



RESEARCH ARTICLE

Modulation of the effects of amphetamine use on cognition and brain electrophysiology by nicotine use

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Abstract: Methamphetamine is widely used worldwide and is the predominant drug in Taiwan. While many studies have looked at differences in cognition associated with amphetamine use, whether these effects are due to amphetamine use alone have been less considered. This means it is difficult to know whether reported differences in cognition are due to methamphetamine use specifically or addiction more generally. Here, inhibitory control and error monitoring were investigated in amphetamine users without cigarette smoking (NSA), amphetamine users with cigarette smoking (SA), and non-smoking controls (NSC) using a drug-cued stop-signal task. For inhibitory control, the NSA group showed the poorest performance. In addition, a negative relationship was found between the number of cigarettes smoked per day and both N2 amplitude and stop-signal reaction time (SSRT), suggesting a link between smoking and improved inhibitory performance. For error-related effects, the SA group showed enhanced Pe responses to drug-related cues, indicating greater error awareness in high-risk contexts. Compared with the NSA group, the SA group demonstrated better inhibitory control and error monitoring, meaning it may be that smoking moderates some cognitive deficits associated with amphetamine use, a possibility which should be further investigated. These findings highlight the importance of considering overall substance-use patterns when examining amphetamine-specific effects.

Keywords: Smoking, Amphetamine, Stop signal task, inhibitory control, error monitoring

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Institutional Review Board and Informed Consent Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Human Research Ethics Committee of National Cheng Kung University (approval number A-ER-107-435, 03.20.2019) and all participants had a clear understanding of the content of the experiment and signed an informed consent form before taking part.

Data availability: Data are available from the authors upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Introduction

As well as amphetamine use being a world-wide problem, it accounts for 30.7% of drug use in Taiwan and remains one of the primary health concerns for the government (Taiwan Food and Drug Administration, 2023). Among the known effects of amphetamine use are structural changes in the prefrontal-striatal circuitry (Tolliver et al., 2012), reduced dopamine levels (Kwon & Han, 2018), and impairment in executive functions that are known to be essential for both addiction recovery and behavior in general, such as inhibitory control (Dakhili et al., 2022; Shiflett et al., 2013). For example, previous work has shown that amphetamine users had longer stop signal reaction times (SSRT) in stop-signal tasks (SST) compared to control groups, indicative of compromised inhibitory control (Monterosso et al., 2005). Moreover, prolonged drug use, with repeated exposure to both drugs and drug-related cues, can heighten the salience and reactivity to drug-related cues and result in attentional bias (Zhao et al., 2024). This can be problematic because research has shown that drug-related cues result in increased deficits in inhibitory control compared to neutral environments, which can, in turn, elevate the risk of relapse (Dawe & Loxton, 2004). This effect is thought to occur because repeated pairings of drugs with conditioned stimuli activates the habit system governed by the dorsal striatum (Detandt et al., 2017a; Xie et al., 2014) and triggers cravings (Tolliver et al., 2010). The combination of cravings, and so users' heightened motivation to use drugs, combined with a deficient inhibitory control system leads to a higher probability of drug-seeking behavior (Lüscher et al., 2020).

Also of importance it that it is frequently the case that amphetamines are not used in isolation. For example, there is a high rate of amphetamine use being associated with a smoking habit (Tseng, 2021). This means that the effects associated with amphetamine use may differ when users also engage in the use of other substance, nicotine in this example, that can also have central nervous system and cognitive effects. Nicotine, as an addictive substance, leads to long-term changes in the dopamine system related to reward processing (Kräplin et al., 2019) and is also associated with changes in responses to cues associated with its use. Such changes have been reported to include a gradual increase attentional bias toward smoking-related cues (Dampuré et al., 2023; Kräplin et al., 2019). Previous fMRI studies using a smoking-cued task showed such cues also activated the mesolimbic reward system (including the amygdala, hippocampus, ventral tegmental area, and thalamus) and areas involved in visual processing (such as the prefrontal cortex, parietal cortex, and fusiform cortex) in smokers (Brody et al., 2002; Brody, 2006). Prolonged exposure to these cues also enhanced activation in the anterior cingulate cortex (ACC) of smokers (Brody et al., 2002). Although previous studies indicate that acute nicotine use can improve task performance in smokers during vigilance-demanding tasks (Newhouse et al., 2004), prolonged nicotine use, much like amphetamine use, impairs inhibitory control (Luijten et al., 2011a) and negatively affects error monitoring (Franken et al., 2010; Luijten et al., 2011b). These abilities are likely critical for addiction recovery with inhibitory control helping to suppress inappropriate behaviors (Brand et al., 2019), and error monitoring enabling individuals to adjust their behavior based on feedback after making mistakes to prevent repeating them (Franken

et al., 2010). Despite the high levels of both types of addiction, and their high level of co-occurrence, most studies have focused separately on the inhibitory control or error-monitoring of amphetamine users or smokers when exposed to substance-related cues. To date, no studies have specifically examined cognitive deficits in smoking amphetamine users. This study, therefore, aimed to investigate whether there were differences in the patterns of inhibitory control and error monitoring in individuals who used amphetamines in isolation and those who used them in as well as using nicotine (smoking). Additionally, whether any cognitive impairments differed for these groups when exposed to drug-related cues was investigated.

