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Trial-by-trial Fluctuations in Brain Responses to Stress Predict Subsequent Smoking Decisions that Occur Several Seconds Later

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Abstract

Background: To investigate the neurobiological mechanisms that determine self-regulation of smoking urges when a person encounters stress, we investigated brain network interactions of smoking self-regulation by employing a real-time smoking (nicotine delivery) decision paradigm and a brain-as-predictor neuroimaging approach.

Methods: While in the fMRI scanner, twenty-five cigarette smokers who abstained from smoking overnight made 200 real smoking decisions regarding whether or not to take a puff of an electronic cigarette during three different stress conditions (cognitive, emotional, and no stress conditions). Cognitive stress was induced by a concurrent working memory load and emotional stress was induced by manipulating a chance of aversive electric shock.

Results: Behaviorally, both cognitive and emotional stress manipulations increased the probability of making a decision to smoke (i.e., taking a puff). In MRI trial-by-trial analyses, the dorsolateral prefrontal cortex (dlPFC) activity measured at the time of the stress cue significantly predicted future smoking decisions that occurred several seconds later. Furthermore, the influence

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of dlPFC activity on smoking decisions was mediated by the ventral striatum activity at the time of smoking decisions.

Conclusions: Our study demonstrated that brain responses at the time of stressful moment determine subsequent trial-by-trial smoking decisions by systematically altering brain executive (dlPFC) and reward (ventral striatum) system network activities. Our results further suggest potential translational importance of neuroscientific approaches to predicting self-regulation failures at critical stressful moments.

Keywords

Smoking; Self-control; Stress; Decision-making; trial-by-trial analysis; fMRI

Introduction

Cigarette smoking, which increases one's risk for cancer, remains one of the most serious health hazards in the United States (1). Despite the clear health benefits of quitting (2) smoking cessation is notoriously difficult to achieve (3) and the decision to quit or reduce smoking does not guarantee success. Clinical studies indicate that urges to smoke fluctuate continuously and at a certain critical moment, such as being exposed to acute stressful events, self-regulation mechanisms that have been inhibiting smoking urges become vulnerable and often fail (4–6). Indeed, stress has been identified to be a primary contributor to relapse (7, 8). Although smokers' response to stress has been clearly linked to smoking behavior, previous studies could not explain the precise neurobiological mechanisms of smoking self-regulation that could potentially predict or proactively prevent self-regulation failures at a particular moment.

The dual processing model of self-regulation that has also been widely applied in addiction research (9) views self-regulated decisions as outcomes of a dynamic interplay between a habitual motivational (incentive processing) system that pursues immediate rewards and a goal-directed executive (cognitive control) system that pursues the long-term best interests (10–13). When self-control weakens, or the urge to smoke becomes too strong and exceeds the available limits of self-control capacity, regulation may fail (i.e., smoking relapse). Also, an acute stress experience can have a critical effect on the moment-to-moment interplay between these two systems. Because acute stress not only increases cravings (or anticipated rewards) but also decreases the ability to regulate smoking urges (13–16), a balanced state between the executive control system and the motivational system can be easily disrupted. Furthermore, the self-control operations that override or regulate immediate desires consume capacity-limited resources (17, 18), and stress management operations that flexibly respond to situational challenges through executive functioning also consume capacity-limited resources (19). Thus, in the capacity-limited resources perspective, the effect of stress on self-regulatory smoking decisions at a particular moment of a stressful encounter can be critically dependent on the current availability of shared executive control resources as well as, the magnitude of stress-induced enhanced urges to smoke.

