, participants were seated in a dimly lit, sound-attenuated, electrically shielded room, 115 cm from a 50 cm Cathode Ray Tube Iiyama Vision Master Pro 512 monitor, with a dot pitch of .24. To ensure consistency of cap placement across participants, measures were made between the inion and nasion and between the left and right pre-auricular notches, using a flexible tape-measure, to identify the vertex of the scalp. This was then designated as the CZ electrode site and the cap was adjusted accordingly. Central fixation was required throughout each block (180 trials). Participants completed one mandatory practice block before the main experiment began. If needed, additional practice blocks were allowed. Participants took breaks as needed between blocks to prevent fatigue.

2.4. Electrophysiological data collection and analysis

Event-related potentials (ERPs) were acquired from a 72-channel montage at a digitization rate of 512 Hz with a pass-band of .05–100 Hz using the BioSemi Amplifier System. BioSemi uses two electrodes—the Common Mode Sense (CMS), which is actively recorded, and the Driven Right Leg (DRL), a passive electrode—that together form a feedback loop that represent the reference. The acquisition of the data occurs referenced to the CMS-DRL ground which drives the average potential of the participant (i.e., the common mode voltage) as close as possible to the AC reference voltage of the Analog-to-Digital box (for a description of the BioSemi active electrode system referencing and grounding conventions, visit www.biosemi.com/faq/cms&drl.htm). Data were referenced offline to the nasion electrode-site. Epochs of 900 ms, including a 100 ms pre-stimulus baseline, were analyzed. Trials with eye movements and blinks were rejected offline based on vertical and horizontal EOG records. An automatic artifact rejection criterion of ±70 μV was used at

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all other scalp sites. All analyses were conducted on individual subject averages that were not digitally filtered but group data were subsequently low-pass filtered at 45 Hz for purposes of illustration.

To ascertain times- and regions-of-interest independently of group effects, we collapsed the grand mean ERP across group (control and abstinent abusers) for each condition (Go and No-Go). Visual inspection of the No-Go condition showed maximal N2 amplitude at 250 ms over fronto-central scalp locations (FCz) and was thus defined as the average amplitude in the time window between 230 and 270 ms at electrode FCz, matching the observed peak latency of this waveform. Maximal P3 amplitude was observed to peak at 430 ms over central–parietal scalp sites (CPz) and sustain until 570 ms. Considering the more sustained nature of this waveform, it was thus defined as the average amplitude in the time window between 400 and 600 ms at electrode CPz, matching the observed peak latency.

A reviewer of an earlier version of this manuscript expressed concern that the P3 component might be influenced by other late components associated with emotional processing, especially the Late Positive Potential (LPP). A PCA analysis for this component performed in an earlier study during a passive emotional picture viewing task found this component to peak during two time-windows, one at 850 ms and the other at 1600 ms, both of which are well beyond the time-window used to measure the P300 here (Foti et al., 2009). Nonetheless, PCA analysis was performed here using the Brain Electrical Source Analysis (BESA) software on the grand average waveform for controls and abstinent abusers separately to test for possible additional contributions to processing in this timeframe. A single component explained 98% of the activity during the neutral task and 97% of the activity during the emotional tasks in the control participant data. A single component also accounted for 90% and 92% of the activity for neutral and valenced activity respectively in data from the abstinent abusers. These results clearly imply that activity in this timeperiod was dominated by the P3 component.

2.5. Statistical analyses

For the neuropsychological data, *t*-tests were employed to test for between group differences on the measures of aggression and impulsivity. In task 1, *t*-tests were employed to test for between group differences in hit rate (i.e., responses to Go trials), error rate and reaction times, and for between group differences on the amplitude of the N2 and P3. For behavioral data in task 2, 2 × 3 ANOVAs were employed to test for factors of group and valence on hit rates, error rates and reaction times. A 2 × 3 ANOVA with factors of group and valence was also employed to test for between and within group differences in the amplitude of the N2 and P3. Correlation coefficients were computed separately for each ERP component for the measures of duration of drug use and duration of abstinence.

