Event-related potentials in a Go/Nogo task of abnormal response inhibition in heroin addicts

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Inhibitory control dysfunction is regarded as a core feature in addicts. The major objective of this study was to explore the time course of response inhibition in chronic heroin addicts and provide the neurophysiological evidence of their inhibitory control dysfunction. The amplitudes and latencies of ERP components were studied in fourteen heroin addicts (mean duration of heroin use being (13.54 ± 5.71) years (Mean ± SD), average abstinence being ((4.67 ± 6.44) months)) and fourteen matched healthy controls with a visual Go/Nogo task. Our results showed that heroin addicts demonstrated significantly larger Go-N2 amplitudes which results in a decreased N2 Go/Nogo effect, but no statistically significant differences were found between heroin addicts and controls in P3. The ERP data suggest that fronto-central areas of heroin addicts were impaired during the inhibition process (200—300 ms) and over-activated to targets. The impaired early process might reflect an abnormal conflict monitoring process in heroin addicts. These results consolidate the inhibitory control dysfunction hypothesis in chronic heroin users.

Inhibitory control is an essential ability for suppressing irrelevant or interfering stimuli and impulses for successful living[1]. Impaired inhibitory control contributes to severe behavioral disinhibition and impulsivity. Drugs Seeking and relapse are strong impulsive behaviors, which are core symptoms of drug addiction[2]. Relapse to heroin use occurs even after long periods of abstinence, induced by drugs and drug-associated cues. Lack of inhibition has been regarded as a key element of drug addiction, including the suppression of emotional, cognitive and behavioral responses[3,4].

One of the primary domains for measuring inhibitory control in the laboratory is response inhibition[5]. Behavioral or motor response inhibition is defined as the process required for stopping a planned movement[6]. In response tasks, behavioral indexes, such as response time, hit rate and false rate, were measured to assess response control ability. Previous research showed that heroin addicts performed inconsistently in different response inhibition tasks. Significant group differences were found in the Porteus Maze Test (PMT)[7] and in the Stop-Signal task[8], but not in the Go/No go task[9] and Stop-Change tasks[10]. Thus, the neuropsychological substrate of disinhibition of heroin addicts remains unclear.

Response inhibition recruits a neural network including the frontal regions and the non-frontal regions, such as the orbital frontal cortex (OFC), the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), the anterior cingulate cortex (ACC), and the parietal, temporal, and striatal lobes[11]. Structural magnetic resonance imaging studies showed that prefrontal and temporal gray matter density decreases in...
chronic heroin addicts\(^{[12,13]}\). Furthermore, function magnetic resonance imaging (fMRI) results indicated that the decreased activity of the frontal and parietal regions was observed not only in current heroin addicts\(^{[14]}\) but also among abstinent\(^{[15]}\) in the response inhibition task. These results demonstrated the neural substrates of impulsive behavior in addicts, but the time course requires further research.

Event-related potentials (ERPs) reveal the time course of information processes with high temporal resolution. ERP studies have provided electrophysiological indices for cognitive functions in heroin addicts\(^{[16,17]}\). In visual ERP recordings, Bauer has found that opioid-dependent patients exhibited decreased P300 amplitudes in a short-term memory test, suggesting that P300 is a useful measure of central nervous system (CNS) recovery\(^{[16]}\). In the laboratory, inhibition and impulsiveness assessed with the Stop task\(^{[18]}\) or with the Go/Nogo task\(^{[19]}\). Both tasks shared the same “inhibitory” neurocognitive network, but the left hemispheric areas were more involved in a Go/Nogo task than in a Stop task, which indicates a left frontoparietal specialization for response selection\(^{[20]}\). However, event-related potentials might be problematic due to the possible overlap of response signals and stop signals. The Go/Nogo task yields a relatively simple ERP structure\(^{[20]}\), which is suitable for comparing differences between clinical groups in ERP research.

