Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Two-Hour Nicotine Withdrawal Improves Inhibitory Control Dysfunction in Male Smokers: Evidence from a Smoking-Cued Go/No-Go Task ERP Study

Lu Hou[1,*], Jing Zhang[2,*], Jing Liu[3], Chang Chen[1], Xuezheng Gao[4], Limin Chen[4], Zhenhe Zhou[1,3], Hongliang Zhou[5]

[1]Department of Psychiatry, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi City, 214151, People's Republic of China; [2]Department of Psychiatry, Huaian Third People's Hospital, Huaian City, 223021, People's Republic of China; [3]School of Humanities and Management Science, Wannan Medical College, Wuhu City, 241000, People's Republic of China; [4]Department of Psychiatry, The Affiliated Mental Health Center of Jiangnan University, Wuxi City, 214151, People's Republic of China; [5]Department of Psychology, The Affiliated Hospital of Jiangnan University, Wuxi City, 214151, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhenhe Zhou, Department of Psychiatry, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi City, 214151, People's Republic of China, Tel +86-1-335-811-8986, Fax +86-510-83219366, Email zhouzh@njmu.edu.cn; Hongliang Zhou, Department of Psychology, the Affiliated Hospital of Jiangnan University, Wuxi City, 214151, People's Republic of China, Tel +86-1-536-525-1126, Fax +86-510-85808820, Email Hongliangzh2022@hotmail.com

Purpose: Nicotine withdrawal is a multifaceted physiological and psychological process that can induce a spectrum of mood disturbances. Gaining a more nuanced understanding of how pure nicotine withdrawal influences cognitive control functions may provide valuable insights for the enhancement of smoking cessation programs. This study investigated changes in inhibitory control function in smokers after 2-hour nicotine withdrawal using the event-related potential (ERP) technique.

Participants and Methods: 28 nicotine dependence (ND) patients and 28 health controls (HCs) completed a smoking-cued Go/No-go task containing two different types of picture stimuli, smoking-cued and neutral picture stimuli. We analyzed the behavioral and ERP data using a mixed model Repeated Measure Analysis of Variance (ANOVA).

Results: No-go trials accuracy rate (ACC) at baseline (time 1) was lower in the ND group compared to HCs with smoking-cued stimuli, and No-go trials ACC after 2-hour nicotine withdrawal (time 2) was not lower in the ND group compared to HCs. When confronted with smoking-cued stimuli, the No-go trials ACC was higher in time 2 than in time 1 in the ND group. For the ERP component, the No-go N2 amplitudes in the ND group with smoking-cued stimuli were lower than that of HCs, whereas after 2-hour nicotine withdrawal, the ND group's No-go N2 amplitudes higher than that at time 1, and did not differ from that of HCs. No-go P3 amplitudes were not significantly different between the two groups.

Conclusion: Evidenced from ERP data, ND patients have an inhibitory control dysfunction in the face of smoking cues, which is mainly manifested in the early stage of response inhibition rather than in the late stage. Two-hour nicotine withdrawal improves inhibitory control dysfunction in ND patients. The No-go N2 component is an important and sensitive neuroelectrophysiological indicator of inhibitory control function in ND patients.

Keywords: nicotine dependence, inhibitory control, 2-hour nicotine withdrawal, event-related potentials, Go/No-go task

Introduction

Nicotine dependence (ND) is characterized by the compulsive use of tobacco products, primarily due to the psychoactive effects of nicotine.[1,2] ND represents a global public health challenge with significant morbidity and mortality.[3] The Nicotine withdrawal, commonly associated with smoking cessation, leads to significant neurochemical alterations in the brain, particularly in the dopaminergic, serotonergic, and noradrenergic systems which play crucial roles in mood

Received: 1 December 2023
Accepted: 10 April 2024
Published: 15 April 2024

regulation.[4,5] Nicotine withdrawal is a multifaceted physiological and psychological process that can induce a spectrum of mood disturbances, notably anxiety and depression.[6,7]

Cognitive function encompasses a range of mental processes that enable humans to acquire knowledge and understanding through thought, experience, and the senses.[8] Inhibitory control belongs to a kind of cognitive function. It includes cognitive control and behavioral inhibition. Cognitive control refers to the ability to orchestrate thought and action in accordance with internal goals. Behavioral inhibition involves the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior.

The Go/No-go task is a widely utilized paradigm for probing the mechanisms of cognitive control and behavioral inhibition. The cognitive control in this task is reflected by the necessity for the participant to constantly monitor the stream of stimuli and to discern between those that require a motor response and those that do not. Behavioral inhibition is demonstrated during the no-go trials. The Go/No-go task is a behavioral assay that provides insight into the interplay between cognitive control and behavioral inhibition. By requiring rapid decision-making concerning whether to execute or suppress a motor response, it encapsulates the essence of self-regulation and the neural circuitry that underlies this complex human capacity.

Numerous studies have demonstrated that nicotine withdrawal can precipitate a range of physiological, psychological, and cognitive disturbances.[9–12] Especially, nicotine withdrawal may trigger depressive symptoms or even catalyze the onset of a major depressive episode.[13] The potential cognitive impairments associated with nicotine withdrawal remain a topic of contention. A substantive body of research suggests that nicotine withdrawal is associated with deficits in working memory during periods of smoking cessation.[14–17] In contrast, other studies have observed that abstaining from smoking may reduce attentional biases towards positive stimuli.[18,19] The array of psychological symptoms manifesting from nicotine withdrawal, such as anxiety and depression, can further exacerbate cognitive dysfunctions. Deficits in cognitive control are notably associated with nicotine withdrawal and are indicative of the challenges faced during the cessation process. These deficits are considered distinctive features of nicotine withdrawal that could be strategically targeted to enhance the success rates of smoking cessation efforts.[20] Consequently, the initial period following withdrawal emerges as a particularly critical juncture for ND patients, presenting an essential opportunity to evaluate the prospects of sustained smoking withdrawal.

As nicotine enters the bloodstream through the lungs, smoking tobacco is an exceptionally addictive method of delivering drugs systemically. Research has demonstrated that nicotine can reach the brain within 10 to 20 seconds. Following the smoking of each cigarette, the concentration of nicotine in the brain spikes and then gradually diminishes over a period of 20 to 30 minutes as nicotine is redistributed to other organs and tissues; the average half-life of nicotine in bodily tissues is approximately 2 hours.[21] Earlier investigations into the effects of nicotine withdrawal on cognitive function primarily focused on periods exceeding 12 hours of withdrawal.[12,22–25] These inquiries often conflated the cognitive dysregulation attributable solely to nicotine deprivation with psychological manifestations emergent from the withdrawal process. Namely, these studies were unable to separate the impairment of cognitive function caused by nicotine withdrawal from the psychological symptoms that withdrawal entails. Furthermore, recent evidence suggests that a nicotine withdrawal period within 2 hours is insufficient to precipitate psychological states commonly associated with withdrawal, such as depression and anxiety.[26] Gaining a more nuanced understanding of how pure nicotine withdrawal influences cognitive control functions may provide valuable insights for the enhancement of smoking cessation programs.