The Go/No-Go task or Stop Signal Tasks (SST) are often used to investigate inhibitory control and error monitoring. Here, interest was in the ability to suppress responses and this can be more suitably measured using the SST because it allows calculation of the Stop Signal Reaction Time (SSRT), a measure thought to be indicative of this ability. This study employed a SST with drug-use-related cues and neutral cues to measure the inhibitory control and error monitoring of amphetamine users with and without smoking habits for different cue conditions in comparison to both each other and to control participants. Electrophysiological recording during performance of such a task also allows insights into the neural mechanisms involved in task performance. This can be done by looking at event-related potentials (averaged electrophysiological signals relative to a specific time-point), particularly those recorded in relation to presentation of the stop signal and to participant responses. Among such components, the N2 and P3 components are considered key indicators of inhibitory control. The N2 component, typically appearing around 200 to 400 ms after a stop signal, is seen in fronto-central electrodes (Cheng et al., 2019; Gajewski & Falkenstein, 2013; Kok et al., 2004) and reflects the early inhibitory control phase, where there is a mismatch between environmental changes and ongoing behavior (Cheng et al., 2019; Gajewski & Falkenstein, 2013; Kok et al., 2004). The P3 component, emerging approximately 300 to 600 ms after the stop signal, represents the later stage of inhibitory control and response suppression (Kilian et al., 2020; Morie et al., 2014). Although few studies have examined electrophysiological markers in amphetamine users, research on cocaine (a stimulant with similar effects) showed reduced N2 and P3 amplitudes in cocaine users compared to non-users (Sokhadze et al., 2008). However, Spronk et al. (2016) found that cocaine users exhibited larger NoGo-P3 amplitudes in a Go/No-Go task, meaning there are inconsistent findings on the impact of stimulants on inhibitory control. In contrast, studies of smokers have consistently reported altered N2 and P3 amplitudes in nicotine users (Luijten et al., 2011a; Yin et al., 2016). When presented with smoking-related cues, smokers showed more NoGo response errors and larger P3 amplitudes in inhibitory control tasks (Detandt et al., 2017b; Zhao et al., 2024). Hou et al. (2024) also showed that smokers had reduced No-Go N2 amplitudes when smoking-related cues were used, reflecting diminished inhibitory control. Despite the lack of consistency in studies of stimulant users and the absence of research on smoking amphetamine users, we hypothesized that all amphetamine users, regardless of smoking status, would show impaired inhibitory control compared to non-users and this would be reflected in reduced N2 and P3 amplitudes. Additionally, it was expected that smoking amphetamine users would exhibit more pronounced inhibitory control deficits when exposed to drug-related cues.

The aforementioned error monitoring has several aspects and refers to an individual's ability to recognize errors, adjust behavior, and prevent future mistakes (Franken et al., 2010). Impairments in this ability may lead to continued engagement in impulsive behaviors with negative consequences, such as substance use (Luijten et al., 2011a). Related to this is the error-related negativity (ERN) component which appears as a negative deflection in the electroencephalographic recording approximately 50 ms after an erroneous response, reflecting a mismatch between response selection and execution (Speed et al., 2017). The error positivity, Pe, occurs around 300 ms

after an erroneous response, and is associated with conscious awareness and evaluation of errors (Di Gregorio et al., 2018). Previous studies showed reduced ERN and Pe amplitudes in cocaine users, indicating deficits in post-error regulation (Lutz et al., 2021; Morie et al., 2014). Similarly, smoking research found smaller Pe amplitudes in smokers (Franken et al., 2010). Another study observed both reduced ERN and Pe amplitudes in smokers (Luijten et al., 2011b), though Luijten et al. (2016) found no significant differences between smokers and non-smokers. Despite the inconsistency in findings regarding smokers, we hypothesized all amphetamine users would exhibit impaired error monitoring compared to controls and this would be reflected in reduced ERN and Pe amplitudes. In light of some previous findings, smoking amphetamine users were expected to show more pronounced error monitoring deficits when exposed to drug-related cues.

Materials and Methods

Participants

All procedures in this experiment were approved by the Human Research Ethics Committee of National Cheng Kung University Hospital. Prior to participation, all participants were informed about the experimental procedures and signed to give their consent before taking part. After the experiment completed, participants received a compensation of NT\$1,000 for their participation. A total of 78 participants were recruited of which 52 were currently abstinent amphetamine users who were recruited from the substance abuse/addiction clinics of National Cheng Kung University Hospital. 26 non-smoking controls (23 male, 3 female, aged 36.5 ± 6.51 years, referred to as NSC) were recruited from the Health Management Center. All participants were right-handed. The 52 amphetamine users were divided into two groups based on their cigarette smoking habits. The smoking amphetamine group was comprised of 22 males and 4 female, ages 37.0 ± 7.01 years and are referred to as the SA group. The non-smoking amphetamine group was comprised 26 males, ages 38.3 ± 8.11 and referred to as the NSA group. All participants in the SA group had a daily smoking habit, with an average of 19.16 ± 2.01 number of cigarettes smoked per day. All amphetamine users recruited in the present study were mandated to treatment under a deferred prosecution program, and official records confirmed that their illegal substance use history was limited to amphetamines. On the day of the experiment, amphetamine users underwent a urine test, and results indicated negative findings for amphetamines, opioids, cannabis, ketamine, cocaine, and other substances. In addition, participants in the SA group were instructed to abstain from smoking for at least two hours prior to the experiment. There were no significant age differences between the groups ($F_{(2, 75)} = 0.438$, $p=0.647$). However, a significant difference was found in Raven's scores, a non-verbal measure of general intelligence ($F_{(2, 75)} = 6.560$, $p=0.002$). Therefore, Raven's score was included as a covariate in data analyses. (Table 1).

Table 1. Participants demographics.

	SA		NSA		NSC		p value
N	26		26		26		
Male: Female	22: 4		26: 0		23: 3		
	M	SD	M	SD	M	SD	
Age	36.96	7.01	38.31	8.11	36.50	6.51	0.647
Revan	14.04	6.44	15.23	6.30	19.62	4.62	0.002**
number of cigarettes smoked per day	19.16	2.01	--	--	--	--	--

SA: smoking methamphetamine users. NSA: non-smoking methamphetamine users. NSC: non-smoking control participants. M indicates mean and SD is standard deviation.

Procedure and Drug-cued Stop Signal Task (Drug-cued SST)

The Drug-cued Stop Signal Task (Drug-cued SST) was programmed using E-Prime 3.0 (Psychology Software Tools Incorporated, Pittsburgh, United States). This task involves presentation of two conditions, one with drug-related images and one with neutral images used as cues in trials of the task. The drug-related images depicted items or scenes associated with substance use (e.g., needles, drug powders, etc.) and were sourced from the National Institute on Drug Abuse (NIDA) (<https://nida.nih.gov/>) and the Substance Abuse and Mental Health Services Administration (SAMHSA) (<https://www.samhsa.gov/>). Neutral images featured scenes unrelated to drug use and were obtained from the International Affective Picture System (IAPS) (Lang et al., 2008). Each condition contained 240 trials, resulting in a total of 480 trials per participant. The trials were evenly divided into six blocks (three drug-related and three neutral), with each block containing 80 trials. Blocks were presented in a randomized order and trial sequences within each block were also randomized. In each block 75% of trials were go trials and 25% were stop trials (see details below). The screen via which the task was presented was positioned 50 cm in front of the participants.