In a Go/Nogo task, participants are asked to respond to quickly presented Go cues and suppress the prepared response whenever a Nogo cue is presented. The seemingly simple task involves multiple cognitive processes, including stimuli discrimination, response selection, motor preparation, response inhibition, and error monitoring\(^{[21]}\). Two major ERP components have been described in Go/Nogo tasks. The first component, the N2 or (Nogo-N2), is regarded as a phasic negative shift in Nogo compared to Go trials, with a maximum amplitude over frontal scalp locations during 250 and 350 ms post-stimulus. The second component, the Nogo-P3, is a positive deflection of around 300 to 600 ms post-stimulus with a larger amplitude than Go-P3 or P3b in the fronto-central area, also called Nogo P300 “anteriorization”\(^{[22,23]}\). It has been suggested that the difference waves (Nogo- minus Go- ERPs) would reflect the Go/Nogo effect, such as the difference waves of N2 (N2d), which were defined as the results of Go-N2 subtracted from the Nogo-N2\(^{[22,23]}\). Although both components are considered to be associated with response inhibition, the exact cognitive processes they reflect remains uncertain.

One view was that the Nogo-N2 reflected a cognitive top-down inhibition mechanism for suppressing the incorrect tendency to respond to stimuli with a larger amplitude than Go-P3 or P3b in the response inhibition task. No significant change of the N2 component was found compared with the control group\(^{[14]}\). However, there are no ERP research reports available for the neuralpsychological mechanism of response inhibition in heroin addicts.

There are few published reports concerning response inhibition of substance addicts by ERPs. Previous research did find that chronic abuse of alcohol\(^{[24]}\) and the drug “ecstasy”\(^{[25]}\) changed the late process (Nogo-P3) in response to the inhibition task. No significant change of the N2 component was found compared with the control group\(^{[14]}\). However, there are no ERP research reports concerning response inhibition in heroin addicts.

To this end, ERPs in the visual Go/Nogo task were compared between heroin addicts and healthy controls to explore the response inhibition time course changes and provide neurophysiological evidence for inhibitory control dysfunction in heroin addicts. An equal probability Go/Nogo task had been used in several clinical studies to elicit robust Nogo ERPs\(^{[24]}\). Because the amplitudes of N2 and P3 in the response inhibition task are sensitive to the Nogo probability\(^{[28]}\), the equal probability task was used to eliminate the bias caused by low-probability stimuli. We hypothesized that heroin addicts would exhibit attenuated Nogo ERP effects in the fronto-central areas compared with healthy controls.

1 Methods

1.1 Participants

Heroin addicts were recruited from the Health Center of
the Beijing Reeducation School. All patients met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)\textsuperscript{[2]} criteria for drug abuse/dependence, exclusively with regard to heroin abuse or dependence. Patients with previous consumption of other drugs, use of psychotropic agents, or excessive alcohol intake were excluded. There were fourteen male heroin addicts in the patient group, with a mean duration of heroin abuse of \((13.54\pm5.71)\) (Mean±SD) years, a mean dosage of \((1.46\pm1.27)\) g per day, and a mean abstinence duration of \((4.67\pm6.44)\) months. The twenty-eight items Opioid Addiction Severity Inventory (OASI-28)\textsuperscript{[36]} was used to rate heroin addiction severity. Three of the patients were classified as moderate addicts, and the others were classified as severe addicts.

Fourteen healthy controls, matched in age and education level (age: patients= \((41\pm7.11)\) years, controls= \((41\pm10.50)\) years; education: patients= \((8.92\pm1.89)\) years, controls= \((9.69\pm2.18)\) years), were recruited from the local community. The Beck Anxiety Inventory (BAI)\textsuperscript{[37]} was used to rate the anxiety level of addicts and controls, and a significant difference was found between the groups (BAI: addicts= \((12.21\pm14.39)\), controls= \((4.57\pm5.69)\), \(t\textsuperscript{(26)}=1.85, P<0.05\) ).

All participants were right-handed with normal or corrected-to-normal vision. These participants had no known history of head trauma or other medical/psychiatric conditions that could cause cognitive impairment. All participants were paid volunteers. The purpose of the study was explained to each participant, and written informed consent was obtained.