Recent neuroimaging studies propose that the brain's reward network and executive network constitute neurobiological bases of the dual processing systems (20–23). The prefrontal

cortex has been suggested as a key brain region for the executive cognitive control as a part of the deliberative system (22, 24). Studies also show that self-regulation and resisting smoking urges involves the reward and motivational circuits that include the ventral striatum and the ventromedial prefrontal cortex (vmPFC) (25, 26) as well as executive cognitive control circuits that include the dorsolateral prefrontal cortex (dlPFC) (27, 28). Interestingly, acute stress experience modulates brain activation in executive cognitive control circuits (19, 29, 30) as well as reward and motivational circuits (31–33). While existing studies have shown that “on average (between groups or conditions)” the stress is linked with drug use (4–6) and brain reward and executive networks are involved in (19, 29–33), the precise nature of moment-to-moment interactions between these two networks that predict self-regulatory decisions “at a particular time” is not known yet.

Scientific investigation of neurobiological mechanisms that determine moment-to-moment smoking self-regulation outcomes will have important clinical implications. However, due to technical difficulties including but not limited to magnetic resonance (MR) safe smoking delivery systems and potential for participant movement artifacts, the neural correlates of real-time smoking behaviors have rarely been studied (34–36) - these previous studies have simply demonstrated initial technical feasibility or group-level averaged neural correlates of smoking with no experimental manipulation. To investigate the neural mechanisms of real smoking self-regulatory behaviors, we presented experimental self-regulatory challenges in the MRI environment by developing a novel smoking choice paradigm in which chronic cigarette smokers abstained from smoking overnight and make a series of e-cigarette smoking choices with experimental stress manipulations. While there are inevitable limitations to represent naturalistic smoking self-regulation behaviors, our experimental paradigm provides the first opportunity to investigate single trial-level smoking (nicotine delivery) self-regulatory decisions in neuroimaging environments.

The main goal of this study was to elucidate the neurobiological mechanisms of smoking self-regulatory decisions under stressful situations on a moment-to-moment basis, which allows us to use brain responses to statistically predict “trial-level” events in advance rather than to describe averaged group-level differences subsequently. Specifically, we postulated that how the brain responds to stress at a particular stressful moment (that taxes capacity-limited shared executive control resources) determines subsequent smoking-related motivational values and self-regulation outcomes (decision to smoke or not). In other words, we hypothesized that the moment-to-moment brain interactions between executive (dlPFC) and reward (ventral striatum and vmPFC) network areas when encountering a stressor would determine the subsequent trial-by-trial smoking self-regulatory decision outcomes (Figure 1). Whereas the smoking self-regulatory decisions would be predicted by the preceding activity in the brain executive network (i.e., executive control response to stressor), this relationship would be, at least partly, mediated by the activity in the brain reward network at the time of choices, given that the moment-to-moment smoking reward signals or motivational urges to smoke are directly related to smoking decisions.

Methods and Materials

See SI for detailed information.

Participants

Twenty-six of 30 participants met the inclusion criteria (>10 cigarettes/day; currently not looking for stop-smoking treatment; between 18~50 years old; able to speak English; right-handed; able to have standard fMRI procedure; enjoyed the e-cigarette trial; complied with overnight abstinence requirement prior to fMRI). One participant who failed to follow fMRI experimental task instructions was excluded from analysis, resulting in a total of twenty-five participants ($M = 29.1$ years, $SD = 6.7$; 40% female) for our data analyses. All participants provided informed consent, as approved by the Human Subjects Committee of the University of Kansas Medical Center and the Institutional Review Board of the University of Missouri - Kansas City.

Experimental Tasks

Inside of the MRI scanner, participants who abstained from smoking overnight (confirmed by measuring exhaled breath Carbon Monoxide level) made a total of 200 of real smoking decisions whether to smoke (i.e., inhale on the e-cigarette) or not. We chose this number of trials to maximize statistical power in trial-by-trial level analyses while still ensuring all the trials could be completed within one fMRI session without discomfort (total scanner time of ~ 90 min). Besides the payment for their study participation, participants were given additional money (\$20) that they could use to pay for a puff of an e-cigarette (at a cost of 10 cents/puff) in the smoking decision trials. Unused money was added to their regular payment after the experiment. To encourage real self-regulation challenges during our experimental smoking decision task, participants were instructed to arrive 2 hours before their MRI scanning schedule and to stay an additional 1-hour after the MRI session during which smoking was not allowed. Thus, if participants who had to abstain from smoking overnight could successfully wait or inhibit their urges to smoke for ~ 3 hours from the beginning of fMRI task, they did not have to spend any extra money by paying a relatively high price for each drag, which constitutes experimental smoking self-regulation challenges in our study.