2.5.1. Statistical cluster plots

A secondary exploratory analysis was also performed to fully explore the richness of these high-density data. The statistical cluster plot (SCP) approach is a simple method for testing the entire data matrix for putative effects and involves the derivation of cluster plots by calculating pointwise paired, two-tailed *t*-tests between the ERP responses to a given pair of experimental conditions. The results of the pointwise *t*-tests from 64 electrodes are displayed as an intensity plot to efficiently summarize and facilitate identification of differences within and between groups in the onset and general topographic distribution of differential activation associated with the No-Go ERP. The abscissa and ordinate axes represent time and electrode location respectively, while the color represents the *t*-value for each data point. This approach offers a statistical cluster plot identifying differences between abstinent substance abusers and healthy participants in scalp distribution and onset of differential ERP responses across the entire epoch. We are aware that conclusions based on statistical cluster plots are undermined because of the large number of *t*-tests calculated across the electrode montage and recording epoch. In the present data treatment, periods of significant difference were only plotted if an alpha criterion of .05 or less was obtained and then only if this criterion was obtained for at least 11 consecutive data points. Only effects exceeding 11 consecutive significant time points (21.5 ms) were retained to reduce type I errors. The rationale for this method of multiple comparison correction is that the likelihood of multiple false positive results occurring by chance at *n* consecutive time points is ∞, assuming statistical independence between the time points. However, since actual EEG signals cannot change arbitrarily fast, one needs to account for the small amount of dependence between adjacent time points, which can be easily achieved by considering the autocorrelation of the signal. Even for high autocorrelations and long sequence lengths, a criterion of 11 consecutive time points has been shown to be quite conservative in avoiding type I errors (Guthrie and Buchwald, 1991; Molholm et al., 2002).

3. Results

3.1. Behavioral results

Because of the small number of abstinent users who reported heroin as their drug of choice vs the larger number of abstinent users who reported cocaine as their drug of choice, investigations of differences between these two groups are not reported here. Those who reported heroin as their drug of choice also reported using cocaine in comparable amounts, and there was no significant difference between months of use of heroin and months of use of cocaine in this subgroup of our population ($t_6 = 1.07$, $p > .3$). For detailed drug use histories in this subset of participants, the reader is referred to the Supplementary Table. Cocaine and heroin users were treated as one group for all reported analyses.

3.1.1. Questionnaires

Abstinent abusers demonstrated significantly higher scores on the Life History of Aggression questionnaire ($t_{39} = 4.2$, $p \leq .001$) and significantly higher scores on the Buss-Perry Aggression questionnaire ($t_{39} = 4.3$, $p \leq .001$). No significant differences were found between the groups on their scores on the Barratt's impulsiveness questionnaire ($t_{39} = .15$, $p = .56$).

3.1.2. Neutral Go/No-Go task 1

Fig. 1 shows reaction times, hit rates and commission error rates in both abstinent abusers and controls for the neutral Go/No-Go task. *t*-tests revealed no differences between groups for reaction times ($t_{39} = .167$, $p \leq = .70$), hit rates ($t_{39} = .78$, $p \leq = .31$), or error rates ($t_{39} = .322$, $p = .62$).

3.1.3. Emotional Go/No-Go task 2

Fig. 2 shows reaction times, hit rates and commission error rates in both abstinent abusers and controls for the emotional Go/No-Go task. An ANOVA for reaction time revealed no significant effects for group ($F_{1,31} = .065$, $p = .8$), valence ($F_{1,31} = 1.25$, $p = .3$) or group by valence interaction ($F_{1,31} = 1.35$, $p = .302$). For hit rates, no significant effects for group ($F_{1,31} = 1.6$, $p = .203$), valence ($F_{1,31} = 2.3$, $p = .1$), or group by valence interaction ($F_{1,31} = .067$, $p = .9$) were found. Similarly, no significant effects for group ($F_{1,31} = .17$, $p = .2$) valence ($F_{1,31} = .19$, $p = .8$) or group by valence interaction ($F_{1,31} = .3$, $p = .6$) were found for error rates.

3.2. Electrophysiological data

3.2.1. Neutral Go/No-Go task 1

Fig. 3 shows the electrophysiological waveforms at three midline, fronto-central, scalp sites associated with each group. The left column illustrates the waveforms for the neutral condition of task 1 and the right columns illustrate the neutral and emotional conditions of task 2. The cluster plots reflect between group *t*-tests for the respective conditions. *t*-tests for task 1 revealed no group differences for either the nogo N2 ($t_{39} = .05$, $p = .8$) or the nogo P3 ($t_{39} = .01$, $p = .9$) associated with correctly withholding a response. The bottom panel of Fig. 4 show the statistical cluster plots, confirming no differential activation between groups across the entire scalp array and recording epoch.