1.2 Stimuli and procedure
Visual stimuli were two equilateral triangles (upright and inverted) of the same size (wide=7.00 cm, high=6.06 cm) in grey background. Each stimulus was presented in the center of a computer screen (light degree= 60 cd/m\textsuperscript{2}) by the Neuroscan STIM-2 system. Participants were seated in a sound-attenuated semi-dark room, facing a monitor placed 100 cm from their eyes, with a visual angle of \(4^\circ\times4^\circ\).

In the task, 100 Go stimuli and 100 Nogo stimuli were pseudorandomly displayed one by one. The participants were instructed to respond by pressing a button using their thumbs as quickly as possible after the Go stimuli appeared and to withhold the response when the Nogo stimuli appeared. The number of times each stimulus was used as “Go” and “No-go” stimulus was counterbalanced across subjects in each group. Each stimulus was presented for 50 ms, with the mean inter-trial intervals (ITI) being 1500 ms (randomly between 1000—2000 ms). The hand to press button was counterbalanced across the participants.

Before EEG recording, participants performed two practice blocks consisting of 20 Go and Nogo trials, to ascertain that their operation was correct. During the experiment, participants were instructed to watch the center of the screen, relax, and minimize eye blinks or body movements.

1.3 Data recording and off-line analysis
Scalp voltages were recorded using a 32-channel Ag/AgCl electrodes cap (10—20 International System). The acquisition software was NeuroScan SynAmps (El Paso, TX). The electrodes were referenced to the linked mastoids and the ground electrode was on the forehead (frontal midline). Eye movements were monitored with a supraorbital vertical lead and a horizontal lead placed on the external canthus of the eyes. Electrode impedance was maintained below 5 kV. The EEG signals were recorded continuously with a bandpass at 0.05—100 Hz and digitized with a 1000 Hz sampling rate.

The software used for analyzing the recorded signals was NeuroScan SCAN4.3. Ocular artifacts were corrected with an eye-movement correction algorithm described by Semlitsch and his colleagues\textsuperscript{[38]}. ERP epochs with a 1000 ms duration were extracted (including 200 ms before and 800 ms after stimulus onset) and corrected by the \(-200\) ms baseline. EEG exceeding \(+100\) μV were automatically rejected as artifacts. Individual ERP averages were derived for correct Go and Nogo trials, and digitally low-pass filtered with zero phase shift (0—17 Hz, 24 dB/octave).

1.4 Statistical analysis
Behavioral indexes, including Go response time, hit rate, and false rate, were compared by \(t\)-test to explore the group difference between the heroin addicts and the controls.

The N2 component was quantified as the most negative amplitude within a 200 to 300 ms window following stimulus onset. The P3 component was quantified as the most positive amplitude within 300 to 500 ms following the N2 peak. In order to highlight the Nogo effect, difference waves (Nogo minus Go) were computed for N2 and P3, respectively designated as N2d and P3d\textsuperscript{[22]}.
peak latency was respectively computed at the site Fz and Fcz, for N2 and P3.

To assess the different effects of response inhibition between addicts and healthy controls, a Response (Go, Nogo) × Site (5 midline sites: Fz, Fcz, Cz, Cpz, Pz) × Group (addicts, controls) repeated measures ANOVA was performed for peak N2 and P3 amplitudes. A Site (5 midline sites: Fz, Fcz, Cz, Cpz, Pz) × Group (addicts, controls) repeated measures ANOVA was performed for peak N2d and P3d amplitudes. A Response (Go, Nogo) × Group (addicts, controls) repeated measures ANOVA was performed for the latency of N2 and P3.

The waveforms and topography of ERPs in heroin addicts and controls during the Nogo as well as the Go alarm (addicts = (0.04±0.04), controls = (0.05±0.07), t (26) = −0.34; P > 0.05) was significant, but the Group main effect was not (F (1,26) = 20.05, P < 0.05, η² = 0.55) and the mean ratio of false alarm (addicts = (0.04±0.04), controls = (0.05±0.07), t (26) = −0.34; P > 0.05).