As described in Figure 2A, the smoking choices were presented in three different types of dual-task conditions. Cognitive stress was induced by a concurrent working memory load (i.e., delayed match-to-sample working memory task), and emotional stress was induced by manipulating the chance of receiving an aversive electric shock (individually set to highly unpleasant but not painful level). The smoking decision task was completed through 4 functional runs, with each run lasting ~ 16 min. Each run included 20 smoking choice trials in the cognitive stress condition (10 easy, 10 hard), 20 smoking choice trials in the emotional stress condition (10 low, 10 high), and 10 smoking choice trials in the non-stress (fixation presentation) condition, with each trial lasting 7-TR duration (17.71 sec).

The structure of the real smoking choice within our dual-task paradigm was identical in all three conditions (Figure 2B). Participants were instructed to monitor their mind and body's states naturally at the very moment of each smoking choice, and then provide their smoking decision using a 4-point scale ("strong no, no, yes, strong yes") during a maximum time limit of 2.5 sec. If participants responded "yes" or "strong yes" (i.e., unsuccessful self-regulation), after a fixation screen of 1 ~ 3 sec duration, the valve connected to the e-cigarette was opened for 3 sec with a word "inhale" on the screen to allow participants to

take a puff of e-cigarette. If participants responded “no” or “strong no” (i.e., successful self-regulation), a fixation screen of 1~3 sec duration continued for additional 3 sec, and the valve remained closed.

Before 4 runs of the main task, participants completed a short practice run (10 smoking choice trials). The practice task was provided to help participants become familiar with our experimental task and devices (nicotine delivery system, shock delivery system, psychophysiological measurements, and button pads), and also used for the Region-of-interest (ROI) selection in the fMRI analyses. If needed, the experimental set-up was adjusted again before the main task.

fMRI data acquisition and data analysis.

Anatomical and functional scans were acquired using a Siemens 3T Magnetom Skyra scanner at the Hoglund Biomedical Imaging Center of University of Kansas Medical Center. Analysis of fMRI data was performed using the AFNI package (37) as well as custom MATLAB scripts.

Although we performed and report results of whole-brain analysis (see SI results) for completeness, the main goal of our study was to investigate the moment-to-moment brain interactions between executive (dlPFC) and reward (ventral striatum and vmPFC) network areas that determine the subsequent trial-by-trial smoking self-regulation outcomes. Therefore, we performed various Regions of Interest (ROIs) analyses with trial-by-trial estimates as well as averaged BOLD responses in these three areas of interest (See SI for details).

Results

See SI for results of whole-brain analyses to examine task-related activations

During the fMRI task, participants chose to take a puff of an electronic cigarette on average 45% (90 trials) of all smoking choices (200 trials). There was no significant difference across 4 runs, $F(3,72) = 1.05$, $P = .377$, which ruled out a potential order effect (Table S2). As expected by employing a real smoking decision paradigm, self-reported craving to smoke was significantly reduced from the beginning to the end of the fMRI task, $t(24) = 3.27$, $P = .003$. Across individuals, the proportion of decisions to smoke (“yes” and “strong yes”) was positively correlated with baseline nicotine dependence levels measured by the Fagerstrom test for nicotine dependence (FTND), $r(23) = .40$, $P < .049$ (Figure 3). This suggests that participants with higher levels of nicotine dependence more frequently chose to smoke e-cigarettes during our experimental task.