Correlations were performed between the electrophysiological measures in this task, abstinence duration, and duration of drug use. No relationships were found between abstinence duration, duration of drug use and amplitude of the nogo N2 (*p*-values > .6) or nogo P3 components (*p*-values > .6) in this task. We also performed a post-hoc analysis where we divided abstinent users into short and long term abstinent groups using a median-split approach and performed an ANOVA with a factor of group (short term abstinent, long term abstinent, and controls) to further assess whether there was any evident relationship between duration of abstinence and measures of response inhibition. This analysis revealed no significant differences for either the N2 or P3 (all *p* values > .2).

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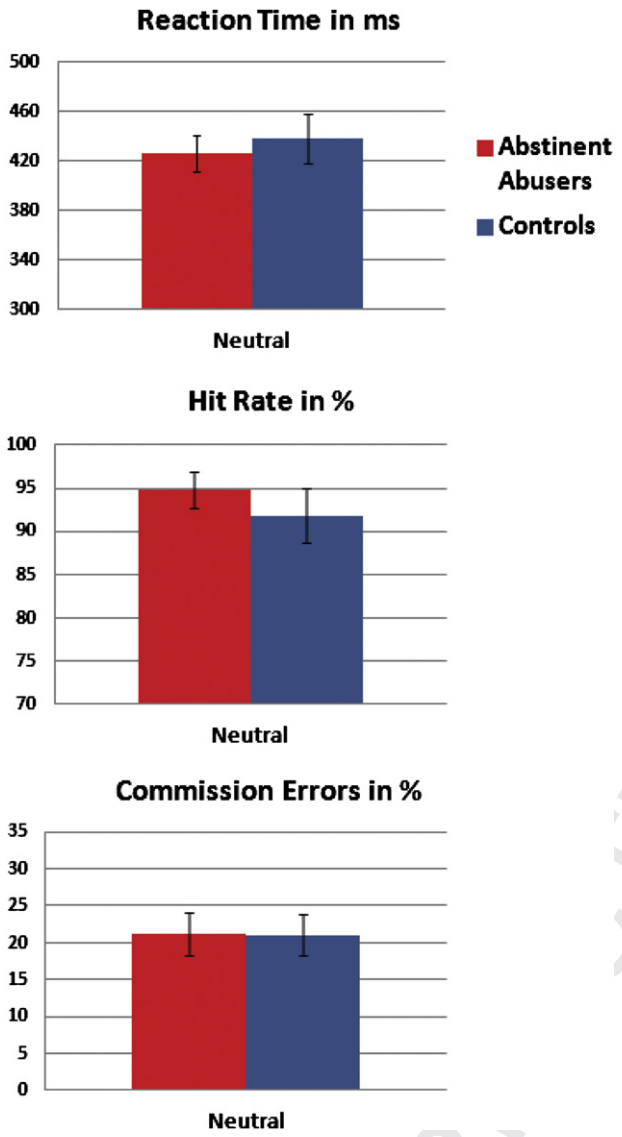

Fig. 1. Reaction times, hit and commission error rates for abstinent drug abusers and non-abusing control participants are displayed for task 1, where only neutrally valenced stimuli were used. No differences in performance between abstinent abusers and controls were found.

