Reduction in N2 amplitude in response to deviant drug-related stimuli during a two-choice oddball task in long-term heroin abstainers

(Response inhibition to heroin cues in heroin abstainers)

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Conflict of interest

None.

Abstract

Rationale Chronic heroin use can cause deficits in response inhibition, leading to a loss of control over drug use, particularly in the context of drug-related cues. Unfortunately, heightened incentive salience and motivational bias in response to drug-related cues may exist following abstinence from heroin use.

Objectives The present study aimed to examine the effect of drug-related cues on response inhibition in long-term heroin abstainers.

Methods Sixteen long-term (8—24 months) male heroin abstainers and 16 male healthy controls completed a modified two-choice oddball paradigm, in which a neutral "chair" picture served as frequent standard stimuli, the neutral and drug-related pictures served as infrequent deviant stimuli of different conditions respectively. Event-related potentials were compared across groups and conditions.

Results Our results showed that heroin abstainers exhibited smaller N2d amplitude (deviant minus standard) in the drug cue condition compared to the neutral condition, due to smaller drug-cue deviant-N2 amplitude compared to neutral deviant-N2. Moreover, heroin abstainers had smaller N2d amplitude compared with the healthy controls in the drug cue condition, due to the heroin abstainers having reduced deviant-N2 amplitude compared to standard-N2 in the drug cue condition, which reversed in the healthy controls.

Conclusions Our findings suggested that heroin addicts still show response inhibition deficits specifically for drug-related cues after longer-term abstinence. The inhibition-related N2 modulation for drug-related could be used as a novel electrophysiological index with clinical implications for assessing the risk of relapse and treatment outcome for heroin users.

Keywords heroin abstainers, response inhibition, drug-related cues, two-choice oddball task, Event-related potentials

Introduction

Heroin is one of the most commonly used illegal drugs in China. Of the 2.35 million drug users during 2015, 41.8% were heroin and other opiates users (Office of China National Narcotics Control Commission, 2016). Despite strict legal penalties, and availability of government-funded behavioral and medical interventions, relapse rate is considerably high (see review Tang et al., 2006). In 2015, over 50% of users were recurrent, with 1.069 million newly identified users. Similar trends have also been found in other countries, including the United States, the United Kingdom and New Zealand (Khan et al., 2014; Michael et al., 2003).

Exposure to drug-related cues contributes to the likelihood of relapse (Field and Cox, 2008; Franken, 2003). Heightened incentive salience and motivational bias, can last years after abstinence from heroin use and leads to automatic attentional bias to drug-related cues (Lubman et al., 2000; Franken et al., 2000; Yang et al., 2015a; Wang et al., 2012). Such bias is a significant predictor of relapse and treatment outcome (Lubman et al., 2009; Marissen et al., 2006).

Executive functions, such as response inhibition, also play an important role in preventing relapse, by providing cognitive resources needed to resist cravings triggered by drug-related cues (Field and Cox, 2008; Goldstein and Volkow, 2002). Evidence suggests that deficits in inhibitory functions associated with heroin use could remain even months after abstinence (Fu et al., 2008; Yang et al., 2009; Yang et al., 2015b; Yuan et al, 2009) and contribute to substance use initiation and escalation (Mahmood et al., 2013; Nigg et al., 2006). From a clinical point of view, being able to inhibit drug seeking and intake when exposed to drug-related cues is very important for heroin abstainers to maintain abstinence. However, mechanisms of response inhibition in the context of drug-related cues in heroin addicts during long-term abstinence remains unclear and have received little research attention.

Event-related potentials (ERP) are an electroencephalographic (EEG) method that allows insight into specific temporally distinct mental processes with high precision, and has been used to investigate the neural processes involved in response inhibition. For example, N2 and P3 are elicited by a Go/NoGo task. N2 is a negative component in the ERP, peaking between 200 and 300 ms over fronto-central scalp regions, which shows increased amplitude in response to the NoGo (compared to Go) stimulus. It has been proposed to reflect conflict-monitoring and cognitive control, processes in the early stages of response inhibition (Bokura et al., 2001; Falkenstein et al., 1999; Kopp et al., 1996; Nieuwenhuis et al., 2003). The P3, a positive component peaking between 300 and 600 ms over central-parietal scalp, appears larger and more anteriorly in response to the NoGo than the Go stimulus,

reflecting conflict resolution through top-down inhibition processing in a later stage of response inhibition (Bokura et al., 2001; Falkenstein et al., 1999; Kopp et al., 1996). The difference waves extracted from NoGo stimulus minus Go stimulus (i.e. N2d and P3d) are considered as the direct index of response inhibition-relevant processing (Bokura et al., 2001; Wang et al., 2011; Yuan et al., 2008; Yuan et al., 2012).