Main behavioral results

To test our main behavioral hypotheses for the influence of stress on smoking self-regulation, we first examined the effect of cognitive and emotional stress on real smoking decisions. Results revealed that on average participants more frequently chose to smoke in the cognitive and emotional stress conditions (Table S2 and Figure 4). When compared to the non-stress control condition, participants showed an 8.7% ($SD = 18.5\%$) increase in the

number of smoking decisions in the cognitive stress condition, $t(24) = 2.34$, $P = .028$, and a 7.1% ($SD = 17.0\%$) increase in the number of smoking decisions in the emotional stress condition, $t(24) = 2.08$, $P = .048$. However, there was no significant difference between the cognitive and emotional stress conditions, suggesting that both stress conditions had similar effects on smoking decisions, $t(24) = .454$, $P = .660$. When we checked subtype trials of each stress condition, no significant differences were observed by cognitive load levels (easy vs. hard), $t(24) = .41$, $P = .684$ (see Table S3 for behavioral data of secondary working memory task), and shock aversiveness levels (low vs. high), $t(24) = 1.03$, $P = .316$. Also, there was no significant interaction effect, $F(1,24) = .10$, $P = .753$. Therefore, we pooled the two subtypes for subsequent analyses to increase statistical power. We also found significant effects of stress on reaction time data. Compared to the non-stress condition, participants' decision times were significantly faster in both cognitive stress and emotional stress conditions, $t(24) = -3.84$, $P < .001$; $t(24) = -3.42$, $P = .002$, respectively, suggesting that the stress manipulation increased behavioral decision impulsivity (i.e., faster RT). Again, there was no significant difference of reaction times between the two stress conditions, $t(24) = -.82$, $P = .418$, suggesting that both stress conditions had similar effect on behavioral decision impulsivity. When compared separately for yes and no decisions, yes decisions in both stress conditions occurred faster than yes decisions in the control condition, $t(24) = 3.63$, $P = .001$; $t(24) = 3.04$, $P = .006$. On the other hand, no decisions in the cognitive stress condition were significantly faster, $t(24) = 2.07$, $P = .049$, but no decisions in the emotional stress condition were not significantly different from the control condition, $t(24) = 1.89$, $P = .071$.

Mean ROI responses comparisons of smoking decisions

To test our main research hypotheses, we analyzed our data in terms of ROIs using two different approaches. We performed mean ROI analyses that collapsed across trials first, and then conducted trial-by-trial analyses (see next section). To focus our network hypotheses, we performed ROI analyses for brain executive (dlPFC) and reward (ventral striatum, vmPFC) regions to compare mean evoked brain responses between successful ("no" or "strong no" decisions) and unsuccessful ("yes" or "strong yes" decisions) efforts to regulate smoking urges. As described in SI Methods, these ROIs were defined independently from the main tasks.

We examined the mean brain activity in the ROIs at the time of the presentation of the stress cue and at the time of the decision to smoke, separately for each time window (GLM-4). As shown in Table S7, at the time of cue presentation period, the dlPFC ROI showed increased activity in the trials in which a participant subsequently made smoking decisions compared to the trials in which they subsequently made non-smoking decisions, $t(24) = 3.39$, $P = .002$. However, the vmPFC ROI showed the reverse pattern of activity, $t(24) = -2.36$, $P = .027$, which might reflect a possible reciprocal relationship between the cognitive and affective brain regions (38). When we examined the period of time during which smoking decisions were made, both ventral striatum and vmPFC ROIs showed increased activity in smoking decision trials compared to non-smoking decision trials, $t(24) = 3.59$, $P = .001$; $t(24) = 2.09$, $P = .048$.