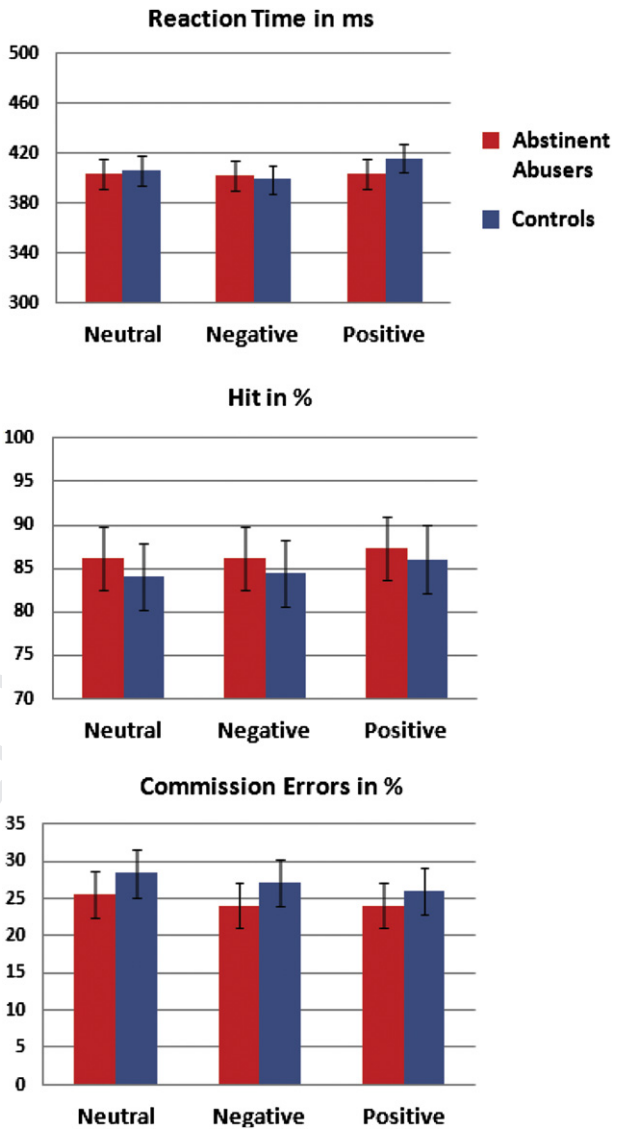

Fig. 2. Reaction times, hit and commission error rates for abstinent drug abusers and non-abusing control participants are displayed for task 2, where both neutrally valenced and emotionally valenced stimuli were used. No differences in performance between abstinent abusers and controls were found, regardless of whether the stimuli were neutrally or emotionally valenced.

3.2.2. *Emotional Go/No-Go task 2*

Fig. 4 displays the electrophysiological responses for each condition in task 2 within each group, and the cluster plots reflect within-group *t*-tests where neutral and emotional conditions were compared against each other. An ANOVA for the nogo N2 revealed no group, valence or group by valence interaction effects (*p*-values $> .3$). An ANOVA for the nogo P3 revealed a main effect of valence ($F_{1,31} = 3.72$, $p \leq .03$), with an interaction of valence × group ($F_{1,31} = 3.47$, $p \leq .04$). *t*-tests to follow up the interaction, also evidenced in the statistical cluster plots, revealed that controls showed modulation of the later stages of the nogo P3 by positive stimuli ($t_{1,31} = 3.9$, $p \leq .02$) and showed modulation of the nogo P3 by negative stimuli ($t_{31} = 2.9$, $p \leq .02$). Abstinent abusers showed no evidence of such modulations.

Correlations were performed between the electrophysiological measures in this task, drug use duration, and abstinence duration. No relationships were found between abstinence duration and the amplitudes of the nogo P3 components in the negative or positive conditions (*p*-values $> .1$). A marginal relationship was found between abstinence duration and nogo P3 amplitude in the neutral condition ($r_{31} = .5$, $p \leq .05$). No relationship was found between drug use duration and the amplitude of the nogo P3, nor were any relationships found between drug use duration, abstinence duration, and the amplitudes of the nogo N2 components (*p*-values $> .3$).

4. Discussion

Recent structural imaging studies point to rapid and considerable changes in white matter structure as a function of duration of abstinence (Bell et al., 2011; Xu et al., 2010), changes that are already manifest within the first few weeks following drug cessation. In the current study, as in the companion neuroimaging paper (Bell et al., in this volume), we hypothesized that abstinent drug abusers would likely show some degree of recovery in their inhibition capabilities. We fully expected that this recovery would

