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

Kristen P. Morie, Hugh Garavan, Ryan P. Bell, Pierfilippo De Sanctis, Menachem I. Krakowski, John J. Foxe

* The Sheryl and Daniel R. Tishman Cognitive Neurophysiology Laboratory, The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA
* The Sheryl and Daniel R. Tishman Cognitive Neurophysiology Laboratory, Children’s Evaluation and Rehabilitation Center (CERC), Department of Pediatrics, Albert Einstein College of Medicine, Van Etten Building, Wing 1C, 1300 Morris Park Avenue, Bronx, NY 10461, USA
† Albert Einstein College of Medicine, Van Etten Building, Wing 1C, 1300 Morris Park Avenue, Bronx, NY 10461, USA
‡ Program in Cognitive Neuroscience, Department of Psychology, The City College of the City University of New York, 138th Street & Convent Ave., New York, NY 10031, USA
¶ Program in Cognitive Neuroscience, Department of Biology, The City College of the City University of New York, 138th Street & Convent Ave., New York, NY 10031, USA
# Department of Psychiatry, University of Vermont, 1 South Prospect St., Burlington, VT 05401, USA

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.

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;
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 (Verdejo-Garcia et al., 2007; 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 orbital-frontal regions, with P3 generators mostly localized to left lateral orbital-frontal 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 absenteeism (the Cognitive Failures Questionnaire) showed higher amplitude N2 and P3 waves, 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 (Chiu et al., 2008; Elliott et al., 2000; Goldstein et al., 2007; Shaderitz et al., 2006). ERP measures of inhibitory control also reveal effects of stimulus valence, 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 Russell E. Blaisdell Addiction treatment center and the Open Arms halfway house in Rockland County, New York. The Russell 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 I 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...
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 addiction. None of the abstinent abusers were current users of alcohol or drugs. Years of drug use were recorded during the initial SCID interviews. Controls were excluded if they had any major Axis I 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 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 the most intense period of use, with the Kreek–McHugh–Schluger–Kellogg (MKS) 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://cice.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 shown 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 six minutes.

#### 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 matched for visual complexity, number of features, and composition. Also, 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 75 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.

Participiant 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, 34–101 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 12 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 (250 μV) (in the mento-bregmatic box of the International 10–20 electrode system referencing and grounding conventions, visit www.biosemi.com/faq/cmsdrl.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 EEG signals. An automatic artifact rejection criterion of ±70 μV was used at
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 time. A 2 × 3 ANOVA was also 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 withing 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. Statistical analyses

A statistical cluster plot was also performed to fully explore the richness of the 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 pairwise t-tests from 64 electrodes are displayed as an intensity plot to efficiently summarize and map the 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 

\[ F \sim \chi^2_{2(n-1)} \]

where \( F \) is the F statistic, \( \chi^2 \) is the chi-squared distribution, and \( n \) is the number of time points. In the present analysis, this correction was applied to all comparisons between groups and within groups in the onset and general topographic distribution of differential activation associated with the No-Go ERP.

2.6. Electrophysiological data

2.6.1. Neutral Go/No-Go task 1

Fig. 3 shows the electrophysiological waveforms at three midline, fronto-centric, scalp sites associated with each group. The left column illustrates the waveforms for the neutral condition of task 1 and the right column illustrates 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) = 0.05, p = .88) or the no-go P3 (t(39) = 0.01, p = .90) 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 no-go N2 (p-values > .6) or no-go 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).
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 ($F_{1,31} = 3.72, p < 0.03$), with an interaction of valence × group ($F_{1,31} = 3.47, p < 0.04$). 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 ($t_{1,31} = 3.9, p < 0.02$) and showed modulation of the nogo P3 by negative stimuli ($t_{1,31} = 2.9, p < 0.02$). 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 ($r_{31} = 0.5, p < 0.05$). 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
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/NoGo task as those in the EEG study, and the results will be reported elsewhere.
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 capacity of this specific cohort returned to levels prior to 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 rigorous 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
reaction times during an inhibition task when they performed the task with positively valenced or valbing 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 meaningfully 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 one-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
References


Plos One 6, e18898.


corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. Neuropsychopharmacology 30, 610–617. 