Event-related potentials (ERPs) provide a noninvasive method to measure the brain's electrical activity with exceptional temporal accuracy. Numerous investigations have utilized the Go/No-go task to explore cognitive control in smokers. During No-go trials, a pronounced enhancement of two principal ERP components is observed-The No-go N2 and No-go P3. Increasing evidence has validated the No-go N2 amplitude as a critical marker for the response inhibition function.[27–29] The No-go P3 component reflects the advanced stages of the inhibitory process. This stage is intricately associated with the actual suppression of motor activities within the pre-motor cortex.[30,31]

Deficits in cognitive control and behavioral inhibition attributed to nicotine withdrawal are generally not observed within the initial two-hour period following tobacco cessation.[32,33] Comprehending the impact of nicotine abstinence on cognitive control function and behavioral inhibition could be instrumental in devising strategies to eradicate nicotine

dependency and avert the recurrence of smoking behaviors. However, the influence of pure nicotine abstinence on cognitive control and behavioral inhibition is still unclear.

In this study, male ND patients were selected as subjects. The cognitive control and behavioral inhibition of nicotine deprivation were measured with a smoking-cued Go/No-go task. To guarantee the influence of pure nicotine withdrawal on cognitive control and behavioral inhibition, above performances were collected at baseline and after 2-hour tobacco deprivation. The hypothesis of this study is that male ND patients present abnormal cognitive control and behavioral inhibition, and 2-hour Nicotine withdrawal would have some effects on these deficits. The purpose of this study was to investigate the effects of 2-hour tobacco abstinence on cognitive control and behavioral inhibition deficits in male ND patients.

Materials and Methods

Time and Setting

This research according to the Helsinki Declaration and was authorized by the Ethics Committee of the affiliated Wuxi mental health center of Nanjing medical university (WXMHCIRB2023LLky066). All of the participants gave written and informed consent. This study was carried out from January 01, 2023 to October 31, 2023 at the Department of psychiatry, the affiliated Wuxi mental health center of Nanjing medical university.

Diagnostic Approaches and Participants

The ND group inclusion criteria were as follows: a) meeting of the criteria for the diagnosis of ND in the Diagnostic and Statistical Manual for Mental Disorders (DSM-5); b) not meeting any of the diagnostic criteria for mental disorders the criteria for any DSM-5 axis I disorder or personality disorders; c) age range from 18 years old to 65 years old; d) never quit smoking and reported smoking at least 10 cigarettes per day in the past twelve months; e) there were no neurological or psychiatric disorders identified by clinical evaluation and medical records, or alcohol or other drug addiction.

The healthy control (HC) group inclusion criteria were as follows: a) not meeting criteria for ND according to the DSM-5; b) age range from 18 years old to 65 years old; c) no history of any kind of mental disorder and physical illness.

We used G-power software to estimate the required sample size in this study. With alpha = 0.05 for statistical significance in *F*-tests, a minimum of 18 persons per group was estimated to achieve high statistical power ($1-\beta = 0.95$). This study included 28 ND patients who only smoked cigarettes, without using e-cigarettes or any other tobacco products. The HC group included 28 healthy persons whose age, education and handedness were matched to the ND group. Recruitment for both groups was carried out through local advertisements, targeting citizens who lived in Wuxi city, Jiangsu Province, China. All participants were compensated 82.0 US dollars.

Experimental Procedures and the Smoking-Cued Go/No-Go Task

The experimental procedures are shown in Figure 1. At least 12 hours prior to the experiment, all participants were prohibited from drinking soft beverages, such as tea, coffee, and other recreational drugs. Prior to testing, the researchers gathered demographic data from participants to confirm/rule out current nicotine addiction. All participants completed the Hamilton Depression Scale (HAMD, 24-item version) and the Hamilton Anxiety Scale (HAMA, 14-item version).[34,35] The Fagerstrom Test for Nicotine Addiction (FTND) was used to measure levels of nicotine dependence.[36] For all participants, the Annett handedness scale was used for the assessment of handedness.[37] The amount of carbon monoxide (CO) in breath was detected using a QT-200PLUS portable carbon monoxide Detector (Shenzhen Wellcome Technology Co., Ltd., China). The ND group were measured under the normal condition (baseline (time 1): just after the last cigarette smoked) and the withdrawal status (time 2: just at 2 hours after the last cigarette smoked). Participants were measured at a distance of 50 centimeters (cm) from the computer screen.

We used E-Prime 3.0 (Psychology Software Tools Incorporated, Pittsburgh, United States) to write the Go/No-go task paradigm. As shown in Figure 2, the Go/No-go task has two blocks, each with 180 Go stimuli and 60 No-go stimuli, and each type of picture is presented as a Go stimulus and a No-go stimulus in the two blocks. Each type of pictures was displayed for 200 ms, after which there was a random black screen between 1, 020 ms and 1, 220 ms. In the Go trials, the participants had to hit the "F" key as quickly as possible, while in the No-go trials, the button was forbidden. This task

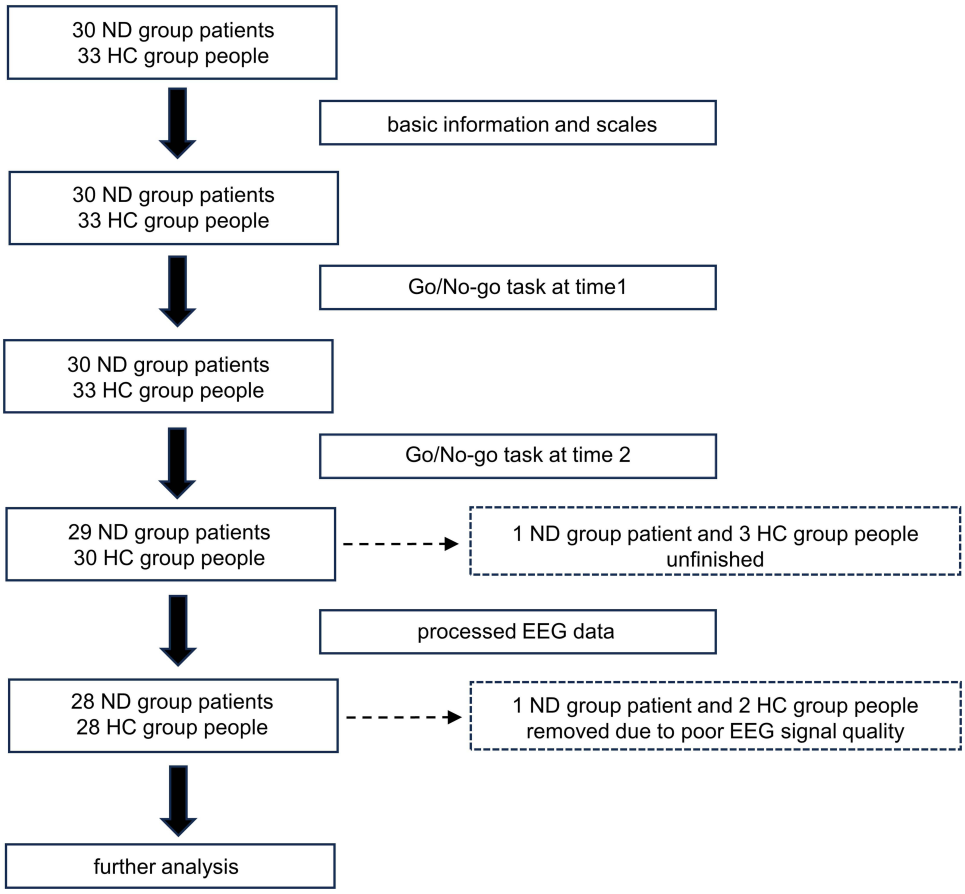

Figure 1 The flowchart for the study. After processing of data, 28 nicotine dependent patients and 28 healthy control people were involved in the task.
Abbreviations: ND, nicotine dependence; HC, healthy control.

included 20 smoking-cued pictures and 20 neutral pictures. Smoking-cued pictures displayed objects related to smoking (such as cigarettes, cigarette packs, etc.), while neutral pictures displayed neutral objects or scenes without smoking behavior. For the smoking-cued pictures and the neutral pictures, the degree of association with smoking cues was evaluated on a 7-point Likert scale ranging from 1 (very disapproved) to 7 (very approved) by thirty-five Senior high school students,[38] and the average scores of the smoking-cued pictures were 6.84 (standard deviation (SD) = 0.07), the average scores of Neutral words were 1.21 (SD = 0.10). Each type of picture appeared as a Go stimulus or No-go stimulus, and two blocks were set up to distinguish between them. Each picture was presented in a pseudo random manner, with a maximum of 4 consecutive Go stimuli and 2 No-go stimuli. The ratio of Go stimulus to No-go stimulus was 3: 1. Before the start of the formal experiment, participants could practice to ensure understanding of the rules. The duration of two-round tests for ND patients in normal and withdrawal states was a total of 28 minutes. The HC group remained consistent.