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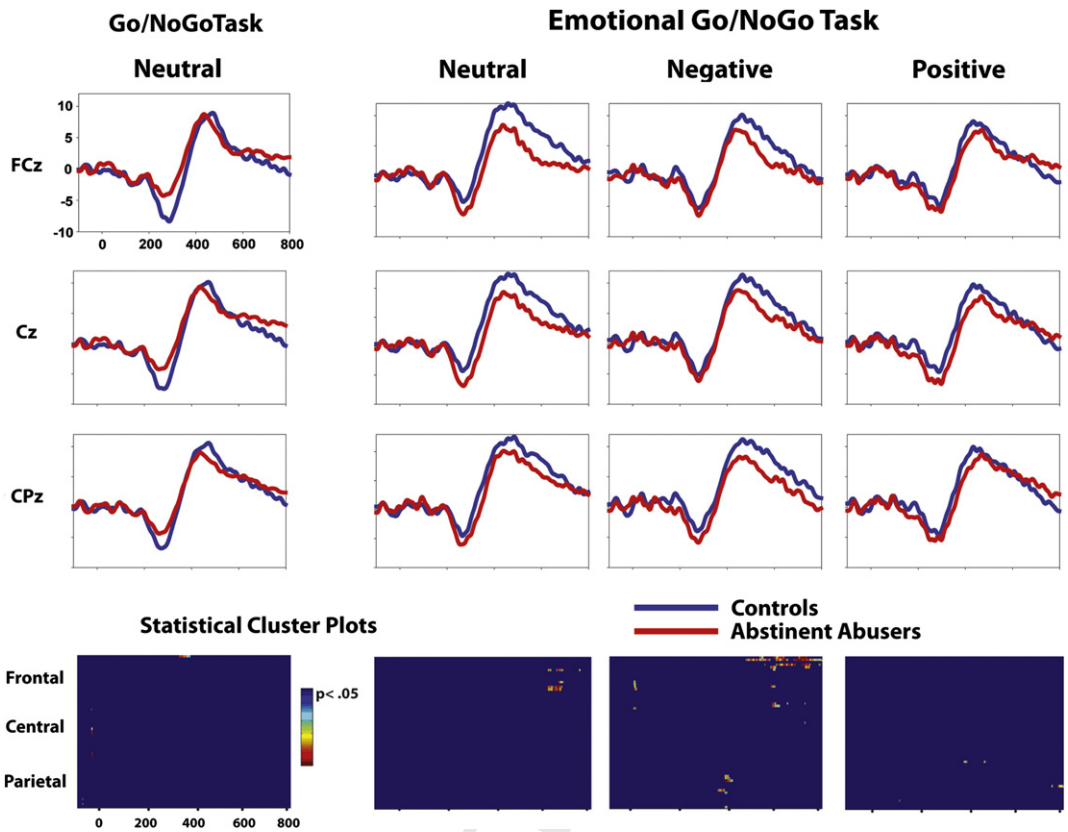

Fig. 3. The nogo N2 and nogo P3 response waveforms associated with successful inhibitions for abstinent drug abusers and non-abusing control participants in the neutral response inhibition task are displayed in the left column. The nogo N2 and nogo P3 responses associated with successful inhibitions in the emotionally valenced response inhibition task are displayed in the right columns. The statistical cluster plots displayed below illustrate tests for between-group differences across the entire electrode array and all timepoints in the epoch of interest. Color values indicate the result of point-wise *t*-tests evaluating controls vs abstinent abusers for the neutral conditions of task 1 and the neutral, negative and positive valenced conditions of task 2 across a 900-ms epoch (*x*-axis) and electrode positions (*y*-axis: arranged from frontal to occipital sites in descending order) for the entire 72-electrode montage (see 'Materials and methods' section for details of electrode locations). For clarity, only tests where $p < .05$ are color-coded and only then when a minimum of 11 consecutive data points exceeded this criterion. As can be seen, there were no statistical differences found between groups during the N2 or P3 timeframes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increase as a function of abstinence duration, and predicted that inhibitory functioning would likely be further enhanced under more salient, emotionally evocative contexts, on the premise that arousing inputs would serve to modulate underlying issues with hedonic tone. While we did find evidence of recovery, we found that abstinent abusers did not show modulation of their inhibition-related activation by emotional stimuli.

4.1. Largely intact inhibitory mechanisms in abstinence

Using a Go/NoGo task with neutrally-valenced pictorial stimuli, we investigated inhibitory capabilities in abstinent former addicts, and found that not only were this group's performance levels equivalent to those of non-using matched controls, but both the nogo N2 and the nogo P3 components of the ERP were found to be of statistically indistinguishable amplitude across groups. That is, abstinent abusers showed no detectable differences in their error rates and no evident difference in how their inhibitory neural circuitry was activated. As such, these results are quite distinct from a considerable body of prior work where inhibitory deficits are found to be prevalent in currently using drug abusers (Franken et al., 2007b; Sokhadze et al., 2008; Yang et al., 2009).