Decreased NoGo-N2 and NoGo-P3 amplitude during Go/NoGo tasks have been reported in various populations with impaired response inhibition, such as offspring of alcoholics (Kamarajan et al., 2005), impulsive violent offenders (Chen et al., 2005) and smokers (Buzzell et al., 2014; Luijten et al., 2011). Using the equiprobable Go/NoGo tasks, it has been found that heroin abstainers have larger Go-N2 amplitude, smaller N2d amplitude and longer P3 latency than healthy controls (Yang et al., 2009; Yang et al., 2015b), suggesting response inhibition deficits. Nevertheless, absence of behavioral deficits and abnormal neural activation during performance of a Go/NoGo task has been found in abstinent heroin and cocaine addicts (Morie et al., 2014). It has been speculated that impairment of inhibition function may be improved following drug abstinence. Other studies have investigated the association between ERP components and abstinence in heroin addicts during some cognitive tasks and found that the reduced P3 amplitude could be improved but not completely normalized through short-term abstinence (i.e. within 6 months) (Bauer, 2001; Motlagh et al., 2016; Papageorgiou et al., 2004; Papageorgiou et al., 2003; Wang et al., 2015), and the P3 amplitude was positively related with duration of abstinence (Bauer, 2001). It is possible that response inhibition deficits may be specifically drug-related and could be reduced with decreased craving of drug use following a period of abstinence.

The aim of the current study was to investigate whether response inhibition deficits still remain after a longer period of drug abstinence and how drug-related cues affect response inhibition in long-term heroin abstainers using a modified two-choice oddball task (Yuan et al., 2008). The two-choice oddball task we employed has been developed by Yuan and colleagues (2008). It requires subjects to respond to both standard and deviant stimuli by pressing different keys as accurately and rapidly as possible, instead of only responding to go stimuli in a traditional Go/NoGo or Stop-signal task. It is suggested that ERPs induced by go stimuli involve motor responses that are absent in those elicited by nogo stimuli during performing the traditional Go/NoGo or Stop-signal task (Wang et al., 2011; Yuan et al., 2008; Yuan et al., 2012). The task we used is similar to a classical Go/NoGo task, standard stimuli are presented much more frequently than deviant stimuli, and subjects have to inhibit prepotent response tendency associated with the standard stimuli, in order to respond accurately to

deviant stimuli. Consequently, reaction time (RT) tends to be prolonged for the deviant stimuli compared to the standard stimuli. It is designed to assess the general response inhibition and provides response inhibition specific ERPs free of motor contamination with an additional RT index of response inhibition (Su et al., 2017; Wang et al., 2011; Yuan et al., 2008; Yuan et al., 2012). To avoid possible interference between trials associated with a random design (Wang et al., 2011), we used block-design to present the neutral and drug-related pictures as deviant stimuli of different blocks respectively.

We hypothesized that long-term heroin abstainers would show markedly smaller deviant-N2, N2d, deviant-P3 and P3d amplitude in the drug-cue condition compared to the neutral condition and (2) long-term heroin abstainers would show markedly smaller deviant-N2, N2d, deviant-P3 and P3d amplitude in the drug-cue condition than healthy controls.