Each trial began with a fixation cross (+) shown for 500 ms, followed by a cue image displayed for another 500 ms. Next, an arrow (the Go stimulus) pointing either to the left or to the right appeared for 500 ms (both directions occurred with equal frequency in a random order). Participants were instructed to respond to the direction of the arrow by pressing the "D" key for left or "L" for right on a PC keyboard as quickly and accurately as possible. For 25% of trials, which were the stop trials, a red circle was used as the stop signal, with presentation of this meaning the participants should not respond. This 'stop-signal' remained visible until the stimulus disappeared (500 ms) or the participant made a response (Fig 1). The onset time of this signal, relative to the onset of the 'go' arrow, was the stop signal delay (SSD) and was initially set at 200 ms and was adjusted based on participant performance to maintain stop accuracy near 50%. Successful inhibition of a response resulted in increase of the SSD by 34 ms, while failure meant the SSD was decreased by 34 ms. Participants were instructed to make their responses to the 'go' signals (arrows) quickly and accurately and there was a 500 ms time-limit for making a response to encourage this. Behavioral data, including Go accuracy, Stop accuracy, Go reaction time (GoRT), Stop signal reaction time (SSRT), and post-error slowing, were calculated for both drug-related and neutral conditions.

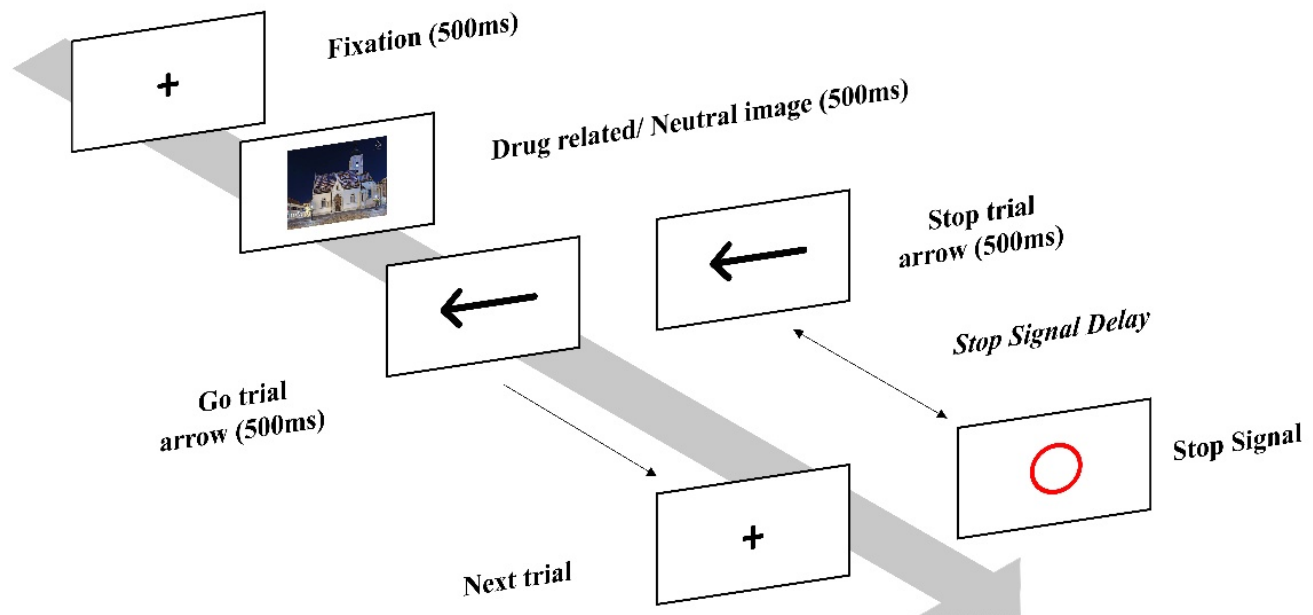


Fig 1. The stop signal task. Participants were instructed to press a button to indicate the direction of the arrow as quickly and accurately as possible but to withhold their response if a stop signal appeared. (Grayscale.)

Electrophysiological Recordings and Analysis

Electroencephalography data were recorded using the NeuroScan Synamps system and the Scan 4.2 software (Compumedics USA, Charlotte, USA). During task performance, vertical and horizontal electrooculograms (EOG) were recorded from electrodes placed above and below the left eye, and 1 cm lateral to the eye. EEG data were collected using a 34-electrode arrangement with placement of electrodes based on the international 10-20 system. Electrode impedance was kept below 5 k Ω throughout the recording, and analog signals were filtered with a 100 Hz low-pass filter and a 60 Hz notch filter, then digitized at a sampling rate of 500 Hz. Data analysis was subsequently performed for data collected from the Fz, Cz and Pz electrodes using the NeuroScan software. First, the data was filtered with a 12 dB band-pass filter, with a high-pass frequency of 0.05 Hz and a low-pass frequency of 30 Hz. Segmentation was then carried out to extract epochs from 100 ms before and 800 ms after either stimulus onset or response onset. Baseline correction was applied using data from the period from -100 to 0 ms of each epoch. Trials containing blinks or movement artifacts exceeding a threshold of 100 μ V were excluded from analysis.

Stop signals were used as the onset to examine the inhibitory control-related N2 and P3 components. The N2 component was analyzed within a time window of 220 to 280 ms (similar to the 200-300 ms window in Hou et al., 2024), while the P3 component was analyzed from 320 to 420 ms (similar to the 300-450 ms window in Xie et al., 2017). The time point of error responses in stop signal trials served as the onset to examine error monitoring. The ERN component was assessed within a window of 180 to 250 ms (refer to the 80-280 ms window in Yu et al., 2022), and the Pe component was measured from 310 to 410 ms (refer to the 200-400 ms window in Boer et al., 2025).

Results

Behavioral Results

See Table 2 for the behavioral results. A repeated-measures analysis of variance (ANOVA) was performed on this data, with factors of group (SA, NSA, and NSC) and cue type (drug-related, neutral). For Go Accuracy, there was no significant interaction between group and cue type ($F_{(2, 74)} = 1.671, p = 0.195, \eta^2_p = 0.043$), nor was there a main effect of group ($F_{(2, 74)} = 1.896, p = 0.157, \eta^2_p = 0.049$). However, a significant main effect of cue type was observed ($F_{(1, 74)} = 5.307, p = 0.024, \eta^2_p = 0.067$), with post hoc comparisons revealing that Go Accuracy was significantly higher for neutral pictures compared to drug-related pictures ($p < 0.01$). Stop Accuracy showed a significant interaction between group and cue type ($F_{(2, 74)} = 3.922, p = 0.024, \eta^2_p = 0.096$). Post hoc tests indicated no simple main effect of emotion on Stop Accuracy (all $p > 0.05$), but the SA group exhibited significantly higher Stop Accuracy for drug-related pictures than for neutral pictures ($t_{(25)} = 3.95, p = 0.001$). GoRT showed no significant interaction ($F_{(2, 74)} = 2.612, p = 0.08, \eta^2_p = 0.066$) or main effects of group ($F_{(2, 74)} = 1.116, p = 0.333, \eta^2_p = 0.045$) or cue type ($F_{(1, 74)} = 3.474, p = 0.066, \eta^2_p = 0.029$). SSRT did not reveal an interaction effect ($F_{(2, 74)} = 0.577, p = 0.564, \eta^2_p = 0.015$) or a main effect of cue type ($F_{(1, 74)} = 0.319, p = 0.574, \eta^2_p = 0.004$), but there was a significant main effect of group ($F_{(2, 74)} = 4.318, p = 0.017, \eta^2_p = 0.105$), with post hoc tests showing that the NSA group had significantly slower SSRTs compared to the NSC group ($p = 0.005$). For post-error slowing, there was no significant interaction between group and cue type ($F_{(2, 74)} = 2.598, p = 0.081, \eta^2_p = 0.066$). There was also no significant main effect of group ($F_{(2, 74)} = 1.308, p = 0.277, \eta^2_p = 0.034$) or cue type ($F_{(1, 74)} = 1.184, p = 0.28, \eta^2_p = 0.016$).