The fact that abstinent abusers showed no behavioral difficulties on the tasks may indicate recovery of inhibitory capabilities, and mimics closely the results of our related neuroimaging study (Bell et al., in this volume). The present results also echo previous EEG work on the recovery of functions in abstinent abusers, where increases in the amplitude of the P300 component were observed (Bauer, 2001). However, it should be pointed out that the study of Bauer tested this in the context of a vigilance task, and unlike the current findings, P300 amplitudes were found to correlate with abstinence duration. We did observe a marginal finding between abstinence duration and P3 amplitude in the neutral condition of the emotional Go/No-Go task, but this was largely driven by a few subjects, was not observed in the other conditions and would not survive correction for multiple comparisons. No relationship was found between nogo N2 and abstinence duration. It is possible that recovery of inhibitory capabilities occurred very rapidly after drug cessation, making the long durations of abstinence inconsequential in this case. The recovery of inhibitory control may also underlie our finding that self-reported impulsivity did not differ significantly between the two groups, in contrast to previous work in active drug abusers where the presence of both impulsivity and aggression was observed (Moeller et al., 2002). Here, we did find that abstinent abusers reported higher scores on questionnaires relating to aggression, but they did not differ significantly from controls on the clinical measure of impulsivity.

To fully investigate the contribution of inhibitory control mechanisms to cessation of substance abuse, our laboratory enrolled a cohort of abstinent cocaine abusers in a functional magnetic resonance imaging (fMRI) study (Bell et al., in this volume). Participants in the fMRI study completed the same Go/

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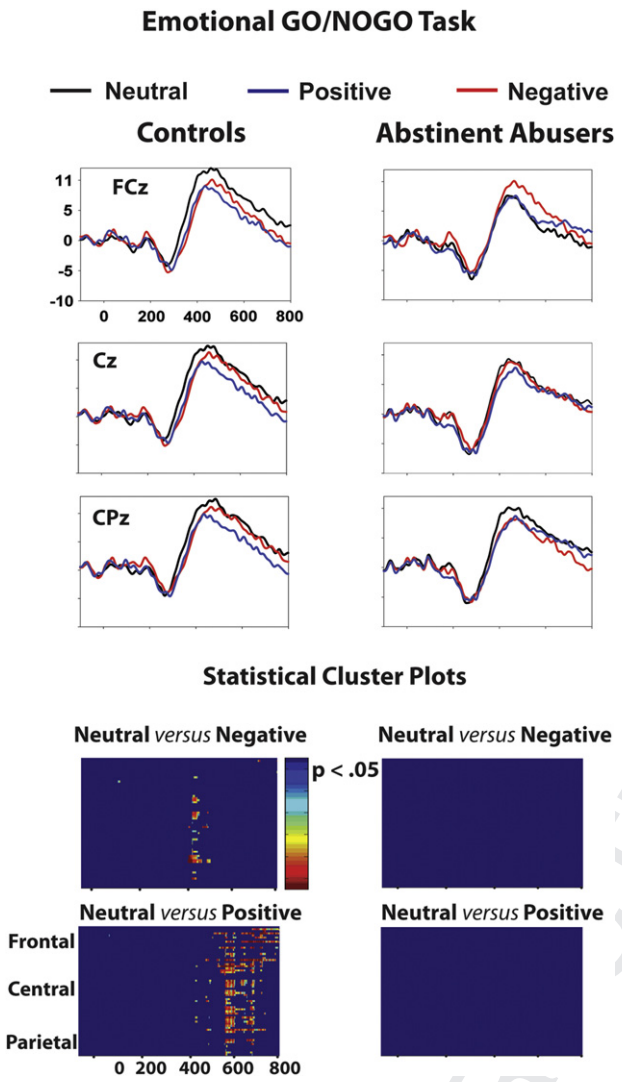

Fig. 4. The within-group modulations of nogo N2 and nogo P3 as a function of emotionally valenced stimuli during successful response inhibitions are displayed in Fig. 4. The statistical cluster plots below illustrate the within-group differences between valenced and neutral conditions for this task. Color values indicate the results of point-wise *t*-tests evaluating neutral vs negative trials and neutral vs positive trials for both groups across a 900-ms epoch (*x*-axis) and all electrode positions (*y*-axis: arranged from frontal to occipital sites in descending order) for the entire 72-electrode montage (see 'Materials and Methods' section for details of electrode locations). For clarity, only tests where $p < .05$ are color coded and only then when a minimum of 11 consecutive data points exceeded this criterion. As can be seen, there were no statistical differences found between as a function of valence for abstinent abusers in the N2 or P3 timeframes, but control participants did show significant differences during the P3 timeframe. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