2 ERP results

2.1 Behavioral results

No significant group differences were found between addicts and control groups in all behavioral indices: the mean Go-response time (addicts = (359.42±59.59) ms, controls = (360.72±26.57) ms, t (26) = −0.07; P > 0.05), the mean ratio of hit (addicts = (0.98±0.03), controls = (0.96±0.06), t (26) = 0.85; P > 0.05), and the mean ratio of false alarm (addicts = (0.04±0.04), controls = (0.05±0.07), t (26) = −0.34; P > 0.05).

2.2 ERP results

The waveforms and topography of ERPs in heroin addicts and controls during the Nogo as well as the Go condition are respectively illustrated in Figure 1 and Figure 2.

(1) N2. With regard to N2 amplitudes, both the response main effect (Nogo-N2 = (3.86±0.66) μV, Go-N2 = (5.85±0.66) μV, F (1,26) = 20.05, P < 0.05, η² = 0.44) and the site main effect (F (4,104) = 4.35, P < 0.05, η² = 0.14) were significant, but the Group main effect was not (F (1,26) = 1.04, P > 0.05). The interaction of the Response and Group was significant (F (1,26) = 13.71, P < 0.05, η² = 0.35). A simple effects analysis further revealed that a larger Nogo-N2 amplitude was observed in the controls but not in the addicts (Controls: Nogo-N2 controls = (3.67±0.93) μV, Go-N2 controls = (7.31±0.94) μV, F (1,26) = 33.46, P < 0.05; Addicts: Nogo-N2 addicts = (4.05±0.92) μV, Go-N2 addicts = (4.39±0.94) μV, F (1,26) = 0.30, P > 0.05). Addicts exhibited enhanced N2 amplitude compared with controls among Go trials (Go-N2 controls = (7.31±0.94) μV, Go-N2 addicts = (4.39±0.94) μV, F (1,26) = 4.84, P < 0.05). Among Nogo trails, no significant group difference in N2 amplitude was observed (Nogo-N2 controls = (3.67±0.93) μV, Nogo-N2 addicts = (4.05±0.92) μV, F (1,26) = 0.01, P > 0.05). There was no significant interaction between the Site and Group (F (1,26) = 0.52, P > 0.05).

The repeated-measures ANOVA on N2 amplitudes of the Nogo-Go difference wave revealed a significant main effect of the Group (N2d controls = (−4.98±0.57) μV, N2d addicts = (−2.72±0.57) μV, F (1,26) = 7.81, P < 0.05, η² = 0.23).

There was no effect observed in the latency of N2 (all P > 0.05).

(2) P3. Neither the Group effect (F (1,26) = 0.15, P > 0.05) nor a Response by Group interaction (F (1,26) = 0.31, P > 0.05) or a Site by Group interaction (F (4,104) = 0.78, P > 0.05) on P3 amplitudes was found. Consistent with previous studies, the Site main effect (F (4,104) = 31.85, P < 0.05, η² = 0.55) and a Response by Site interaction (F (4,104) = 45.00, P < 0.05, η² = 0.63) were observed. Post-hoc tests revealed that Nogo-P3 was significantly larger than Go-P3 in anterior sites (Fz, Fcz) (P < 0.05) while the Go-P3 was larger than Nogo-P3 in posterior sites (Cpz, Cz) (P < 0.05), which led to the Site effect of P3. There was a significant Site effect in P3d (F (4,104) = 63.84, P < 0.05, η² = 0.71) and the largest P3d was shown in Fcz.

There was no effect observed in the latency of P3 (all P > 0.05).

3 Discussion

In the present study, we used a visual Go/Nogo paradigm for investigating N2 and P3 in heroin addicts and healthy controls. No performance differences were found between the two groups[20,24]. This finding was probably due to the fact that relatively little effort is required for participants to perform the simple Go/Nogo task. Consistent with previous research, the equal probability Go/Nogo task elicited a strong Nogo effect, a larger Nogo-N2 amplitude and anterior Nogo-P3, especially in healthy controls[19,20]. The Nogo effect was attenuated in the fronto-central area of heroin addicts,
Figure 1  Grand mean ERP for the Go and Nogo stimuli for heroin addicts and controls.