Electroencephalogram Recording and Analysis

The BioSemi Active Two system (BioSemi Inc., Amsterdam, Netherlands) recorded the electroencephalogram (EEG) at 500 Hertz (Hz). Electroencephalogram (EEG) was recorded using the International 10/20 system and a customized BrainCap (EasyCap, Herrsching, Germany) with 64 Ag/AgCl ring electrodes. The electrodes that record vertical and horizontal electrooculograms (EOG) were located under the left eye and on the lateral canthi of both eyes. The reference electrodes were on the right and left mastoid bone, and a grounding electrode was placed below the left collarbone. The band-pass-filtered of EEG and EOG was 0.05–100 Hz, and the electrode impedance was less than 5 kiloohm (kΩ). EEG was filtered offline using a band-pass-filtered with a cutoff frequency of 0.1–30 Hz. Independent Component Analysis

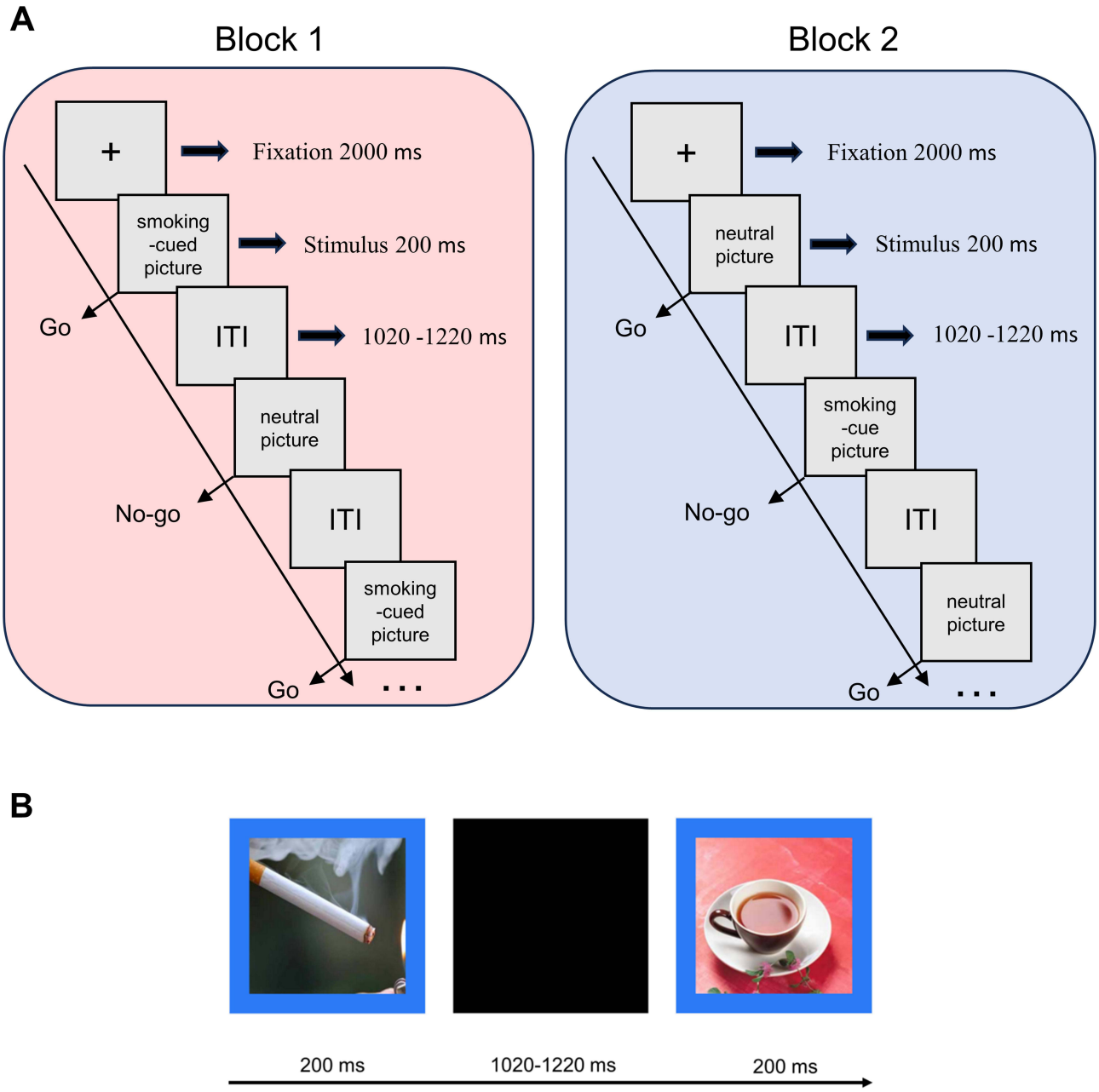

Figure 2 (**A**) Sketch map of the Go/No-go task process. (**B**) Diagrams for different types of picture stimuli.

(ICA) was used to remove eye movement artefacts, muscle electrical activity and electrocardiography. For ERPs analysis, the continuous EEG data were segmented from −200 to 800 ms according to stimulus markers. Following that, a baseline correction was performed from −200 to 0 ms before stimulation, and all amplitude segments below −70 microvolt (μV) or above 70 μV were removed. The segments with diverse stimulus markers were averaged within the specified time frame.

In the Go/No-go task, the occurrence of the Go stimulus was marked as S1, and the occurrence of the No-go stimulus was marked as S2. Based on a previous nicotine dependence study on the Go/No-go task related to smoking cues,[39] combined with waveforms and topography, two time-related components were identified, namely No-go N2 and No-go P3. The amplitudes of No-go N2 were the mean amplitudes of the Fz electrode site at 200–300 ms, and the No-go P3 amplitudes were the mean amplitudes of the Cz electrode site at 380–600 ms.

Statistical Analysis

IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, United States) was used to analyze data. The mean age, education level, handiness, HAMD and HAMA scores were compared by independent *t*-test or Chi-square test. Comparison of CO levels in the ND group were conducted with a paired sample *t*-test. The Reactive times (RTs), accuracy rate (ACC) of the stimuli, the mean amplitudes and latencies of No-go N2 and No-go P3 were compared by using a mixed model Repeated Measure Analysis of Variance (ANOVA) with a 2 group (ND group vs HC group) × 2 time point (time 1 vs time 2) × picture type (smoking-cued picture vs neutral picture) design. The degrees of freedom were corrected using the Greenhouse-Geisser method if the assumption of sphericity was violated. Effect sizes were further estimated using partial eta squared (η^2_p). Post hoc analyses were performed when there was a significant interaction, and Bonferroni correction was employed to manage the possible type I errors caused by multiple comparisons. Alpha values of 0.05 were regarded as significant.