To further examine how brain activity in the ROIs systematically varied over time across successful and unsuccessful smoking self-regulation decisions in our dual-task paradigm, we constructed time-series graphs for the beta-weights (effect size) within the ROIs separately for two smoking self-regulation outcomes (Figure 5). Consistent with the previously described ROI results, the mean dlPFC ROI activity differed significantly between successful and unsuccessful smoking self-regulation trials from the time of the cue presentation onward, $t(24) = 3.58, P = .005$; $t(24) = 3.77, P = .003$; $t(24) = 3.02, P = .018$ (for each TR; Bonferroni corrected), and the same pattern of activities continued during the delay period, $t(24) = 2.52, P = .057$; $t(24) = 2.79, P = .031$; $t(24) = 2.92, P = .023$ (for each TR; Bonferroni corrected). The mean dlPFC ROI activity didn't show a significant difference at the time of the smoking choice, suggesting that cognitive effort for decision process itself was not different between successful and unsuccessful smoking trials. Contrary to what was observed with the dlPFC ROI, the mean ventral striatum ROI activity didn't show a significant difference at the time of cue presentation, but showed significant differences at the time of the smoking choice, $t(24) = 2.93, P = .022$; $t(24) = 3.36, P = .008$; $t(24) = 2.81, P = .029$ (for each TR; Bonferroni corrected). However, the mean vmPFC ROI activity didn't show any significant difference in our time-series beta-weight analyses, all $P > .05$. Note that in our experimental paradigm, the vmPFC ROI responses were negative (below baseline), consistent with previous reports that the brain responses in this area decrease relative to baseline or control state during cognitively demanding mental operations (39).

Trial-by-trial ROI analyses to predict subsequent smoking decisions

To evaluate whether smoking self-regulation was statically predicted by trial-by-trial fMRI fluctuations, we first performed robust logistic regression analyses and separately modeled the probability of smoking decisions (self-regulation failure) as a function of single-trial ROI amplitude (estimated for each trial separately; see Experimental Procedures) at the time of cue presentation and at the time of smoking decision. A robust logistic regression model was estimated for each individual, and then one-sample t -tests with regression beta-weights were performed across individuals for group-level inference (Table S8 and Figure 6; individual data are shown in Figure S4 and S5). As hypothesized, the mean logistic slope (beta weights) of dlPFC ROI, which represents the strength of the predictive effect, was significantly greater than zero (i.e., chance level) at the time of the cue presentation, $\beta = .20, SE = .06, t(24) = 3.47, P = .002$. Importantly, this dlPFC ROI finding demonstrates that the dlPFC brain activity measured 2~4 sec before the decision period reliably predicted subsequent smoking self-regulation failures. The logistic regression prediction model based on ventral striatum and vmPFC ROI fluctuations at the time of the cue presentation did not show a significant effect. On the other hand, the mean logistic slopes of ventral striatum and dlPFC ROIs at the time of smoking decision, were significant, $\beta = .17, SE = .06, t(24) = 2.91, P = .008$; $\beta = .15, SE = .06, t(24) = 2.49, P = .020$, suggesting both brain executive and reward networks were involved in smoking self-regulation. The vmPFC ROI did not show a significant effect in the trial-by-trial ROI analysis.

To further explain the brain network interactions, we carried out additional statistical robust mediation analysis with single trial ROI amplitude estimates within these two ROIs. Most

importantly, we speculated that the activity in the brain executive network (executive control resources) at the time of cue presentation would systematically influence the effect of the activity in the brain reward network (motivational value system) on behavioral outcomes of smoking self-regulation (i.e., whether to smoke or not on individual trials) at the time of smoking decision. As shown in Figure 7, the effect of the dlPFC activity (measured at the time of the cue presentation) on smoking self-regulation, c path coefficient (total effect) $M = .24$ ($SE = .08$), $t(24) = 2.83$, $P = .009$, was mediated by the effect of the ventral striatum activity (measured at the time of smoking decision), a path coefficient $M = .26$ ($SE = .02$), $t(24) = 15.71$, $P < .001$; b path coefficient $M = .20$ ($SE = .09$), $t(24) = 2.24$, $P = .034$; $a \times b$ path coefficient $M = .06$ ($SE = .03$), $t(24) = 2.21$, $P = .037$. The direct path c' coefficient was also significant, $M = .20$ ($SE = .08$), $t(24) = 2.44$, $P = .022$, indicating a partial mediation effect rather than a full mediation effect by the ventral striatum.