Figure 2  Topographic maps of N2 and P3 amplitude in heroin addicts and controls.
which confirmed our hypothesis. The ERP results showed the diminished N2 Go/Nogo effect and decreased N2d amplitudes in heroin addicts compared with the controls. The most significant finding of this study was that heroin addicts had larger Go-N2 amplitudes than controls, which resulted in reduced N2d amplitudes. We also observed a Nogo P3 ‘anteriorization’ which probably reflected the response inhibition in Nogo trails. No significant group effect of P3 on either the amplitudes or the distribution on the scalp was found. Those results indicated that the heroin addicts had an abnormal early process (200—350 ms) in the response inhibition task compared with the healthy controls. The abnormal ERP pattern was first reported in heroin addiction and other substance abuse studies. Possible implications and causative factors concerning the special ERP characteristics of heroin addicts will be discussed.

3.1 Response inhibitory process of heroin addicts

As noted earlier, Nogo N2 and P3 are two primary components related to inhibitory control in the Go/Nogo task. However, no consensus on the psychological significance of Nogo-N2 and Nogo-P3 has been reached. The Nogo-N2 or N2 Nogo effect was presumed to reflect a top-down inhibition or conflict monitoring. However, the inhibition hypothesis could not explain the enhanced Go-N2 amplitudes, such as the N2 likeness negative component in the rare frequency Go condition. Neither could the inhibition hypothesis explain the enhanced Go-N2 amplitudes in heroin addicts. Otherwise, inhibition would not occur in a Go response which involves no control inhibition, and the change of N2d amplitude would be attributed to the Nogo-N2. According to the inhibition hypothesis, enhanced N2d was related to more efficient inhibition. In our study, a significantly larger N2d was observed in the controls, but no significant behavioral differences, such as false alarm rates, were found between two groups. The ceiling effect of the simple task could also lead to such behavioral results.

Furthermore, Dipole source analysis located the Nogo-N2 as well as the Error related negative (ERN) in ACC. N2 was supposed to reflect a general conflict monitoring process. Substantial evidence indicates that the early ERP components reflect attentional processes triggered by task demands, and the enhanced N2 to Go stimuli may reflect enhanced cognitive resources allocated to the Go stimuli. According to the conflict monitoring hypothesis, we speculated that the Go stimuli would be a strong conflict signal to heroin addicts, which led to the increased Go-N2 and decreased N2 Nogo effect (N2d). fMRI results suggested that ACC activities decreased in heroin addicts compared with controls, consistent with the attenuated N2d amplitudes in the fronto-central sites. As the ACC function was assessed by subtracting the Go condition from the Nogo condition, we supposed that the attenuation of activity in the anterior cingulate might be due to hyperactivity in the Go condition, based on the increased Go-N2 amplitudes in heroin addicts.

Nogo-P3 or anterior P3-No Go was supposed to reflect a general inhibition process. No significant differences in the amplitude and the latency of P3 (P3d, Go-P3, Nogo-P3) were found between the addicts and the controls. We supposed that the general inhibition process of the addicts was normal. In support of this idea, the behavioral data demonstrated that the addicts performed as well as the healthy controls, consistent with previous research.

We supposed that (i) the diminished N2 Nogo effect (Nogo vs. Go) and attenuated N2d amplitudes of the heroin addicts reflected an abnormal early process. (ii) the increased Go-N2 amplitudes indicated that more attentional resources were engaged or required for heroin addicts to monitor the response signal. In addition, the group difference was observed using the difference wave (N2d) but not the original ERP waves in the Nogo condition (Nogo-N2) as the index of the N2 Go/Nogo effect, which indicated that the difference wave might be a more sensitive index for detecting neuropsychological changes in heroin addition.

3.2 Potential reasons for the abnormal process

The unique ERPs pattern identified in this study may be caused by two salient factors.