Results

Demographic Characteristics of Participants

The demographic characteristics of all participants are shown in Table 1. There were no significant differences in average age, average years of education, handedness, HAMD score, and HAMA score between the ND group and the HC group. In ND group, Mean score on the FTND was 6.04 (Standard deviation (SD) = 1.71), which reflects a moderate-to-high level of nicotine dependence.

Comparisons of CO Levels in the ND Group

Using paired *t*-tests to compare CO levels at two time points, there was a significant difference between the withdrawal state (mean 9.96 parts per million (ppm); SD = 3.27) and the normal state (mean 13.35 ppm; SD = 4.43) in the ND group ($t = 8.939$, $p < 0.001$), with CO levels in the withdrawal state being lower than those in the normal state.

Behavioral Data Analysis

Acc

As shown in Table 2, for the ACC of Go trials, the interaction effect for group × time × picture was not significant ($F_{1, 54} = 1.933$, $p = 0.170$, $\eta^2_p = 0.035$). There was no significant interaction effect for group × time ($F_{1, 54} = 0.437$, $p = 0.512$, $\eta^2_p = 0.008$), group × picture ($F_{1, 54} = 0.031$, $p = 0.862$, $\eta^2_p = 0.001$), and time × picture ($F_{1, 54} = 1.405$, $p = 0.241$, $\eta^2_p = 0.025$). The main effects of time ($F_{1, 54} = 2.671$, $p = 0.108$, $\eta^2_p = 0.047$) and picture ($F_{1, 54} = 0.692$, $p = 0.409$, $\eta^2_p = 0.013$) were not significant. Although the

Table 1 Demographic Characteristics and Clinical Information of Two Groups

Variables	ND (n = 28)	HC (n = 28)	Statistics	*p*-value
Age range (years)	22–58	24–53	-	-
Mean age (SD)	38.89 (10.69)	34.61 (8.35)	$t = 1.672$	0.100
Year of education (SD)	13.75 (2.63)	14.79 (2.04)	$t = -1.644$	0.106
Handedness (R/M/L)	10/9/9	10/8/10	$\chi2 = 0.111$	0.946
FTND	6.04 (1.71)	-	-	-
The number of cigarettes smoked per day (SD)	17.04 (6.52)	-	-	-
HAMD-24 (SD)	5.25 (0.59)	5.04 (0.69)	$t = 1.250$	0.217
HAMA-14 (SD)	4.50 (0.69)	4.21 (0.99)	$t = 1.247$	0.219

Abbreviations: ND, nicotine dependence; HC, healthy control; SD, standard deviation; R, right; M, mixed; L, left; FTND, Fagerstrom Test of Nicotine Dependence; HAMD-24, Hamilton depression scale (24-item edition); HAMA-14, Hamilton anxiety scale (14-item edition).

Table 2 Behavior Data (Mean (SD)) of ND Group (n = 28) and HC Group (n = 28)

Variables	Go trial RTs				Go trial ACC				No-go trial ACC			
	ND		HC		ND		HC		ND		HC	
	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
Smoking-cued picture	371.97 (51.33)	400.49 (57.55)	372.89 (56.68)	396.29 (59.64)	0.98 (0.05)	0.99 (0.02)	0.99 (0.01)	1.00 (0.00)	0.83 (0.10	0.88 (0.07)	0.84 (0.11)	0.86 (0.10)
Neutral picture	434.31 (60.43)	440.28 (61.94)	421.90 (53.30)	418.80 (57.23)	0.98 (0.05)	0.99 (0.02)	1.00 (0.01)	1.00 (0.01)	0.90 (0.08)	0.92 (0.05)	0.87 (0.09)	0.89 (0.10)

Abbreviations: ND, nicotine dependence; HC, healthy control; RTs, reaction times; ACC, accuracy rate; SD, standard deviation; T1, time 1; T2, time 2.

main effect of group ($F_{1, 54} = 3.487$, $p = 0.067$, $\eta^2_p = 0.061$) was not significant, but Post hoc analyses revealed that the ACC of ND group under the smoking-cued pictures stimuli was lower than the HC group at time 2 ($p = 0.012$).

For the ACC of No-go trials, the interaction effect for group × time × picture was not significant ($F_{1, 54} = 0.921$, $p = 0.342$, $\eta^2 p = 0.017$). There was no significant interaction effect for group × time ($F_{1, 54} = 0.237$, $p = 0.629$, $\eta^2_p = 0.004$), group × picture ($F_{1, 54} = 2.636$, $p = 0.110$, $\eta^2_p = 0.047$), and time × picture ($F_{1, 54} = 2.075$, $p = 0.155$, $\eta^2_p = 0.037$). The main effect of group ($F_{1, 54} = 0.792$, $p = 0.377$, $\eta^2_p = 0.014$) was not significant. The main effects of time ($F_{1, 54} = 10.338$, $p = 0.002$, $\eta^2_p = 0.161$) and picture ($F_{1, 54} = 32.946$, $p < 0.001$, $\eta^2_p = 0.379$) were significant. Post hoc analyses revealed that the ND group had higher ACC at time 2 than at time 1 under the stimulation of smoking-cued pictures ($p = 0.005$). The ACC of neutral pictures stimuli was higher than the ACC of smoking-cued pictures stimuli at time 1 and at time 2 for the two groups (all $p < 0.05$).

RTs

For the RTs of Go trials, the interaction effect for group × time point × picture type was not significant ($F_{1, 54} = 0.139$, $p = 0.711$, $\eta^2_p = 0.003$). There was no significant interaction effect for group × time point ($F_{1, 54} = 1.081$, $p = 0.303$, $\eta^2_p = 0.020$). The interaction effect for group × picture type ($F_{1, 54} = 5.275$, $p = 0.026$, $\eta^2_p = 0.089$) and time point × picture type ($F_{1, 54} = 21.497$, $p < 0.001$, $\eta^2_p = 0.285$) was significant. The main effects of time point ($F_{1, 54} = 16.140$, $p < 0.001$, $\eta^2_p = 0.758$) and picture type ($F_{1, 54} = 169.555$, $p < 0.001$, $\eta^2_p = 0.015$) were significant. The RTs at time 1 were shorter than at time 2 with smoking-cued picture stimuli, and RTs for smoking-cued picture stimuli were shorter than those for neutral picture stimuli at all times for two groups. While the main effect of group ($F_{1, 54} = 0.421$, $p = 0.519$, $\eta^2_p = 0.008$) was not significant.