Table 2. Behavioral results for the stop signal task.

Behavioral results		SA		NSA		NSC	
		M	SD	M	SD	M	SD
Drug-related cues	Go Accuracy	0.86	0.11	0.85	0.11	0.93	0.06
	Stop Accuracy	0.50	0.06	0.47	0.06	0.48	0.05
	GORT (ms) ^a	449.45	32.40	442.20	26.71	430.82	32.04
	SSRT (ms) ^b	265.56	33.58	280.34	41.01	255.56	20.38
	Post-error slowing ^c (ms)	11.63	16.62	5.56	21.49	3.68	18.78
Neutral cues	Go Accuracy	0.89	0.08	0.87	0.11	0.93	0.07
	Stop Accuracy	0.47	0.07	0.46	0.08	0.48	0.06
	GORT (ms)	435.64	33.74	430.50	27.50	428.08	35.78
	SSRT (ms)	262.51	34.92	276.43	39.65	245.52	19.25
	Post-error slowing (ms)	7.01	19.85	0.91	17.13	13.95	13.49

^aGORT: Go Reaction Time. ^bSSRT: Stop Signal Reaction Time. ^cPost-error slowing: Post-error GoRT – GoRT. SA: smoking methamphetamine users. NSA: non-smoking methamphetamine users. NSC: non-smoking control participants. M indicates mean and SD is standard deviation.

ERP results

See Fig 2 for the ERP results. Fig 3 and Fig 4 show a series of topographical maps of the N2, P3, ERN and Pe components for each group (SA/NSA/NSC) and cue type (Drug related/Neutral). A repeated-measures analysis of variance (ANOVA) was performed for this data, with factors of group (SA, NSA, and NSC) and cue type (drug-related, neutral). For inhibitory control-related components, the N2 did not show a significant interaction effect (Fz: $F_{(2, 74)} = 0.126$, $p = 0.882$, $\eta^2_p = 0.003$; Cz: $F_{(2, 74)} = 0.063$, $p = 0.939$, $\eta^2_p = 0.002$; Pz: $F_{(2, 74)} = 0.081$, $p = 0.922$, $\eta^2_p = 0.002$), nor was there a significant main effect of cue type (Fz: $F_{(1, 74)} = 0.22$, $p = 0.64$, $\eta^2_p = 0.003$; Cz: $F_{(1, 74)} = 0.499$, $p = 0.482$, $\eta^2_p = 0.007$; Pz: $F_{(1, 74)} = 0.188$, $p = 0.666$, $\eta^2_p = 0.003$). However, a significant main effect of group was observed at Fz ($F_{(2, 74)} = 3.982$, $p = 0.023$, $\eta^2_p = 0.097$), with post hoc tests showing that the SA group had a significantly larger N2 amplitude compared to the NSA group ($p = 0.006$). At Cz, the main effect of group approached significance ($F_{(2, 74)} = 2.971$, $p = 0.057$, $\eta^2_p = 0.074$), while no significant effect was found at Pz ($F_{(2, 74)} = 0.738$, $p = 0.481$, $\eta^2_p = 0.020$). The P3 component also showed no interaction (Fz: $F_{(2, 74)} = 0.398$, $p = 0.673$, $\eta^2_p = 0.011$; Cz: $F_{(2, 74)} = 0.167$, $p = 0.847$, $\eta^2_p = 0.004$; Pz: $F_{(2, 74)} = 0.097$, $p = 0.908$, $\eta^2_p = 0.003$), nor was there a significant main effect of cue type (Fz: $F_{(1, 74)} = 0.28$, $p = 0.598$, $\eta^2_p = 0.004$; Cz: $F_{(1, 74)} = 0.482$, $p = 0.489$, $\eta^2_p = 0.006$; Pz: $F_{(1, 74)} = 0.138$, $p = 0.711$, $\eta^2_p = 0.02$). However, a significant main effect of group was found at Fz ($F_{(2, 74)} = 3.384$, $p = 0.039$, $\eta^2_p = 0.084$, $\eta^2_p = 0.084$), with post hoc tests showing that the NSC group had a significantly larger P3 amplitude compared to the NSA group ($p = 0.047$) and SA group ($p = 0.015$). In contrast, no significant main effect of group was found at Cz ($F_{(2, 74)} = 2.658$, $p = 0.077$, $\eta^2_p = 0.067$) or Pz ($F_{(2, 74)} = 1.596$, $p = 0.210$, $\eta^2_p = 0.041$).