Method

Participants

This study received ethical approval from the Northwest Normal University Research Ethics Board, and written consent was obtained from all participants prior to their enrollment in the study. A total of 32 participants (all males) took part in the experiment. Females were not recruited because there were low rates of drug use in female (14.4%) (Office of China National Narcotics Control Commission, 2016), and human ERPs could affected by hormonal changes during the menstrual cycle. Sixteen heroin abstainers (HA) were recruited from the Addiction Recovery Center (ARC) of Gansu province in Lanzhou city, who were all receiving compulsory isolated abstinence treatment at the ARC during the period of study. Compulsory isolated abstinence treatment is one of major treatment options in China, which is designed for drug users who have a relapse after the compulsory detoxification. During the treatment, participants must undertake mandatory placement in compulsory re-education through-labor centers for 1–3 years (See a review Tang et al., 2006). Strict regulation and close monitor on participants' contacts and behaviors are applied to ensure drug abstinence. Educational programme including literacy education, instruction in good citizenship and vocational skills training are also delivered. Drug users can admit themselves to the treatment voluntarily or be referred by their family members and/or primary care physicians. Inclusion criteria for the heroin abstainers were to meet the criteria for heroin dependence according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed, DSM-IV, American Psychiatric Association, 1994), and to show a positive urine test for opioid before entering the ARC, which was confirmed by the ARC of Gansu province. The length of drug abstinence was calculated from the time the participants entering the ARC to the time they enrolling in

our study. Mean duration of their current abstinence was 18.67 ± 4.2 (range: 8-24) months (Table 1). Four HA occasionally consumed other drugs prior to the treatment, but heroin was their primary drug of choice. Sixteen age matched healthy controls (HC) with no history of drug abuse were recruited via advertisement. All participants reported normal color vision, and normal or corrected-to-normal visual acuity. Participants were excluded if they had either history or current mental deficiency, learning disabilities, medication for any neurological or psychiatric disorder, currently use of psychotropic medication or other recreational drugs.

Participants completed a two-choice oddball paradigm (see below) followed by a short break and questionnaires to assess clinical and demographic information. The entire study lasted for approximately 50 minutes. Participants were compensated 50 *yuan* RMB for their participation.

Clinical and demographic data

Participants completed the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Beck Depression Inventory (BDI) (Beck et al., 1996), and Barratt Impulsiveness Scale-11 (BIS-11) (Patton et al., 1995). Demographic information (age, years of education, marital status, etc.) and drug use history (age at onset of drug use, frequency and amount of daily substance use, history of previous treatment, etc.) were also collected by a self-completion form developed for the study. Subjective drug craving level was assessed prior to and after the experiment using the Visual Analog Scale (Franken et al., 2000). This scale required participants rate craving intensity on a 10-point scale by selecting an appropriate position along a 10cm-line ranging from 0 (not at all) to 9 (strong craving) according to their current urge for drugs.

Two-choice oddball paradigm

Stimuli and Procedure

Pictures used in our two-choice oddball paradigm were the same as those used in our previous studies (Su et al., 2017; Yang et al., 2015a) which included 20 neutral pictures (e.g. household objects, tools, neutral facial expressions) selected from International Affective Pictures System (IAPS) (Lang et al., 2005), and 20 heroin-related pictures consisting of the scenario of preparing or using heroin, drug or drug tool collected from freely available online sources. The heroin pictures were matched to the neutral pictures in ratio of human to non-human content. For the valence, neutral pictures were 5.17 ± 0.19, heroin-related pictures were 4.29 ± 0.44; and for the arousal, neutral pictures were 4.13 ± 1.10, heroin-related pictures were 5.70±1.25 (Yang et al., 2015a). A neutral "chair" picture was also selected from IAPS. All pictures were identical in terms of size (12 cm × 8 cm).

The two-choice oddball paradigm had four blocks of 150 trials, with each block including 120 standard stimuli and 30 deviant stimuli (80% vs. 20%). The four blocks were equally divided into two different task conditions: In the neutral condition, a neutral "chair" picture served as the standard stimuli and neutral pictures served as deviant stimuli; in the cued condition, a neutral "chair" picture served as standard stimuli and heroin-related pictures served as deviant stimuli. Participants were asked to press different keys on the keyboard in response to standard stimuli and deviant stimuli as rapidly and accurately as possible. Half the participants were asked to press "F" key when the "chair" picture (standard stimuli) appeared and to press "J" key if others pictures (deviant stimuli) appeared; For the remaining subjects, the assignment of response hands was reversed. The sequence of the task conditions was counterbalanced and randomly assigned for each subject.