ERPs Data Analysis

No-Go N2 Component

As shown in Figure 3, using No-go N2 mean amplitudes as dependent variables, a 2 group (ND group vs HC group) × 2 time point (time 1 vs time 2) × 2 picture type (smoking-cued picture vs neutral picture) repeated measures ANOVA with group (ND group vs HC group) as a between-subjects factor and time point (time 1 vs time 2) and picture type (smoking-cued picture vs neutral picture) as a within-subjects factor revealed the interaction effect for group × time point × picture type was not significant ($F_{1, 54} = 0.113$, $p = 0.738$, $\eta^2_p = 0.002$). There were also no significant interaction effects for group × time point ($F_{1, 54} = 0.597$, $p = 0.443$, $\eta^2_p = 0.011$), group × picture type ($F_{1, 54} = 0.023$, $p = 0.881$, $\eta^2_p < 0.001$), and time point × picture type ($F_{1, 54} = 0.169$, $p = 0.682$, $\eta^2_p = 0.003$). The main effect of group was significant ($F_{1, 54} = 4.669$, $p = 0.035$, $\eta^2_p = 0.080$). The main effects of time point and picture type were also observed (For time point: $F_{1, 54} = 15.831$, $p < 0.001$, $\eta^2_p = 0.227$; for picture type: $F_{1, 54} = 71.567$, $p < 0.001$, $\eta^2_p = 0.570$). Post hoc analyses revealed that the No-go N2 mean amplitudes in the ND group was lower than that in the HC group ($p = 0.024$) under the stimulation of smoking-cued pictures at time 1. However, there were no differences in the No-go N2 mean amplitudes between the ND group and the HC group at time 2 ($p = 0.070$). In the ND group, the No-go N2 mean amplitudes were higher at time 2 than that at time 1 under various types of picture stimuli (all $p < 0.05$). In both groups, the No-go N2 mean amplitudes under the smoking-cued picture stimuli were higher than that under the neutral picture stimuli (all $p < 0.001$).

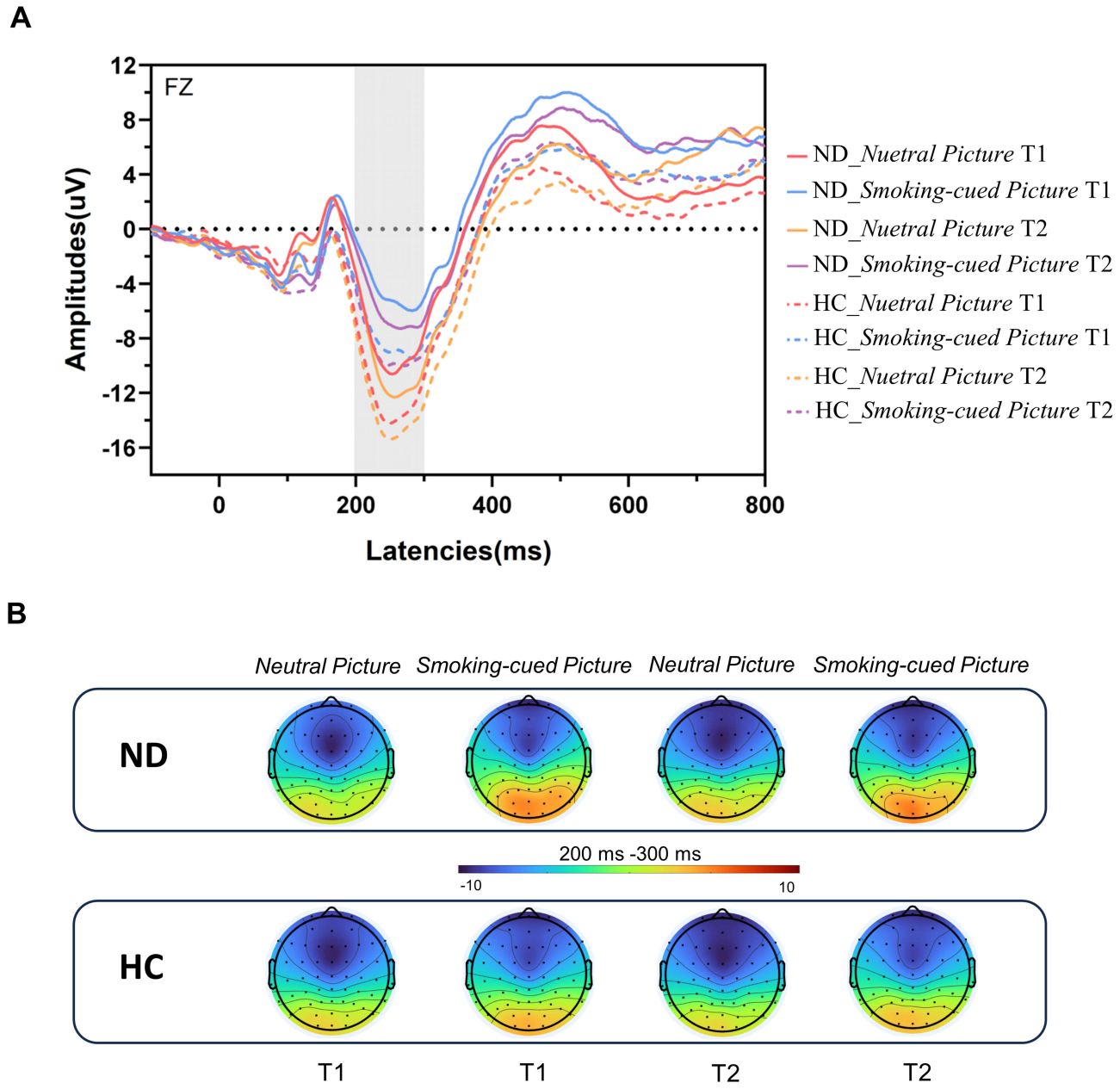

Figure 3 Averaged ERPs and topographic maps of both groups under different types of picture stimuli and time points. (**A**) Averaged ERPs of the No-go N2 was elicited by No-go task at time 1 and time 2. The No-go N2 components were presented within a 200–300 ms latency window at the FZ electrode site. (**B**) Topographic maps of the distribution of No-go N2 components within a time window of 200–300 ms.
Abbreviations: ND, nicotine dependence; HC, healthy control; T1, Time 1; T2, Time 2.

For the latencies of No-go N2, the significant interaction effect for group × time × picture was not significant ($F_{1,\ 54}$ = 0.002, p = 0.962, η^2_p < 0.001). There were also no significant interaction effects for group × time point ($F_{1,\ 54}$ = 0.009, p = 0.927, η^2_p < 0.001), group × picture type ($F_{1,\ 54}$ = 0.851, p = 0.360, η^2_p = 0.016), and time point × picture type ($F_{1,\ 54}$ = 0.090, p = 0.766, η^2_p = 0.002). The main effects of time point ($F_{1,\ 54}$ = 0.177, p = 0.675, η^2_p = 0.003), picture type ($F_{1,\ 54}$ = 2.129, p = 0.150, η^2_p = 0.038) and group ($F_{1,\ 54}$ = 0.004, p = 0.949, η^2_p < 0.001) were not significant.