For error monitoring, there was no significant interaction between group and cue type (Fz: $F_{(2, 74)} = 1.52$, $p = 0.226$, $\eta^2_p = 0.039$; Cz: $F_{(2, 74)} = 0.708$, $p = 0.496$, $\eta^2_p = 0.019$; Pz: $F_{(2, 74)} = 0.327$, $p = 0.722$, $\eta^2_p = 0.009$), nor was there a main effect of group (Fz: $F_{(2, 74)} = 1.389$, $p = 0.256$, $\eta^2_p = 0.036$; Cz: $F_{(2, 74)} = 1.460$, $p = 0.239$, $\eta^2_p = 0.038$; Pz: $F_{(2, 74)} = 1.475$, $p = 0.236$, $\eta^2_p = 0.038$) for ERN. Although the ERN showed a significant main effect for cue type at Fz ($F_{(1, 74)} = 4.023$, $p = 0.049$, $\eta^2_p = 0.052$), post hoc analyses did not reveal any significant findings (all $p > 0.05$). The main effect of cue type did not reach significance at Cz or Pz (Cz: $F_{(1, 74)} = 2.958$, $p = 0.090$, $\eta^2_p = 0.038$; Pz: $F_{(1, 74)} = 1.729$, $p = 0.193$, $\eta^2_p = 0.023$). For Pe there was a significant interaction between group and cue type at Fz ($F_{(2, 74)} = 6.32$, $p = 0.003$, $\eta^2_p = 0.146$) and Cz ($F_{(2, 74)} = 4.134$, $p = 0.020$, $\eta^2_p = 0.14600$). Post hoc analysis showed that at Fz, under neutral picture conditions ($F_{(2, 74)} = 4.376$, $p = 0.016$, $\eta^2_p = 0.106$), the Pe amplitude in the NSC group was significantly greater than that in both the NSA ($p = 0.005$) and the SA group ($p = 0.03$). At Cz, the post hoc comparisons for the neutral picture condition showed a marginally significant group difference ($F_{(2, 74)} = 2.993$, $p = 0.056$, $\eta^2_p = 0.075$), with the Pe amplitude in the NSC group being significantly greater than that in the NSA group ($p = 0.017$). Additionally, the SA group exhibited significantly larger Pe amplitudes at Fz in response to drug-related picture cues compared to neutral cues ($t_{(25)} = 2.683$, $p = 0.013$). However, no significant effects were observed at Cz across cue types (all $p > 0.05$). At Pz, no significant interaction between group and cue type was found ($F_{(2, 74)} = 2.796$, $p = 0.067$, $\eta^2_p = 0.070$), and there was no main effect of group ($F_{(2, 74)} = 2.474$, $p = 0.091$, $\eta^2_p = 0.063$) or of cue type ($F_{(1, 74)} = 0.069$, $p = 0.794$, $\eta^2_p = 0.001$).

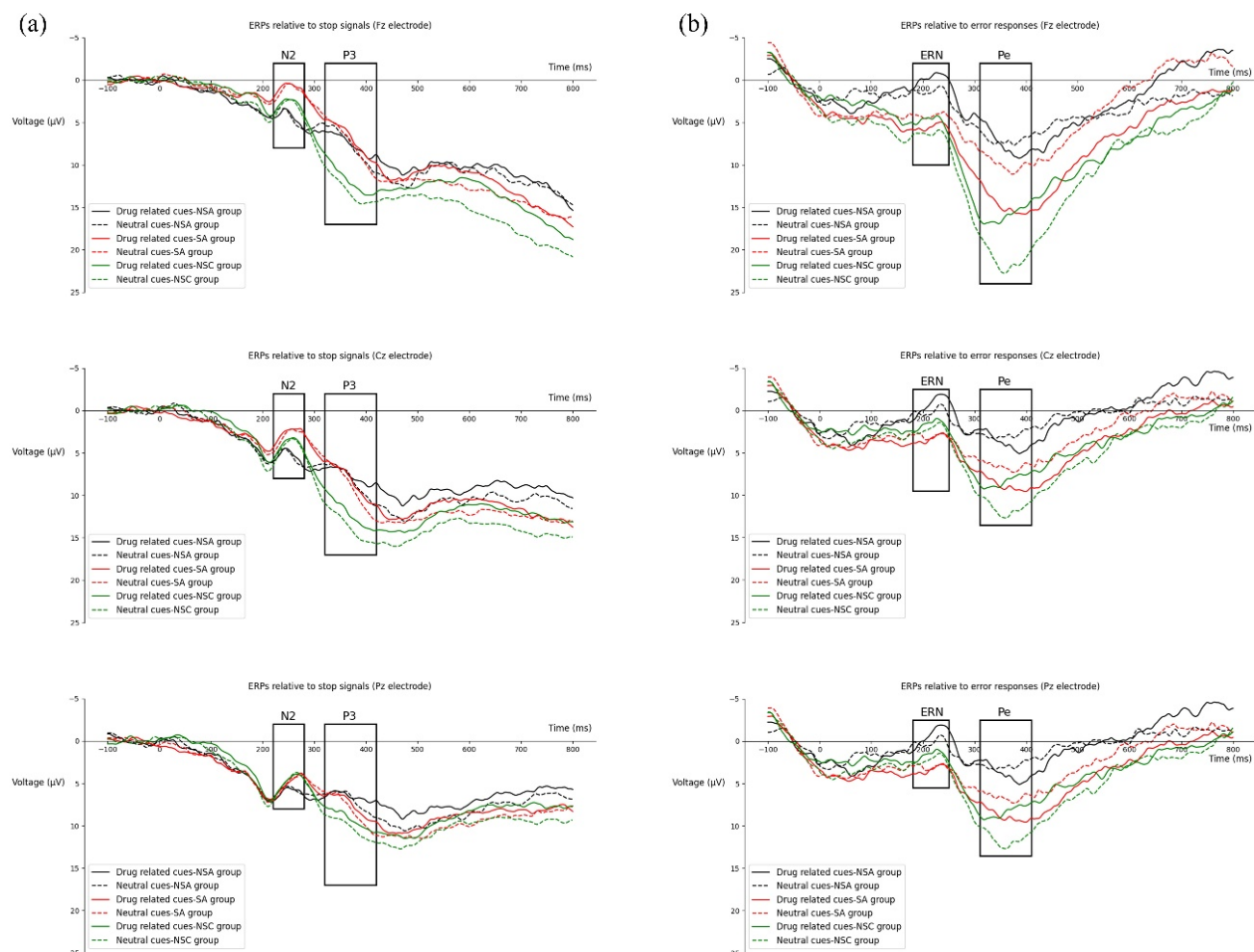


Fig 2. (a) Event-related potential (ERP) grand averages relative to the onset of the stop signal. (b) ERP grand averages relative to error responses.