One is the structural damage in brains of chronic heroin users. At the gross structure level, opiate-dependent addicts exhibited decreased gray matter density in both the prefrontal and the temporal cortex. At the cellular level, neuron damage in the bilateral frontal cortex have been reported. fMRI studies have found that heroin addicts had a hypoactivation of PFC which involves response inhibition, whereby addicts exhibited decreased N2d amplitudes on fronto-central scalp sites compared with the controls. These results might have been caused by structural damage in the frontal lobe.
However, the neuropathological changes in opiate users have been far less investigated to date\[45\]. The exact mechanism of damage to brain structure and function caused by opioids remains uncertain with further neuropharmacological research is indicated.

Another possible reason is personality trait or heredity. One of the primary personality dimensions that have been consistently linked to addicts is impulsivity\[44\]. People who had higher scores on Eysenck’s Impulsiveness Questionnaire (EIQ)\[45\] or decreased response times in the Go/Nogo task\[46\] display decreased Nogo-P3 but no change of N2 in response to inhibition tasks. By contrast, heroin addicts in the present study and impulsive-violent offenders\[47\] exhibited significantly lower amplitudes of N2 difference waves. Because the Nogo-P3 was thought to be motor or response inhibition itself\[28,29\], we suspected that the sort criteria as EIQ or response time might reflect only one component of impulsivity, i.e., decreased motor inhibition. The attenuated N2 effect in behavioral abnormal individuals might indicate another component of impulsivity, such as excessive conflict monitoring due to an earlier inhibition control process dysfunction\[26,27\].

In twin studies, genetic model-fitting analysis showed that about 60% of the variance in frontal N2 (N2d) and P3 (Go-P3, Nogo-P3) amplitudes in the Go/Nogo task could be attributed to genetic factors\[48\]. This finding indicates that the abnormal ERP patterns in heroin addicts may be inherited from their parents and cause them to be more impulsive. It may explain why individuals who manifest impulsive behaviors are more likely to engage in substance misuse\[49\].

As most addicts have been involved in the cycle of addiction, rehabilitation, and relapse, the abnormal ERP pattern might be caused by the interaction of drugs and heredity.

3.3 Limitations and future directions

As our study was the first ERP research of inhibitory control in heroin addiction, our data leaves many questions unanswered concerning neuropsychological process of response inhibition in heroin addicts.

First, in this study heroin abistent addicts (of more than one month) were compared with normal controls but not with current users. Using a short memory task, Papageorgiou and his colleagues found that the P3 amplitude was smaller in opioid-abstinent addicts than in current users and no significant difference existed between current users and healthy controls\[17\]. Whether or not the N2 component of current users in the response inhibition task might show “normal” amplitudes should be confirmed in future studies.

Second, a simple Go/Nogo task was used to compare the neural activation in the response inhibition process between the heroin addicts and healthy controls. Although the response inhibition process revealed a general mechanism of inhibitory control or a possible neural basis such as the frontal-hypothalamic loop, whether or not other inhibition processes, such as inhibition of emotion or memory, share the same inhibitory control mechanism or not, remains uncertain\[50]. We will extend our studies of heroin addiction to other inhibitory control fields, such as emotional inhibition.

Finally, impulsive behavior, especially drug seeking and relapse in heroin addicts, generally occur in sociologically complex environments. Emotional stress is a well known context factor contributing to drug use and relapse\[50\]. The N2 component was sensitive to time pressure\[51\] and emotional valence\[52\] in Go/Nogo task. Manipulating the emotional stress variables in the Go/Nogo task may help to illustrate the relationship between emotional stress, inhibitory control, and drug abuse\[53\].

4 Conclusions

We found that heroin addicts exhibited a diminished Go/Nogo effect in the response inhibition process (200—300 ms), and the attenuated effect was due to the overactivation towards the target stimuli. The results reflected the impaired conflict monitoring process of the response inhibition in chronic heroin addicts. The ERP data provided neurophysiological evidence for impulsivity or impaired inhibition control in heroin addicts.

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