Discussion

Our primary goal was to identify and characterize precise brain network mechanisms that determine smoking self-regulatory decisions on a *moment-to-moment basis* so that fluctuations in fMRI responses in response to stress could be systematically linked to variability in behavioral self-regulation outcomes. At the behavioral level, the stress manipulation significantly increased the likelihood of participants making a decision to smoke, demonstrating a direct association between laboratory-induced stress and subsequent increase of smoking (nicotine delivery) decisions. Functional neuroimaging data complemented our behavioral observations. In terms of mean brain responses, we confirmed that both brain executive and reward networks including the dlPFC and ventral striatum were involved in smoking self-regulation decisions. Importantly, in trial-by-trial analyses, the dlPFC activity measured at the time of the display of the stress cue statistically predicted smoking decisions that occurred several seconds later. Furthermore, this influence of dlPFC activity on smoking decisions was mediated by the ventral striatum activity at the time of smoking decisions. In other words, our findings demonstrate that the smoking self-regulation decisions can be determined by how brain executive and reward systems interact before and at the moment of a stressful condition.

Self-regulation is important for engaging in healthy behaviors, but the capacity to resist momentary temptations can be affected by contextual factors. In particular, psychological stress can critically compromise our self-regulatory behaviors in everyday life. In our study, both cognitive and emotional stress manipulations produced similar negative effects on smoking self-regulation decisions. A limited-resource model of self-regulation and executive function suggests that both rely upon limited resources (17, 18), so that engaging in acts that consumes these resources undermines subsequent psychological operations that share the same resources. Acute stress and self-regulation processes may consume the same executive control resources which are limited in capacity. When executive control resources were already occupied by cognitive or affective stress conditions, consequently fewer resources were available to override smoking urges at the moment of decisions. Therefore, consistent with the dual-process model of self-control (9–12), the limited or inefficient resources remained for self-regulation of smoking decisions (which were indirectly postulated by the dlPFC activity taxed by stress manipulation at the time of cue presentation) could result in

more frequent smoking self-control failures. Moreover, as suggested by previous behavioral studies (14–16) as well as our neuroimaging findings, the motivational signal for immediate rewards might also be enhanced by acute stress.

Our findings are also largely compatible with previous studies that have found that stress impairs prefrontal cognitive functions that are fundamental for goal-directed regulatory decisions (40), biases decisions toward habitual actions (41), and amplifies craving signals toward immediately rewarding options (42, 43). However, while previous studies identified basic neural circuits involved in motivation and self-regulation (44–46), they do not explain the neural mechanism of *moment-to-moment “real” self-control exertion* under acute stress due to technical obstacles to implement real choices in the MRI environment and limitations of traditional “averaged” response-based approach.

In general, although there are some debates over the limited-resource model of self-regulation to be further investigated (47–50), our findings support the dual-processing model (10–12) that explains self-control failures of smoking urges (i.e., smoking decisions at stressful moment) as a consequence of a momentary overwhelming of the executive control system by the motivational system. Acute stress can negatively influence self-regulatory behaviors by both enhancing the impact of immediate rewards and reducing the efficacy of self-control that is consistent with long-term goals (43). As expected by the dual-processing model (10–12), both dlPFC and ventral striatum activities significantly determined smoking decisions. Moreover, in our network analysis, the influence of dlPFC activity on smoking decisions was partially mediated by ventral striatum activation at the time of making a smoking decision.