The participants were seated approximately 80cm from a computer screen in an acoustically isolated room. After a brief description of the experiment, participants were given practice tests to ensure that they fully understand the experiment. They were required to complete 30 trials with 80% accuracy prior to the real experiment. The pictures appeared in the practice tests were not used in the formal experiment except the neutral picture "chair". Each trial began with a 300ms presentation of a small white cross on a black computer screen; then, a black blank screen whose duration varied randomly between 500 and 1000ms was followed by the onset of picture stimulus with their order randomized. The stimulus picture was terminated by a key pressing, or was terminated when it elapsed for 1000 ms. Followed by a blank screen lasting 1000 ms, the next trial started (Figure 1). At the end of each block, accuracy rates for both standard and deviant stimuli were given to the subjects as a feedback of their performance. In order to distinguish general inhibitory control from the effect of drug-related cues on response inhibition, the sequence of the task conditions was counterbalanced.

For behavioral data, the mean accuracy rates and mean reaction times (RT) (150 ms < RT < 1000 ms) were calculated for each condition.

EEG recording and analysis

The electrical brain activity was recorded with a 256-channel EEG system (EGI, Eugene, USA) and filtered with an on-line bandpass filter from 0.1-100 Hz. The EEG signal was digitized at a 500 Hz sampling rate with a 22-bit A/D converter. Data were continuously recorded with the vertex sensor (Cz) as reference electrode. Electrode impedance was kept below 50 kΩ.

Offline processing was carried out using the Net Station acquisition software and Electrical Geodesics (EGI, Eugene, USA) that involved the following steps: first, EEG data were digitally filtered

using a 0.01-Hz digital high-pass and a 30-Hz digital low-pass filter. Second, stimulus-synchronized epochs lasting from 200 ms before until 800 ms after picture onset were extracted. Then, EEG activity for correct response during each condition was overlapped and averaged separately, re-referenced off-line to an average reference value. Epochs of EEG data in the same condition were corrected to the 200 ms pre-stimulus baseline. Artifacts were screened using automatic detection methods provided by Net Station. The artifact rejection was based on the exclusion of all epochs that were contaminated by eye blinks and movement artifacts or epochs that had 10 or more channels exceeding a voltage threshold of 200 μV or fluctuation more than 100 μV. Trials were excluded if the signal variation of horizontal electrooculography and vertical electrooculography exceeded 140 μV and 55 μV, respectively. Flawed channel data were replaced using spherical spline interpolation of neighboring channel values.

Based on the previous studies (Wang et al., 2011; Yuan et al., 2008; Yuan et al., 2012) and the topographic distribution of the components observed in our participants. We formed five different clusters of scalp sites: frontal (F3, Fz, F4), frontal-central (FC3, FCz, FC4), central (C3, Cz, C4), central-parietal (CP3, CPz, CP4), and parietal (P3, Pz, P4) areas. For the N2, the mean activity in each cluster was calculated between 230 ms and 310 ms, and the P3 was between 350ms and 550ms. We calculated the difference waves of N2 (N2d) and P3 (P3d) from deviant stimulus minus standard stimulus at specified time windows in each condition respectively, which are considered as the a direct index of response inhibition-relevant processing (Bokura et al., 2001; Wang et al., 2011; Yuan et al.,2008; Yuan et al., 2012).

Data Analysis

Statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) version 23. Separate mixed-design repeated-measures analyses of variance (ANOVA) were performed for behavioural measures, as well as amplitudes and latencies of N2, P3, N2d and P3d. For all analysis within-subjects variables included *condition* (drug-cue, neutral) and *stimulus* (standard, deviant), with *group* (HA, HC) as the between-subject variable. ANOVA for ERP measures also included the within subject variable *scalp region* (frontal, frontal-central, central, central-parietal, parietal). Significant interaction effects were followed by post-hoc lower order ANOVA. Given that a greater number of participants in HA group were smokers relative to HC, we also run additional ANOVA for all ERPs with the average number of cigarettes daily smoked as a covariate. Where sphericity could

not be assumed, statistical values were reported with Greenhouse–Geisser corrections. Alpha level of significance was set at $p < 0.05$.