No-Go task, consisting of neutrally valenced stimuli from the IAPS, as described in task 1. The imaging data were entirely consistent with the electrophysiological findings presented here. As in this study, participants in the fMRI study demonstrated no differences in commission error rates and no detectable activation differences within the response inhibition circuit. Utilizing two different methodologies and two virtually discrete cohorts (with an overlap of only two participants), both studies independently provide evidence pointing to substantial recovery of inhibitory control in this population. Some consideration should be given, however, to the fact that all of the participants in our study were involved in inpatient treatment centers, where they were required to attend meetings with counselors at least three times a week and received instruction on cognitive strategies focused on overcoming urges to use. This may have been a significant contributor to the observed recovery of inhibitory control, and may ultimately speak to the efficacy of such treatment strategies.

Previous work in addiction has suggested that inhibitory dysfunction, abnormalities in event-related oscillations and reduced P300 amplitude exist as vulnerability markers for drug and alcohol abuse (Kamarajan et al., 2006; Porjesz et al., 2005). Several avenues of research support the vulnerability model, including animal models (Belin et al., 2008; Dalley et al., 2007) demonstrating that animals with low inhibitory control are more likely to escalate drug taking. Investigations into inhibitory control in the siblings of substance abusers (Ersche et al., 2010) have also revealed that the siblings demonstrate reduced inhibitory control, suggesting a predisposition to drug abuse that may run in families. Similar to this, much work has shown that reduced inhibitory control leads to worse substance abuse outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Streeter et al., 2008).

The present findings would seem to contradict this idea of reduced inhibitory control as a vulnerability marker for drug abuse. This line of reasoning would hold that the inhibitory control capabilities of this specific cohort returned to levels present before drug abuse began indicating that no vulnerability originally existed. However, it is also plausible that dysfunctional inhibitory control was indeed present before drug use began but that the rigors and imposed discipline of maintaining abstinence (i.e., exercising inhibitory control over drug use urges) corrected that previous vulnerability. Previous work by our group investigating abstinent cocaine abusers performing a similar Go/No-Go task reported that successfully abstinent cocaine abusers demonstrated hyperactivity in prefrontal and cingulate cortex during response inhibitions and during errors of commission (Connolly et al., 2012). In this scenario, the findings presented here and in our previous fMRI study would be explained by these hyperactive inhibitory mechanisms masking any previous, vulnerability-related deficit. While it is possible that there was no inhibitory deficit present in our cohort to begin with, and that it is because of their intact inhibitory capabilities that they were ultimately capable of remaining abstinent, this seems quite unlikely considering their once chronic use. To disentangle these interpretations, a longitudinal study investigating inhibitory control both before drug use begins and how it recovers after sustained abstinence would be required.

4.2. Emotional modulation

During inhibitions, healthy non-users showed modulation of the nogo P3 by valence. This aligns well with work demonstrating emotional modulation of different levels of processing (De Sanctis et al., 2012) and also aligns well with previous data demonstrating the sensitivity of inhibitory processes to emotionally valenced inputs (Albert et al., 2010; Wang et al., 2011; Yuan et al., 2012). However, in those studies, the P3 was found to be enhanced in emotional conditions, whereas here it was reduced. Perhaps one explanation lies in the unequal distribution of neutral to valenced stimuli in the current paradigm, with the smaller number of positive trials providing enough salience to overcome the typically more effortful inhibition to valenced stimuli, and potentially by the fact that the valenced trials were intermixed with neutral trials and not separated into distinct blocks.

Abstinent abusers, on the other hand, showed no significant modulation of their inhibitory processes by emotion. This does not fit with the initial hypothesis which predicted improved performance in response to salient stimuli, and is in contrast to previous work in problem gamblers that showed improved accuracy and

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reaction times during an inhibition task when they performed the task with positively valenced or gambling stimuli (van Holst et al., 2012). However, the current data does correspond well with previous work demonstrating blunted emotional processing in drug abusers, both with cocaine cues present (Dunning et al., 2011), with smoking cues present (Luijten et al., 2011), and without any drug cues present (Aguilar de Arcos et al., 2005). This also echoes work illustrating the anhedonic, unmotivated state that many drug abusers encounter (Franken et al., 2007a; Janiri et al., 2005), which may underlie their failure to respond adequately to emotional stimuli, especially during more recent abstinence. Work in adolescent substance abusers also demonstrates a tendency of this population to worsen their inhibitory performance during salient and reward-related tasks (Castellanos-Ryan et al., 2011). The inability of our current sample to modulate their electrophysiological responses by emotion, and perhaps even the finding of persistent differences relating to self-reported aggression, may be related to this tendency, indicating altered inhibitory processing in the face of more salient stimuli in this population.