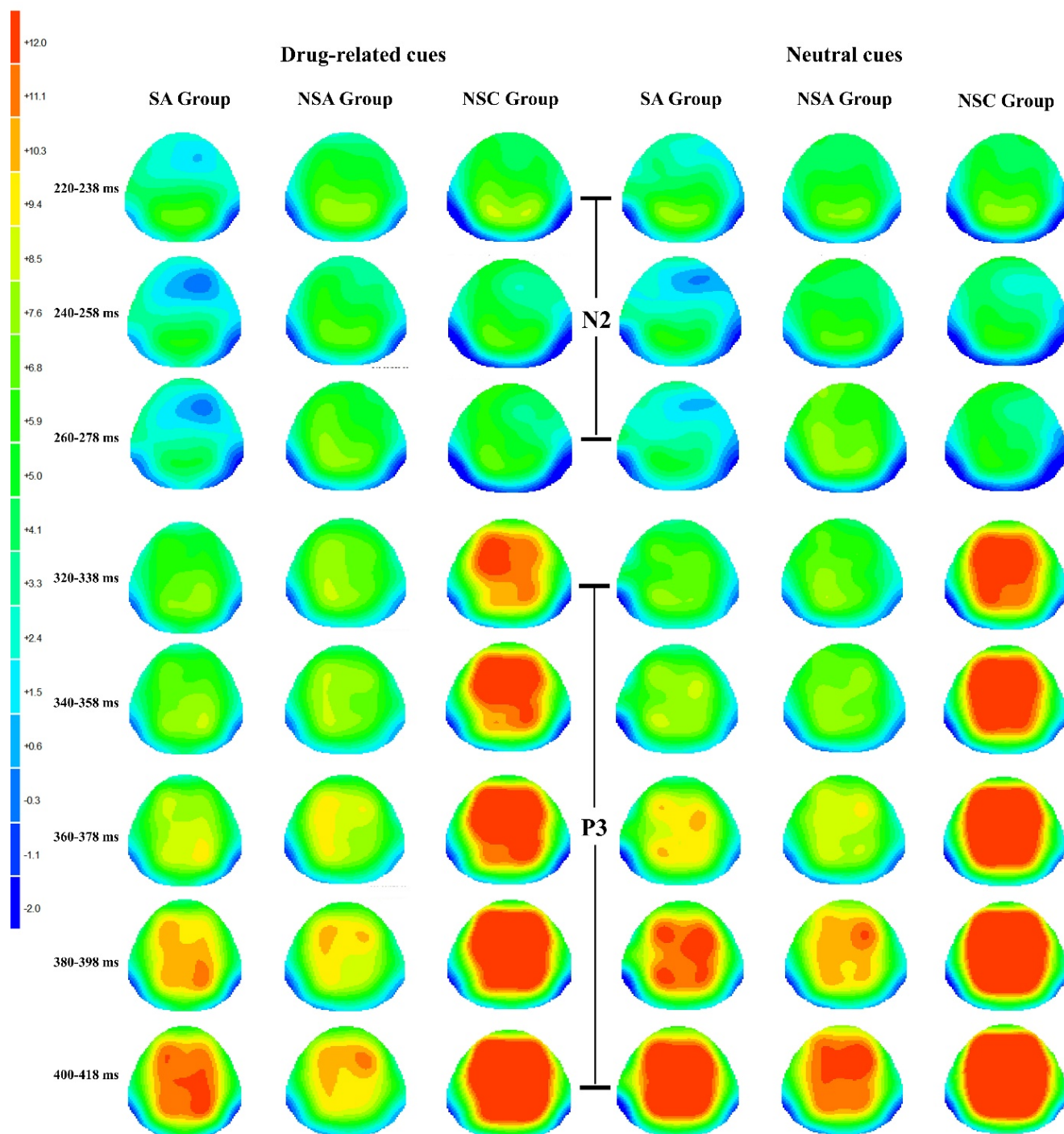


Fig 3. A depiction of the map series for N2 and P3 development for each group and cue type. Abbreviations: SA: smoking amphetamine; NSA: non-smoking amphetamine; NSC: non-smoking controls.

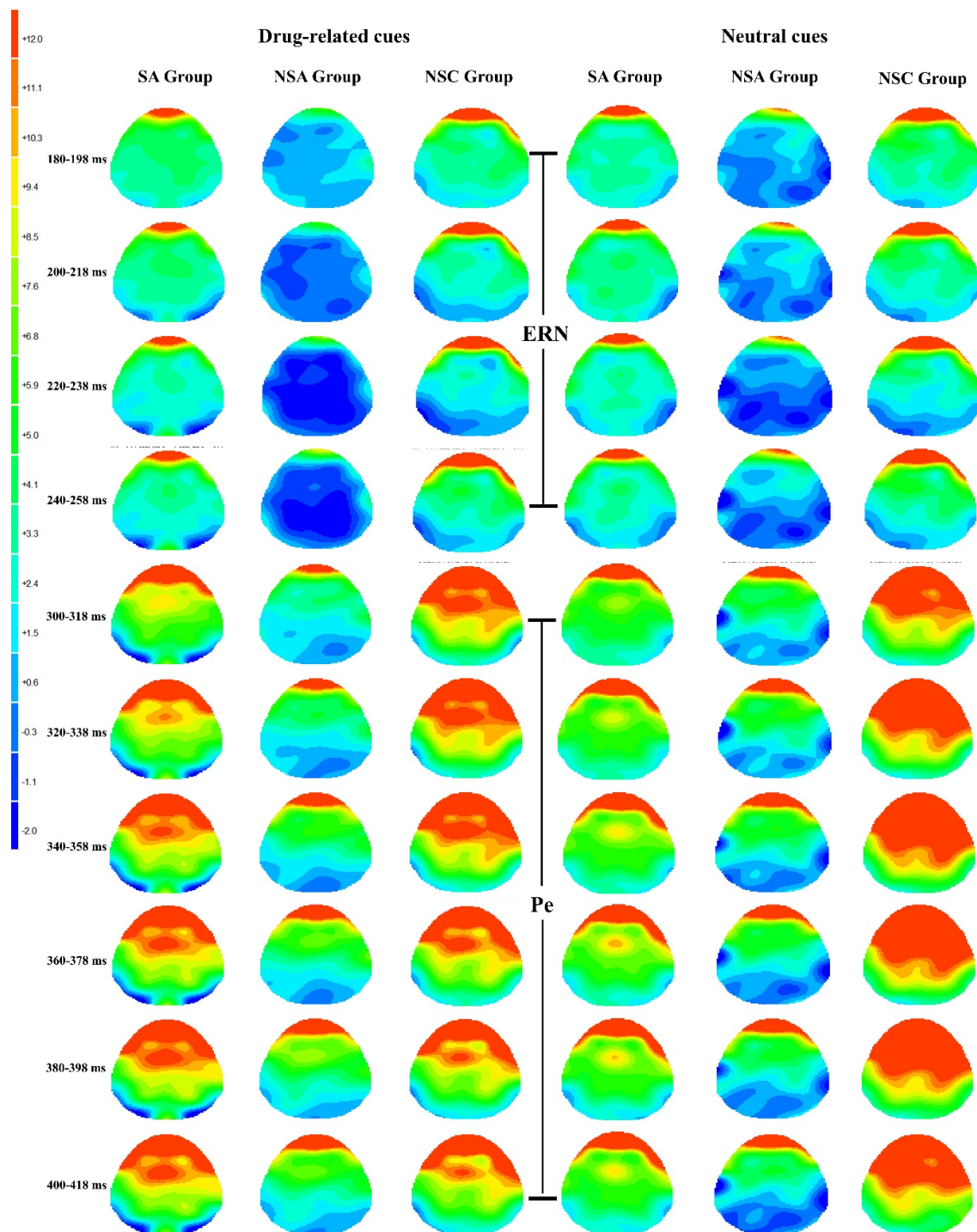


Fig 4. A depiction of the map series for ERN and Pe development for each group and cue type. Abbreviations: SA: smoking amphetamine; NSA: non-smoking amphetamine; NSC: non-smoking controls.