Additionally, for the HA, we conducted correlational analysis with the ERP (deviant-N2 and deviant-P3) amplitudes of interest,task performance (deviant-standard RT and accuracy) across conditions of the task and clinical variables, including length of abstinence, length of heroin use and amount of heroin used before treatment, respectively. Results for an individual correlation coefficient were Bonferroni-adjusted and considered statistically meaningful at $p < 0.001$.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the two groups are shown in Table 1. There were significant group differences in smoking [t (30) = 5.311, $p < 0.001$] and education [t (30)= -3.989, $p < 0.001$]. Compared to HC, HA had significantly greater levels of anxiety [t (30)= -2.554, $p = 0.016$], depression [t (30)= -2.688, $p = 0.012$] and unplanned impulsivity [t (30)= -2.112, $p = 0.045$]. In terms of drug craving, there was no significant difference between pre- and post-study in HA.

Behavioral results

For RT, the ANOVA only revealed a significant main effect of stimulus (F (1, 30) = 344.51, $p < 0.001$, $\eta_p^2 = 0.92$). All participants had longer RT for deviant stimuli than standard stimuli, regardless of condition.

For accuracy, the ANOVA only revealed a significant main effect of stimulus (F (1, 30) = 24.63, $p < 0.001$, $\eta_p^2 = 0.45$), all participants had lower accuracy for deviant stimuli than standard stimuli, regardless of condition.

Event-Related Potentials

Figure 2 and Figure 3 show ERP waveforms at middle line scalp sites (Fz, FCz, Cz, CPz, and Pz). The scalp topographies of the grand-mean ERP for the N2 and N2d components are shown in Figure 4. The scalp topographies of the grand-mean ERP for the P3 and P3d component are shown in Figure 5.

N2 effects

N2 Amplitude

There was a significant *Condition*Stimulus*Group* interaction (see Figure 6) [F (1, 30) = 13.03, $p < 0.001$, $\eta_p^2 = 0.31$], which was in part due to a significant *Condition*Stimulus* interaction for the HA [F (1, 15) = 30.83, $p < 0.001$, $\eta_p^2 = 0.67$], that was not present for the HC [F (1, 15) = 0.049, p =.83, $\eta_p^2 = 0.003$]. Furthermore, there was a significant *Condition*Group* interaction for deviant stimuli [F (1,

30) = 10.57, p = 0.003, η_p^2 = 0.26] that was not present for standards [F (1, 30) = 1.17, p = 0.29, η_p^2 = 0.037]; and a significant *Stimulus*Group* interaction for the drug-cue condition [F (1, 30) = 8.40, p = 0.007, η_p^2 = 0.22] that was not present for the neutral condition [F (1, 30) = .14, p =.71, η_p^2 = 0.005]. In the drug-cue condition, the HA showed a pattern of standard > deviant [F (1, 15) = 5.0, p = 0.042, η_p^2 = 0.25] and the HC showed a trend for deviant > standard [F (1, 15) = 4.22, p = 0.058, η_p^2 = 0.25]. Also for deviant stimuli, the HA had higher N2 amplitude in the neutral compared to the drug-cue condition [F (1, 15) = 17.8, p = 0.001, η_p^2 = 0.54], whilst no effect of condition was seen for the HC [F (1, 15) = .48, p = 0.50, η_p^2 = 0.03].

N2d Amplitude

There was a significant *Group*Condition* interaction [F (1, 30) = 13.30, p = 0.001, η_p^2 = 0.31), due to a significant effect of *Condition* (Neutral > Drug-cue) in the HA [F (1, 15) = 30.83, p < 0.001, η_p^2 = 0.67], but not in the HC [F (1, 15) = 0.049, p = 0.83, η_p^2 = 0.003]. In addition, there was a significant effect of *Group* for the drug-cue condition only [F (1, 15) = 8.85, p = 0.006, η_p^2 = 0.23], with higher amplitudes in the HC compared to the HA.