No-Go P3 Component

The grand averaged amplitude and topographical map of the No-go P3 that correctly responded to both groups under different times and pictures stimuli were shown in Figure 4. For the mean amplitude of No-go P3, the interaction effect

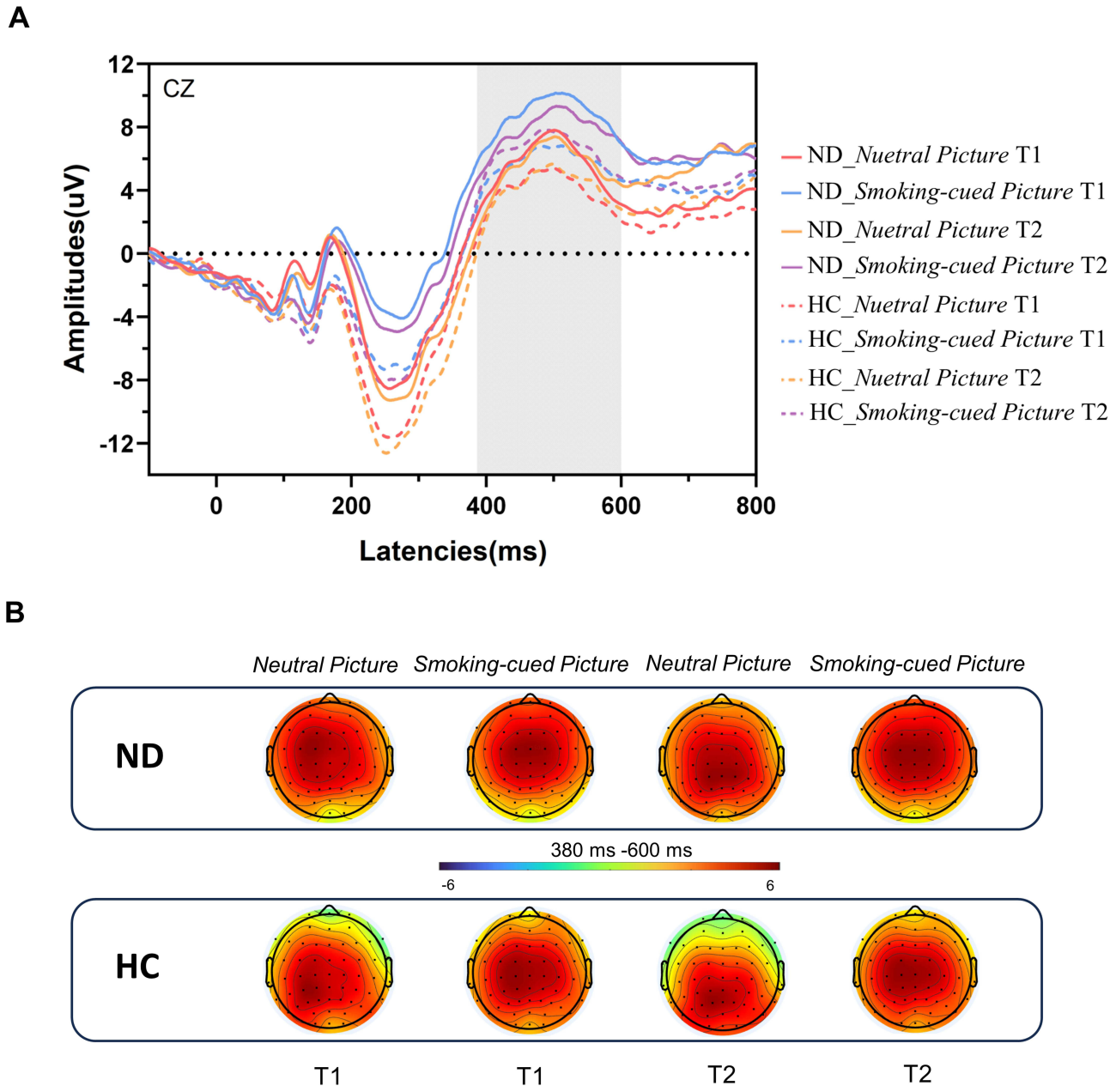

Figure 4 Averaged ERPs and topographic maps of both groups under different types of picture stimuli and time points. (**A**) Averaged ERPs of the No-go P3 was elicited by No-go task at time 1 and time 2. The No-go P3 components were presented within a 380–600 ms latency window at the CZ electrode site. (**B**) Topographic maps of the distribution of No-go P3 components within a time window of 380–600 ms.
Abbreviations: ND, nicotine dependence; HC, healthy control; T1, Time 1; T2, Time 2.

for group × time × picture was not significant ($F_{1,\ 54}$ = 1.670, p = 0.202, η^2_p = 0.030). There were no significant interaction effects for group × time ($F_{1,\ 54}$ = 1.757, p = 0.191, η^2_p = 0.032), group × picture ($F_{1,\ 54}$ = 0.682, p = 0.412, η^2_p = 0.012), and time × picture ($F_{1,\ 54}$ = 0.033, p = 0.857, η^2_p = 0.001). The main effects of group ($F_{1,\ 54}$ = 2.124, p = 0.151, η^2_p = 0.038) and time ($F_{1,\ 54}$ = 0.034, p = 0.854, η^2_p = 0.001) were not significant. The main effect of picture was significant ($F_{1,\ 54}$ = 37.118, p < 0.001, η^2_p = 0.407). Post hoc analyses revealed that the mean amplitude of No-go P3 under the stimulation of smoking-cued pictures was higher than the amplitude under the stimulation of neutral pictures for two group at time 1 and time 2 (all p < 0.05).

For the latencies of No-go P3, the significant interaction effect for group × time × picture was not significant ($F_{1,\ 54}$ = 0.125, p = 0.725, η^2_p = 0.002). There were also no significant interaction effects for group × time point ($F_{1,\ 54}$ = 0.090,

$p = 0.765$, $\eta^2_p = 0.002$), group × picture type ($F_{1, 54} = 0.014$, $p = 0.907$, $\eta^2_p < 0.001$), and time point × picture type ($F_{1, 54} = 0.706$, $p = 0.404$, $\eta^2_p = 0.013$). The main effects of time point ($F_{1, 54} = 0.125$, $p = 0.725$, $\eta^2_p = 0.002$), picture type ($F_{1, 54} = 0.125$, $p = 0.725$, $\eta^2_p = 0.002$) and group ($F_{1, 54} = 1.217$, $p = 0.275$, $\eta^2_p = 0.022$) were not significant.

Analysis of Correlations

The Pearson correlation analysis method was used to analyze the correlations among the Go trials RTs, No-go trials ACC and the amplitudes and latencies of the No-go N2 and No-go P3 under the smoking-cued pictures stimuli for the ND group. No-go P3 amplitudes were negatively correlated with latencies (for time 1: $r = -0.496$, $p = 0.007$; for time 2: $r = -0.472$, $p = 0.011$). The ACC was negatively correlated with No-go P3 amplitudes ($r = -0.463$, $p = 0.013$) at time 2. The No-go P3 amplitudes and ACC were uncorrelated at time 1. The ACC did not correlate with the amplitudes and latencies of No-go N2 and the latencies of No-go P3. RTs did not correlate with the amplitudes and latencies of No-go N2 and No-go P3.

Discussion

This study is the first to explore the influence of a 2-hour tobacco abstinence on cognitive control and behavioral inhibition deficits in ND patients using a smoking-cued Go/No-go task. Additionally, we utilized the ERP components N2 (No-go N2) and No-go P3 to assess changes in inhibitory control function following a 2-hour nicotine withdrawal in male ND patients. Our findings indicate that while ACC during No-go trials triggered by smoking-cued picture was lower in the ND group compared to the HC group, this difference was not statistically significant. Interestingly, the ACC in No-go trials for the ND group was higher after 2 hours of nicotine withdrawal compared to baseline (time 1) under the same smoking-cued picture stimulation. The RTs for smoking-cued pictures at baseline were shorter than those observed after 2 hours of nicotine withdrawal. Most notably, the average No-go N2 amplitudes in the ND group were lower than those in the HC group under smoking-cued pictures at baseline. However, no differences were found in the No-go N2 mean amplitudes between the ND and HC groups after 2 hours of nicotine withdrawal. In the ND group, the No-go N2 mean amplitudes were higher after 2 hours of nicotine withdrawal compared to baseline under various types of picture stimuli. Additionally, No-go P3 amplitudes were negatively correlated with latencies in both time 1 and time 2 in the ND group. Our study confirms that a two-hour nicotine withdrawal improves inhibitory control dysfunction in male smokers, as evidenced by ERP data.