Correlation analysis

Correlation analyses were conducted between the number of cigarettes smoked per day and both behavioral and ERP data for the SA group (see Tables 3-6). The results showed a negative correlation between the number of cigarettes smoked per day and SSRT for the drug-related picture conditions ($r = -0.398$; $p = 0.044$). Additionally, the correlation analysis with ERP data revealed a negative correlation between the number of cigarettes smoked per day and N2 amplitude at Fz and Cz across both cue types (Fz: drug-related: $r = -0.529$, $p = 0.005$; neutral: $r = -0.538$, $p = 0.005$; Cz: drug-related: $r = -0.557$, $p = 0.003$; neutral: $r = -0.476$, $p = 0.014$).

Table 3. Correlation analysis between the number of cigarettes smoked per day and behavioral data

	<i>Drug-related cues</i>					<i>Neutral cues</i>				
	Go accuracy	Stop accuracy	GORT ^a	SSRT ^b	Post-error slowing	Go accuracy	Stop accuracy	GORT ^a	SSRT ^b	Post-error slowing
Pearson's correlation coefficient	0.197	0.168	-0.057	-0.398*	-0.019	0.162	0.272	0.184	-0.265	0.079
p value	0.334	0.412	0.782	0.044	0.926	0.428	0.178	0.368	0.191	0.703

^aGORT: Go Reaction Time. ^bSSRT: Stop Signal Reaction Time.

Table 4. Correlation analysis between the number of cigarettes smoked per day and ERP (Fz)

	<i>Drug-related cues</i>				<i>Neutral cues</i>			
	N2	P3	ERN	Pe	N2	P3	ERN	Pe
Pearson's correlation coefficient	-0.529**	0.070	-0.241	0.009	-0.538**	-0.026	-0.023	0.234
p value	0.005	0.735	0.236	0.967	0.005	0.898	0.911	0.249

Table 5. Correlation analysis between the number of cigarettes smoked per day and Cz ERP amplitudes

	<i>Drug-related cues</i>				<i>Neutral cues</i>			
	N2	P3	ERN	Pe	N2	P3	ERN	Pe
Pearson's correlation coefficient	-.557**	0.025	-0.147	0.025	-.476*	-0.035	0.036	0.192
p value	0.003	0.902	0.474	0.905	0.014	0.864	0.862	0.349

Table 6. Correlation analysis between the number of cigarettes smoked per day and Pz ERP amplitudes

	<i>Drug-related cues</i>				<i>Neutral cues</i>			
	N2	P3	ERN	Pe	N2	P3	ERN	Pe
Pearson's correlation coefficient	-0.200	-0.099	-0.062	0.093	-0.249	-0.169	0.049	0.189
p value	0.328	0.631	0.765	0.652	0.220	0.410	0.813	0.355

Discussion

This study used a drug-cued stop signal task to investigate inhibitory control and error monitoring for amphetamine users who smoked (SA), amphetamine users who did not smoke (NSA) and non-smoking control participants (NSC) with neutral and drug-related cue conditions. The data showed that while there were effects associated with amphetamine use for the two user groups, differences were also seen between these two groups, a difference that could have been caused by a modulatory effect of smoking.

For general effects, there was a main effect of cue type on behavioral performance of the task indexed by Go accuracy, with all groups showing significantly lower Go accuracy when drug-related cues were used compared to neutral cues, consistent with the different cues having a notable impact on the participants' performance.

In the electrophysiology data, the P3 ERP results showed that all amphetamine users (both SA and NSA) had significantly smaller P3 amplitudes than the NSC group. This finding was consistent with numerous previous addiction studies (Luijten et al., 2011a; Monterosso et al., 2005; Spronk et al., 2016; Yin et al., 2016) that reported

amphetamine users had a common impairment in later-stage inhibitory control, similar to other substance users. However, and contrary to our expectations, the N2 results showed that, under any cue condition, the SA group had significantly larger N2 amplitudes than the NSA group. Additionally, across all cue types, the best performance of the SSRT was seen in the NSC group, followed by the SA group, with the worst performance observed in the NSA group. Although statistically only the SSRT in the NSA group was significantly slower than the NSC group, the data indicated that not only was the inhibitory control of NSA group significantly worse than that of the NSC group, but it also indirectly reflected the SA group tending to perform better in inhibitory control than the NSA group. The findings from Stop accuracy also showed that the SA group had better Stop accuracy under drug-related cues, suggesting that SA group performed better in inhibitory control in the drug-related cue context. These results contrast with most previous studies on smokers or substance users, which typically reported impaired inhibitory control (Hou et al., 2024; Luijten et al., 2011a; Sokhadze et al., 2008; Spronk et al., 2016; Yin et al., 2016). However, given the lack of studies on smoking amphetamine users specifically, this result may represent a novel finding for this particular group of substance users.

Combining the ERP and behavioral results, the nature of the better inhibitory control observed in SA group may relate to the increased N2 amplitude in the early stages of inhibition. As an indicator of early inhibitory control, N2 relates to mismatch detection or conflicts between sudden changes in the environment and ongoing behavior, which plays a role in response inhibition (Cheng et al., 2019; Gajewski & Falkenstein, 2013; Kok et al., 2004). Thus, even though the SA group exhibited impairment in the later inhibitory control stage with smaller P3 amplitudes, the increase in N2 amplitude during the early phase could reflect a compensatory mechanism related to these processes and leading to enhanced overall inhibitory control effectiveness resulting in better task performance. The correlational analysis further revealed the specificity of the improvement in inhibitory performance in the SA group. The outcome of this analysis showed a negative correlation between the number of cigarettes smoked per day and the SSRT under drug-related cues, indicating that higher the number of cigarettes smoked per day was associated with a faster SSRT for this condition. On the other hand, the number of cigarettes smoked per day was negatively correlated with N2 amplitude under both drug and neutral cues, suggesting that regardless of cue condition, higher the number of cigarettes smoked per day was associated with larger N2 amplitudes (since N2 is a negative wave). These two findings may reflect that higher the number of cigarettes smoked per day in SA led to greater increases in the early inhibitory N2 amplitude, potentially improving their SSRT. Additionally, the negative correlation between the number of cigarettes smoked per day and SSRT under drug cues was consistent with the Stop accuracy results, showing that the SA group had better inhibition for drug cues. Therefore, the increase in early inhibitory N2 amplitude in SA group was associated with enhanced inhibitory control behavior, with this enhancement being even more pronounced in the presence of drug-related cues. It should be noted, of course, that these are all correlations in a cross-sectional study and so do not prove that the differences are a causal effect of cigarette consumption. Further investigation into this with more individuals or as part of a longitudinal study may help to determine the underlying cause of the patterns of data seen here.