N2 Latency

There was a significant *Scalp Region*Stimulus*Group* interaction (see Figure 7) [F (1, 30) = 8.85, p < 0.001, η_p^2 = 0.23], in part due to a significant *Scalp Region*Stimulus* interaction in the HC [F (2.08, 31.20) = 15.98, p < 0.001, η_p^2 = 0.52], but not the HA [F (2.2, 33.0) = 1.62, p = 0.21, η_p^2 = 0.10]. Also there was a significant *Scalp region*Group* interaction for deviant stimuli [F (1.64, 49.14) = 6.20, p = 0.006, η_p^2 = 0.17], but not for standards [F (1.45, 43.59) = 1.6, p = 0.79, η_p^2 = 0.005]. Significant *Stimulus*Group* interactions were seen at frontal [F (1, 30) = 4.55, p = 0.41, η_p^2 = 0.13], frontal-central [F (1, 30) = 5.63, p = 0.24, η_p^2 = 0.16] and parietal [F (1, 30) = 5.70, p = 0.023, η_p^2 = 0.16] regions. The HC showed a pattern for faster latencies at anterior compared to posterior sites. Whilst both groups showed faster latencies to standard stimuli, compared to deviant at posterior sites [in all cases F (1, 15) = 17.23, p < 0.001, η_p^2 < 0.53], only the HA showed a similar effect at anterior sites [frontal F (1, 15) = 6.90, p = 0.019, η_p^2 = 0.32; frontal-central F (1, 15) = 19.49, p = 0.001, η_p^2 = 0.57].

P3 effects

No significant effects involving the Group variable were observed for P3 and P3d amplitude.

P3 Latency

There was a marginal significant *Condition*Stimulus*Group* interaction [F (1, 30) = 4.10, p = 0.052, η_p^2 = 0.12].

Effect of smoking on ERPs

The marginal significant Condition*Stimulus*Group interaction in P3 latencies was disappeared after controlling the smoking status. The rest of our ERP findings were not affected by daily consumption of cigarettes.

Correlation analyses

No significant correlations were found between clinical variables, task performance and ERPs.

Discussion

The current study used a modified two-choice oddball task to investigate the neural mechanisms responsible for modulation of response inhibition during the presentation of heroin-related cues in heroin addicts who had remained abstinent for at least 8 months. HA showed enhanced N2 amplitude to standards, reduced N2 to deviants and lower N2d in the drug cue condition. In addition, the pattern for faster N2 latencies to deviants at anterior compared to posterior sites seen in HC was disrupted in HA, due to delayed N2 latencies at anterior sites.

We have found that the reduced deviant-N2 and N2d amplitude induced by the two-choice oddball task are only observed when drug-related stimuli are involved in the HA. Consistent with a previous study (Morie et al., 2014), which failed to find any differences for amplitude between both groups in the neutral task. The reduced NoGo-N2 amplitude during a Go/NoGo task has been recognized as a sensitive index of impaired inhibition in individuals with substance abuse (Luijten et al., 2011). Our findings suggest that heroin abstainers show response inhibition deficits specifically for drug-related cues. This, it is possible that alterations in response inhibition induced by a history of drug use remain after a long period of drug abstinence, but become only measurable when drug-related stimuli are involved. Drug addicts tend to prioritize attentive processing for drug-related cues due to their motivational salience through conditioning, which depletes cognitive resource (Franken, 2003; Robinson and Berridge, 1993; Ryan, 2002). Therefore, they have more difficulty to inhibit their dominant response in contexts related to drug use (e.g. drug-cue deviants).

We also found that the HA showed delayed N2 latencies to deviants at anterior sites. The peak latency of ERP component is associated with cognitive processing speed (Gajewski et al., 2008; Polich and Criado, 2006), and the stronger the inhibitory ability was, the shorter the latencies of ERP appeared (Aotsuka et al., 1996). It suggests that heroin abstainers may have a general slowing of frontal function, at least at the N2 stage.

This is not to say that deficits in inhibition are permanent. It has been proposed that drug abuse-induced neurocognitive deficits are recoverable limitations of neuronal plasticity, rather than as permanent 'lesions' (Rapeli et al., 2006; Robinson and Kolb 2004; Wang et al., 2015). However, the incentive motivational properties of drug-related cues may be long-lasting because repeated drug administration produces incremental neuroadaptations in the dopaminergic system (Robinson and Berridge 1993).