4.3. Study limitations

While it was hypothesized that anhedonia might be a contributing factor to the blunted responses found in abstinent abusers, this trait was not directly measured in the abstinent cohort here. Future studies should focus on the relationship between anhedonia and inhibitory mechanisms, as well as determining how anhedonia may contribute to emotional blunting, using direct clinical measures of anhedonia.

While the lack of group differences between controls and once-chronic recovered users implies recovery, a cross-sectional design is not the most effective way to determine if recovery has truly taken place. A longitudinal study examining users as they begin abstinence would be necessary to more accurately document the recovery of these processes.

While it was hoped that self reports of drug of abuse would lead to measurable differences between those who chose cocaine as their drug of choice and those who chose heroin, we did not have enough heroin users to pursue any such analyses reliably and there were no trends toward any differences. It is important to note that all participants met criteria for former cocaine dependence, even if heroin was the drug of choice of a subset. Future work on any potential differences in inhibitory control based on drug of choice would be a worthy research goal.

Our sample consisted of mostly men, which limits any ability to provide information about sex differences in abstinence. Future work should investigate normalization of inhibitory processes in female as well as male abstinent users.

One concern that was raised during review of this work was that the use of a delimited set of the IAPS stimuli ($N = 478$) might have resulted in some habituation of responses to repeated instances of the same stimuli. It bears reiterating that stimuli typically repeated only once every 4–5 min in task 1 and once every 6–7 min in task 2, and only then after more than 150 or 200 unique stimulus presentations had intervened for task 1 and task 2 respectively. As such, the extent of any habituation seems likely to have been modest at best. Even if habituation did occur, in order for this to meaningful impact the results of the present study, it would have had to differentially affect one group over the other. We are aware of no evidence that habituation functions differ between neurotypicals and former drug abusers, or any theoretical basis to expect such a difference. Nonetheless, it bears pointing out that differential habituation functions cannot be definitively ruled out as potential contributing factors here, although we feel that this is very unlikely.

5. Conclusions

Abstinent former heroin and cocaine abusers were found to have wholly similar inhibitory control capabilities to those of a cohort of healthy non-addicts. The finding that the amplitudes of the nogo N2 and nogo P3 ERP components during successful inhibition were indistinguishable between groups, and that former addicts performed the task as efficiently as controls, suggests that long-term abstinent abusers recovered normal inhibitory capabilities as abstinence progresses. Of course, an alternate account could be that those users with stronger inhibitory capabilities ultimately have an easier time staying “clean”. However, the sample here consisted of once-chronic users, suggesting that the findings are a function of recovery and not indicative of a pre-existing “normal” state of inhibitory control. The combination of findings from this study and those of Bell et al. (in this volume) provide compelling evidence for recovery of inhibitory control after sustained abstinence.

However, abstinent substance users still demonstrate aberrant processing of emotional stimuli, showing attenuated modulation of their electrophysiological responses compared to controls. This may explain why many abusers relapse in emotional situations, especially early in their recovery. It also suggests that drug abusers, even well into abstinence, may fail to modulate inhibitory effort in the face of any appetitive stimulus, resulting in comparatively reduced control when confronted with salient reinforcers such as drugs of abuse.

The findings suggest that future work should focus on determining what roles emotional dysregulation, reward and anhedonia play in drug abuse, in order to determine how best to guide treatment to achieve normalized executive states that are associated with successful long term abstinence.

Author contributions

JJF and HG were responsible for initial study concept and design. RPB and KPM were responsible for participant recruitment, phenotyping and coordinating data collection. KPM, PDS and JJF all contributed to data analysis and data interpretation. KPM wrote the first draft of the manuscript. JJF, PDS, MIK, RPB and HG provided extensive editorial input throughout the process, and critical revisions of the manuscript for important intellectual content. All authors critically reviewed the content of the paper and approved the final version for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at HYPERLINK http://dx.doi.org/10.1016/j.neuropharm.2013.02.023

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