Previous research has established that inhibitory control is markedly diminished in substance-dependent individuals when confronted with drug-related cues [48–50]. From a neuroelectrophysiological perspective, No-go N2 amplitudes are a crucial metric for response inhibition, often demonstrating greater sensitivity to behavioral outcomes in the Go/No-go paradigm.[40,41] Earlier neuroimaging studies have pinpointed the anterior cingulate cortex and the inferior/orbital prefrontal cortex as the neural origins of the No-go N2 component.[42] According to conflict monitoring theory, the anterior cingulate cortex communicates conflict data to other systems, such as the prefrontal cortex.[43] These systems then engage cognitive control strategies, including attentional selection, response initiation, and goal maintenance. The No-go N2 is indicative of the inhibitory processes in early behavioral planning, occurring before action levels, and thus reflects the capacity to prevent erroneous responses before they manifest behaviorally.[44,45]

Our findings reveal that No-go N2 mean amplitudes are reduced in nicotine-dependent patients under smoking cues, suggesting a decrease in response inhibition consistent with many addiction studies.[46–48] Furthermore, we observed an increase in mean No-go N2 amplitudes after a 2-hour nicotine withdrawal, indicating an improvement in response inhibition deficits in nicotine-dependent patients. This improvement was associated with lower nicotine concentrations in the brain, and there was also consistency in the behavioural data, ie smokers had a higher ACC after 2 hours of nicotine withdrawal than before withdrawal. Nicotine's entry into the body activates the anterior cingulate cortex, with morphological changes in this area closely linked to addiction.[49,50] Our results suggest that high nicotine concentrations impact the anterior cingulate cortex, diminishing response inhibition. Conversely, a decrease in nicotine levels appears to lessen this impact, leading to enhanced inhibitory control.

Previous research has shown that the No-go N2 component is indicative of the early stages of response inhibition, while the No-go P3 may represent the latter stages, linked to the actual suppression of motor activity.[31] Our findings suggest that reduced inhibitory control in nicotine-dependent individuals stems from impaired cortical processing during

the initial phases of inhibition, whereas the later stages appear to function normally. This aligns with earlier studies on patients dependent on nicotine and heroin.[39,51]

We correlated No-go P3 amplitudes with latencies in the ND group and found that they were negatively correlated, which is an interesting result. We speculate that the shorter the latency, the faster the brain detects the stimulus, the more fully it processes the stimulus, the more brain resources it uses, and the larger the amplitudes.

According to existing literature, nicotine's average half-life in human tissue is about 2 hours, and typically, no withdrawal symptoms are observed during a 2-hour nicotine abstinence.[21,26] In our study, we collected behavioral and ERP data 2 hours post-nicotine withdrawal. This timing was strategic, as it mitigated cognitive deficits that might arise from psychological symptoms, allowing for a clearer investigation into the influences of pure nicotine withdrawal on response inhibition. Our findings shed light on the characteristics of inhibitory control dysfunction and its underlying neural mechanisms in nicotine-dependent patients. This has significant implications for the treatment and prevention of relapse in individuals addicted to nicotine.

The present study is constrained by several limitations. Firstly, the results must be considered preliminary, primarily due to the small sample size. Secondly, the study's participants were exclusively male smokers, with an absence of female smokers. Consequently, the applicability of the results to the general smoking population is limited. Furthermore, while the use of ERP in this study offered advantageous temporal resolution, it is important to note the method's inherent limitation in spatial resolution. Future investigations could benefit from integrating high spatial resolution methodologies, such as functional Magnetic Resonance Imaging and Positron Emission Tomography.

Conclusion

Our results confirm that No-go N2 amplitudes are an important and sensitive neuroelectrophysiological indicator of inhibitory control function. Nicotine dependent patients have an inhibitory control dysfunction in the face of smoking cues, which is mainly manifested in the early stage of response inhibition rather than in the late stage, which may be reflected by the decrease in No-go N2 amplitudes. After two-hour nicotine withdrawal, there was an improvement in inhibitory control deficits, which is supported by the increase in No-go N2 amplitudes.

Acknowledgments

We are grateful to all the people who took part in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Funding

This study is supported by Wuxi Municipal Health Commission Major Project (No. 202107) and Wuxi Taihu Talent Project (No. WXTTP2020008 and WXTTP 2021).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Grant BF, Shmulewitz D, Compton WM. Nicotine Use and DSM-IV nicotine dependence in the United States, 2001–2002 and 2012–2013. *Am J Psychiatry*. 2020;177(11):1082–1090. doi:10.1176/appi.ajp.2020.19090900
2. Le Foll B, Piper ME, Fowler CD, et al. Tobacco and nicotine use. *Nat Rev Dis Primers*. 2022;8(1):19. doi:10.1038/s41572-022-00346-w
3. Sreeramareddy CT, Aye SN. Changes in adult smoking behaviours in ten global adult tobacco survey (GATS) countries during 2008–2018 - A test of 'hardening' hypothesis'. *BMC Public Health*. 2021;21(1):1209. doi:10.1186/s12889-021-11201-0
4. Leventhal AM, Ameringer KJ, Osborn E, Zvolensky MJ, Langdon KJ. Anxiety and depressive symptoms and affective patterns of tobacco withdrawal. *Drug Alcohol Depend*. 2013;133(2):324–329. doi:10.1016/j.drugalcdep.2013.06.015