The neural generators of the N2 are believed to be localized in regions associated with conflict monitoring and response inhibition, such as the lateral orbital frontal cortex (OFC) and anterior cingulate cortex (ACC) (Bokuraet al., 2001; Botvinick et al., 2004; Nieuwenhuis et al., 2003). It has been found that after exposure to drug-related cues, heroin users show resting state (free of cues) dysfunctional connectivity in a network involving OFC, dorsolateral prefrontal cortex, ACC, and supramarginal motor area. This may contribute to impairments in self-control and inhibitory functions (Liu et al., 2009). However, it should be noted that tasks other than the two-choice oddball task used in the current study, might be differentially sensitive to inhibitory and conflict monitoring networks (e.g. Stop-signal task, Flanker, error feedback). Future research should further investigate mechanisms of executive function using these tasks in abstaining heroin addicts.

Interestingly, the P3 amplitude was not affected significantly in heroin users, and the marginal significance of group effect on P3 latency was disappeared after controlling the smoking status. The P300 amplitude reflects the attentional resource allocated to memory updating during task processing, while its latency indicates the speed of stimulus evaluation (Bokura et al., 2001; Wang et al., 2015). Our findings suggest that some aspects of cognition may remain relatively well preserved in heroin users and polydurg use, i.e. tobacco, may play a role in observed cognitive deficits.

Based on our findings, in addition to capturing attention, drug-related cues can disrupt mechanisms of response inhibition even though a longer period of abstinence, which expanded upon general inhibition function deficits associated with heroin use (Yang et al., 2009; Yang et al., 2015; Yuan et al, 2009). Our findings highlight the importance of assessing and improving the ability of inhibiting drug-related cue reactivity in heroin abstainers. Given the absence of behavioral impairments, the inhibition-related N2 modulation specifically for heroin cues could be used as a novel electrophysiological index with clinical implications for assessing the risk of relapse or treatment outcome for drug users.

The current study limited participation male heroin addicts, and thus caution is warranted when inferring results to female drug users. Liu et al. (2006) have investigated sex differences in recovery of central nervous system function through abstinence. That is, whilst they found significant slowing of the simple reaction time in both sex with 1–3 months of abstinence, after 3 months of abstinence this was seen in males, but not in females. Sex-related effects of the recovery of response inhibition deficits should be investigated by further studies in larger cohorts of heroin abstainers. Moreover, the present study cannot confirm the dynamic changes of response inhibition. It is possible that deficits of inhibitions may be reduced with increased length of abstinence. In our recent study, we found that RT for drug-related deviants were shorted in longer-term heroin abstainers (16-24 months) compared to those having shorter period of abstinence (2-6 months) (Su et al., 2017). Longitudinal research should be implemented to clarify the cognition change induced by length of abstinence.

In conclusion, the current study provides novel and important information on the effect of drug-related cues during response inhibition in long-term heroin abstainers. Although heroin addicts exhibit normal response inhibition to general stimuli after a longer period of abstinence, there remains a measurable deficit in response inhibition when heroin-related cues are present. Our findings thus make a valuable contribution to assessing the risk of relapse and affirming the intervention target in drug treatment.

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Table 1. Demographic and clinical characteristics of two groups

	HA (*n*=16) *M*(*SD*)	HC (*n*=16) *M*(*SD*)
Age (years)	42.00 (8.74)	40.69 (8.50)
*Education（years）	7.50 (3.95)	13.88 (2.19)
*BAI	15.63(17.45)	4.31(3.00)
*BDI	21.50(11.70)	11.31(9.64)
BIS-C-11		
Attention impulsivity	13.38(1.70)	13.19(2.23)
Motion impulsivity	20.25(3.73)	18.06(2.91)
*Unplanned impulsivity	26.38(4.57)	23.56(2.73)
*Number of Cigarettes smoked /day	21.25 (9.92)	7.81 (9.12)
Age at onset of heroin use (years)	29.38(10.16)	Na
Average of heroin use (years)	3.49(4.34)	Na
Duration of current abstinence (months)	18.67 (4.2)	Na
Heroin use before abstinent (gram/day)	0.42(0.29)	Na
Drug craving level prior to/after the study	2.88(2.99)/2.88(2.99)	Na

Na=Not applicable; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; BIS=Barratt e Impulsivity Scale

*Significant effect of group ($p < .05$)