Previous neuroimaging evidence has suggested that both smokers (Brody et al., 2002; Engelmann et al., 2012) and also drug addicts had increased activity in the entire mesocorticolimbic system when exposed to drug cues, with this including the amygdala, striatum, and ACC (Yalachkov et al., 2012). Such ACC activation induced by cues may be related to the increased N2 amplitude observed in the SA group in this study. ACC activation is associated with anxiety, alertness, and arousal (Critchley et al., 2001; Naito et al., 2000), and is involved in

cognitive control and conflict monitoring (Nee et al., 2007). The N2 component is thought to originate from the ACC (Kok et al., 2004) and, as mentioned above, reflects a mismatch or conflict between sudden environmental changes and ongoing behavior (Cheng et al., 2019; Gajewski & Falkenstein, 2013; Kok et al., 2004). We speculate that the simultaneous addiction to smoking and amphetamines strengthened the ACC response in the SA group when faced with cues, leading to an enhanced N2 amplitude. However, the ERN, another conflict indicator in error monitoring originating from the ACC (Holroyd and Coles, 2002), did not show the same performance differences between the SA and NSA groups. This may indicate that ACC activation in response to cues was unable to sustain the same enhancement for subsequent error monitoring, and that the cognitive resources from the increased ACC activation were depleted during the early conflicts in the inhibitory control. However, this hypothesis requires further testing in future research.

For error monitoring, although no group differences were found for post-error slowing or ERN amplitudes, the Pe results showed that under neutral cues, the Pe amplitudes of all amphetamine users (both SA and NSA) were significantly smaller than those of the NSC group. This suggested that for general neutral contexts, amphetamine users were not impaired during the early phase of error processing but their later error awareness and motivational attribution of errors was impaired, leading to a reduced ability to correct errors. Interestingly, the SA group showed significantly larger Pe amplitudes under drug cues than under neutral cues, which was not seen in the NSA group. Contrary to our hypothesis, this finding may suggest that Pe, which is related to conscious error awareness, was heightened in the SA group when facing drug cues. This may indicate that the SA group, but not the NSA group, exhibited enhanced subjective awareness and evaluative processing of errors in the context of drug cues. SA users may subconsciously recognize drug cues as high-risk or indicative of loss-of-control behavior, resulting in stronger internal error evaluation mechanisms to potentially improve subsequent behavior.

When summarizing both inhibitory control and error monitoring results, the SA group outperformed the NSA group, which was contrary to our initial expectations. The findings suggest that when amphetamine use is combined with smoking, although impairments still exist when compared to non-drug-using controls, better cognitive performance is seen than in users of amphetamines alone. Although previous research has generally demonstrated that nicotine impairs inhibitory control and error monitoring (Luijten et al., 2011a; Luijten et al., 2011b; Yin et al., 2016), several studies have also shown that nicotine can regulate anxiety and depression (Xiao et al., 2018) and may offer neuroprotection in Parkinson's disease (Kumari et al., 2025; Rose et al., 2024). For long-term drug users, downregulation of dopamine receptors in the striatum leads to a desensitized dopamine system and blunted responses to natural rewards (Volkow et al., 2016). Notably, there is significant overlap between striatal cholinergic interneurons and the terminals of ascending nigrostriatal dopaminergic projections from the substantia nigra (Zhou et al., 2002). Thus, nicotine use may enhance dopamine release (Kumari et al., 2025), exerting a compensatory effect on the desensitized striatal dopamine system caused by chronic drug use and resulting in improved cognitive performance. However, further research is needed to clarify the timing, dosage, and chronic effects of nicotine use on these cognitive functions, particularly when nicotine is used in combination with other substances that affect the central nervous system. Given the lack of prior studies specifically examining cognitive functioning in amphetamine users who smoke, our findings may represent a novel contribution to the field.

There were some limitations in our study. First, as the aim was investigation of the effects related to amphetamine use, there was no smoking control group in the study design. Although previous literature has described cognitive deficits associated with smoking, the current study cannot directly differentiate the results of the SA group from a

smoking control group. Therefore, future studies should ideally include a smoking control group to better address this. Furthermore, this study only used drug-related cues as the manipulation to induce craving. Smoking-related cues may also trigger craving in smokers, but this cue condition was not included in the current study and might also be a beneficial addition to future work to more thoroughly examine the cognitive function differences between groups in different cue contexts.

Conclusions

Inhibitory control, measured with behavior and electrophysiology, differed between amphetamine users and control participants as well as, importantly, differing for amphetamine users depending on whether or not they also smoked. The group of amphetamine users who smoked (SA) showed differences in inhibitory control and error monitoring compared to amphetamine users who did not smoke (NSA). Future work should aim to directly assess whether the difference seen for SA individuals is a *consequence* of smoking/nicotine intake in conjunction with amphetamine use. It may be, but is not currently possible to be certain that, this group has compensation, due to smoking, for deficits in later inhibitory control as a result of increases in the processes indicated by the N2 ERP component during the early inhibition phase, a phenomenon that is more pronounced under drug-related cues. In line with this, the frequency of smoking was negatively correlated with both N2 amplitude and SSRT, further supporting the link between smoking behavior and enhanced inhibitory control in these amphetamine users. Furthermore, the SA group exhibited an increase in Pe amplitude when drug-related cues were used, unlike the NSA group, which may reflect enhanced subjective error awareness and evaluative processing in drug-related contexts. This heightened Pe response may mean that the SA group allocates more cognitive resources to processing drug-related errors, potentially as a subconscious strategy to mitigate future lapses. Given that there are no previous studies assessing such evidence in smoking amphetamine users, these results can be considered as new findings in this area.

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