5. Conti AA, Tolomeo S, Steele JD, Baldacchino AM. Severity of negative mood and anxiety symptoms occurring during acute abstinence from tobacco: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2020;115:48–63. doi:10.1016/j.neubiorev.2020.04.018
6. Kaye JT, Baker TB, Beckham JC, Cook JW. Tobacco withdrawal symptoms before and after nicotine deprivation in veteran smokers with posttraumatic stress disorder and with major depressive disorder. *Nicotine Tob Res*. 2021;23(7):1239–1247. doi:10.1093/ntr/ntaa242
7. Mildrum Chana S, Palenski PE, Hawes ES, et al. Discrimination and insomnia: examining depressive symptoms and nicotine withdrawal through a serial mediation model in a sample of smokers. *Addict Behav*. 2023;137:107506. doi:10.1016/j.addbeh.2022.107506
8. Zhao B, Lucas CG, Bramley NR. A model of conceptual bootstrapping in human cognition. *Nat Hum Behav*. 2023;8:125–136. doi:10.1038/s41562-023-01719-1
9. Corwin EJ, Klein LC. C-reactive protein and depressed mood in a sub-group of smokers during nicotine abstinence. *Hum Psychopharmacol*. 2003;18(5):329–337. doi:10.1002/hup.487
10. Shiffman S. Effect of nicotine lozenges on affective smoking withdrawal symptoms: secondary analysis of a randomized, double-blind, placebo-controlled clinical trial. *Clin Ther*. 2008;30(8):1461–1475. doi:10.1016/j.clinthera.2008.07.019
11. Shiffman S, West R, Gilbert D; SRNT Work Group on the Assessment of Craving and Withdrawal in Clinical Trials. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine Tob Res*. 2004;6(4):599–614. doi:10.1080/14622200410001734067
12. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res*. 2007;9(3):315–327. doi:10.1080/14622200701188919
13. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;2014(1):CD000031. doi:10.1002/14651858.CD000031.pub4
14. Myers CS, Taylor RC, Moolchan ET, Heishman SJ. Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology*. 2008;33(3):588–598. doi:10.1038/sj.npp.1301425
15. Mendrek A, Monterosso J, Simon SL, et al. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. *Addict Behav*. 2006;31(5):833–844. doi:10.1016/j.addbeh.2005.06.009
16. Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: implications for nicotine dependence treatment. *Neuropharmacology*. 2014;76(1):581–591. doi:10.1016/j.neuropharm.2013.04.034
17. Waters AJ, Carter BL, Robinson JD, et al. Attentional bias is associated with incentive-related physiological and subjective measures. *Exp Clin Psychopharmacol*. 2009;17(4):247–257. doi:10.1037/a0016658
18. Powell JH, Pickering AD, Dawkins L, West R, Powell JF. Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation. *Addict Behav*. 2004;29(7):1407–1426. doi:10.1016/j.addbeh.2004.06.006
19. Dawkins L, Powell JH, West R, Powell J, Pickering A. A double-blind placebo controlled experimental study of nicotine: i--effects on incentive motivation. *Psychopharmacology*. 2006;189(3):355–367. doi:10.1007/s00213-006-0588-8
20. Ashare RL, Schmidt HD. Optimizing treatments for nicotine dependence by increasing cognitive performance during withdrawal. *Expert Opin Drug Discov*. 2014;9(6):579–594. doi:10.1517/17460441.2014.908180
21. Le Houezec J. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. *Int J Tuberc Lung Dis*. 2003;7(9):811–819.
22. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*. 2010;210(4):453–469. doi:10.1007/s00213-010-1848-1
23. Evans DE, Maxfield ND, Van Rensburg KJ, Oliver JA, Jentink KG, Drobes DJ. Nicotine deprivation influences P300 markers of cognitive control. *Neuropsychopharmacology*. 2013;38(12):2525–2531. doi:10.1038/npp.2013.159
24. Hughes JR. Effects of abstinence from tobacco: etiology, animal models, epidemiology, and significance: a subjective review. *Nicotine Tob Res*. 2007;9(3):329–339. doi:10.1080/14622200701188927
25. Liu C, Dong F, Li Y, et al. 12 h abstinence-induced ERP changes in young smokers: electrophysiological evidence from a go/NoGo study. *Front Psychol*. 2019;10:1814. doi:10.3389/fpsyg.2019.01814
26. Xue Y, Zhou H, Jiang C, Liu X, Zhou Z, Wang J. Two-hour tobacco abstinence has no effect on cognitive control in male patients with nicotine dependence: an ERP study. *Front Psychiatry*. 2020;11:604684. doi:10.3389/fpsyt.2020.604684
27. Falkenstein M, Hoormann J, Hohnsbein J. ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychol*. 1999;101(2–3):267–291. doi:10.1016/S0001-6918(99)00008-6
28. Kaiser S, Weiss O, Hill H, Markela-Lerenc J, Kiefer M, Weisbrod M. N2 event-related potential correlates of response inhibition in an auditory Go/Nogo task. *Int J Psychophysiol*. 2006;61(2):279–282. doi:10.1016/j.ijpsycho.2005.09.006
29. Nakata H, Inui K, Nishihira Y, et al. Effects of a go/nogo task on event-related potentials following somatosensory stimulation. *Clin Neurophysiol*. 2004;115(2):361–368. doi:10.1016/j.clinph.2003.09.013
30. Dimoska A, Johnstone SJ, Barry RJ. The auditory-evoked N2 and P3 components in the stop-signal task: indices of inhibition, response-conflict or error-detection? *Brain Cogn*. 2006;62(2):98–112. doi:10.1016/j.bandc.2006.03.011
31. Kok A, Ramautar JR, De Ruiter MB, Band GP, Ridderinkhof KR. ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology*. 2004;41(1):9–20. doi:10.1046/j.1469-8986.2003.00127.x
32. Hendricks PS, Ditre JW, Drobes DJ, Brandon TH. The early time course of smoking withdrawal effects. *Psychopharmacology*. 2006;187(3):385–396. doi:10.1007/s00213-006-0429-9
33. Parrott AC, Garnham NJ, Wesnes K, Pincock C. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. *Hum Psychopharmacol*. 1996;11:391–400. doi:10.1002/(SICI)1099-1077(199609)11:5<391::AID-HUP780>3.0.CO;2-Z
34. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56
35. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55. doi:10.1111/j.2044-8341.1959.tb00467.x
36. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the fagerstrom tolerance questionnaire. *J Behav Med*. 1989;12(2):159–182. doi:10.1007/BF00846549
37. Annett M. A classification of hand preference by association analysis. *Br J Psychol*. 1970;61:303–321. doi:10.1111/j.2044-8295.1970.tb01248.x
38. Joshi A, Kale S, Chandel S, Pal DK. Likert scale: explored and explained. *Br J Appl Sci Technol*. 2015;7(4):396. doi:10.9734/BJAST/2015/14975

39. Luijten M, Littel M, Franken IH. Deficits in inhibitory control in smokers during a Go/NoGo task: an investigation using event-related brain potentials. *PLoS One*. 2011;6(4):e18898. doi:10.1371/journal.pone.0018898
40. Nakata H, Inui K, Wasaka T, et al. Higher anticipated force required a stronger inhibitory process in go/nogo tasks. *Clin Neurophysiol*. 2006;117(8):1669–1676. doi:10.1016/j.clinph.2006.03.032
41. Falkenstein M. Inhibition, conflict and the Nogo-N2. *Clin Neurophysiol*. 2006;117(8):1638–1640. doi:10.1016/j.clinph.2006.05.002
42. Bokura H, Yamaguchi S, Kobayashi S. Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clin Neurophysiol*. 2001;112(12):2224–2232. doi:10.1016/S1388-2457(01)00691-5
43. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cognit Sci*. 2004;8(12):539–546. doi:10.1016/j.tics.2004.10.003
44. Kim MS, Kim YY, Yoo SY, Kwon JS. Electrophysiological correlates of behavioral response inhibition in patients with obsessive-compulsive disorder. *Depress Anxiety*. 2007;24(1):22–31. doi:10.1002/da.20195
45. Huster RJ, Enriquez-Geppert CF, Lavallee S, Falkenstein M, Herrmann CSM. Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. *Int J Psychophysiol*. 2013;87(3):217–233. doi:10.1016/j.ijpsycho.2012.08.001
46. Rubio G, Jiménez M, Rodríguez-Jiménez R, et al. The role of behavioral impulsivity in the development of alcohol dependence: a 4-year follow-up study. *Alcohol Clin Exp Res*. 2008;32(9):1681–1687. doi:10.1111/j.1530-0277.2008.00746.x
47. Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend*. 2002;66(3):265–273. doi:10.1016/S0376-8716(01)00206-X
48. Fu LP, Bi GH, Zou ZT, et al. Impaired response inhibition function in abstinent heroin dependents: an fMRI study. *Neurosci Lett*. 2008;438(3):322–326. doi:10.1016/j.neulet.2008.04.033
49. Kumari V, Gray JA, Ffytche DH, et al. Cognitive effects of nicotine in humans: an fMRI study. *Neuroimage*. 2003;19(3):1002–1013. doi:10.1016/S1053-8119(03)00110-1
50. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am j Psychiatry*. 2005;162:1403–1413. doi:10.1176/appi.ajp.162.8.1403
51. Yang B, Yang S, Zhao L, Yin L, Liu X, An S. Event-related potentials in a Go/Nogo task of abnormal response inhibition in heroin addicts. *Sci China C Life Sci*. 2009;52(8):780–788. doi:10.1007/s11427-009-0106-4