Overall, our first-of-a-kind study successfully demonstrated that how the brain responses at the time of stressful moment determine the ‘real’ smoking decisions through both direct and indirect paths that involves the brain executive and reward networks. However, there are several caveats. First, while we successfully demonstrated the brain network interactions that statistically predicted subsequent smoking decisions that occurred several seconds later, our findings themselves do not prove a causal relationship or the best model that includes all relevant paths that were not included in our relatively simple network model. Second, due to technical challenges with the MRI environment, trial-by-trial stress experiences were not directly assessed, while our study measured trial-by-trial dlPFC activities to indirectly index executive control resources taxed by stress. Third, for experimental implementation, our study manipulated smoking (nicotine delivery) self-regulation motivation by charging a relatively high cost (10 cents per puff), which might not fully represent a naturalistic smoking self-regulation process (e.g., relapse during abstinence).

In spite of these limitations, the brain network interactions identified in this study could be potentially informative for other self-control related lifestyle behaviors (e.g., obesity, alcohol and drug abuse, etc.). To evaluate the generalizability and external validity of our findings, future studies are needed from other clinical populations in naturalistic self-regulation situations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Brain network interaction model of smoking self-regulation. The effect of brain executive network responses to stressful events on subsequent smoking self-regulation was hypothesized to be mediated by the brain reward network responses, importantly when trial-by-trial fluctuations in brain responses and behavioral decisions were considered.

Figure 2. Experimental tasks.

(A) During fMRI scans, participants made real smoking decisions in cognitive stress, emotional stress, and control conditions. The order of cognitive stress, emotional stress, control blocks was randomized. (B) For each smoking decision trial, participants entered their decision by using a 4-point scale. If participants entered yes or strong yes, the switch value connected to e-cigarette was opened for 3 sec to allow participants to take a puff.

Figure 3. Smoking decision and nicotine dependency.

Participants' level of nicotine dependence measured by Fagerstrom Test for Nicotine Dependence (FTND) was positively correlated with the proportion of yes responses regarding the decision on whether or not to smoke.

Figure 4. Box-and-whisker plot of behavioral smoking decision data.

(A) In both cognitive stress and emotional stress conditions, participants chose to smoke more frequently than in the control condition. (B) In both cognitive stress and emotional stress conditions, participants made smoking decisions more quickly than in the control condition. The symbol X denotes the mean. * $P < .05$, ** $P < .01$ (two-tailed).

Figure 5. dlPFC, ventral striatum, and vmPFC ROI time series of beta weights.

(A) dlPFC ROI time series of the beta-weights. The dark gray box represents a visual aid for the approximate cue period, adjusted for the fMRI hemodynamic response lag. (B) ventral striatum ROI time series of the beta-weights. (C) vmPFC ROI time series of the beta-weights. The dark gray box represents a visual aid for the approximate smoking decision period, adjusted for the fMRI hemodynamic response lag. All error bars denote the standard error of the mean computed across participants. * $P < .05$, ** $P < .01$, *** $P < .005$ (one sample t -test against zero, two-tailed, Bonferroni corrected for each time period).

Figure 6. Trial-by-trial logistic analysis.

(A) Trial-by-trial activity in the dIPFC ROI at the time of cue presentation (measured 2-4 sec before the smoking decision) significantly predicted subsequent smoking decisions. (B) Trial-by-trial activity in the ventral striatum ROI at the time of the smoking decision also significantly predicted smoking decisions. The x-axis represents the estimated single-trial fMRI signal amplitudes and the y-axis represents the proportion of yes decisions. For illustration purposes, the binned behavioral data (black dots) aggregated across participants are plotted. The curved lines represent the fitted logistic regression functions.

Figure 7. Trial-by-trial mediation analysis.

Mediation analysis examining ventral Striatum activation as a mediator of the effect of dIPFC activation on smoking decision value was performed based on each individual's trial-by-trial data. Both mean path coefficients and standard errors are provided. Statistical significance for path coefficients was evaluated by one-sample *t* test across participants. **P* < .05, ***P* < .01, (one-sample *t*-test against zero, two-tailed).