HHS Public Access

Author manuscript

*Behav Brain Res*. Author manuscript; available in PMC 2023 February 14.

Published in final edited form as:

*Behav Brain Res*. 2023 February 02; 437: 114120. doi:10.1016/j.bbr.2022.114120.

# Prepared and reactive inhibition in smokers and non-smokers

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## Abstract

**Introduction:** Models of addiction have identified deficits in inhibitory control, or the ability to inhibit inappropriate or unwanted behaviors, as one factor in the development and maintenance of addictive behaviors. Current literature supports disruption of the prefrontal circuits that mediate reactive inhibitory control processes (i.e., inhibition in response to sudden, unplanned changes in environmental demands) in substance use disorders. However, the relationship between disorders of addiction, such as nicotine dependence, and *planned* inhibitory processes (i.e., inhibition that occurs after advance warning) is unclear. The goal of the present study was to examine the extent to which reactive and planned inhibitory processes are differentially disrupted in nicotine dependent individuals.

**Method:** We employed an internet-based novel stop signal task wherein participants were instructed to stop a continuous movement at either a predictable or unpredictable time. This task explicitly separated planned and reactive inhibitory processes and assessed group differences in task performance between smokers ($N = 281$) and non-smokers ($N = 164$). The smoker group was defined as any participant that identified as a smoker and reported an average daily nicotine consumption of at least 2 mg. The non-smoker group was defined as any participant that identified as a non-smoker and had not been a former smoker that quit within the last year. The smoker group also completed a questionnaire regarding smoking behaviors which included the Fägerstrom Test of Nicotine Dependence (FTND). We used these data to assess the continuous relation between planned stopping, unplanned stopping, and smoking behaviors.



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CRediT authorship contribution statement

**Schultz:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing (original draft). **Mantell:** data curation, project administration, resources, software. **Berkman:** Conceptualization, funding acquisition, supervision, validation, writing (review and editing). **Swann:** conceptualization, funding acquisition, supervision, validation, writing (review and editing).

Declaration of Competing interest

None Declared.

**Results:** We found significant differences in stop times for both reactive and planned stopping between groups as well as within the smoker group. Additionally, in the smoker group, dependence as measured by the FTND was associated with longer stop times on planned stop trials. Surprisingly, greater daily average consumption of nicotine was related to faster stopping for both trial types.

**Conclusion:** These results indicate the relevance of measuring both reactive and planned inhibitory processes for elucidating the relationship between nicotine addiction and mechanisms of inhibitory control.

### Keywords

Prepared inhibition; Reactive inhibition; Nicotine; Movement termination

## 1. Introduction

Cigarette smoking is the leading cause of preventable death in the United States [1]. Most cigarette smokers are addicted to nicotine and struggle to quit despite their desire to do so. Between 2000 and 2015, 68 % of smokers indicated a desire to quit, but only 7.4 % were able to do so successfully [2]. Neurophysiological models of addiction have identified disruption in cortico-striatal circuits underlying inhibitory control, or the ability to inhibit inappropriate or unwanted behaviors, as one factor in the development and maintenance of addictive behaviors [3,4]. In other words, if the neural circuitry that allows for deliberate control or suppression of automatic behaviors (such as picking up a cigarette) is disrupted, the ability to resist the impulse to smoke is diminished and addictive behaviors persist. Neuroimaging and electrophysiological studies in smokers support the role of dysfunction in inhibitory control circuits in nicotine addiction [5–11]. Previous research also suggests that the relationship between inhibitory control dysfunction and nicotine consumption may be dose-dependent in the sense that individuals who consume a greater amount of nicotine also express greater deficits in measures of inhibitory control [12–14].

Inhibitory control is commonly studied using simple motor inhibition tasks, such as the stop signal task (SST; [15,16]). In this task subjects develop a pre-potent response, typically to rapidly press a button in response to a “go” cue, but on a minority of trials must withhold the button press when presented with a stop signal (“stop” trials). Efficiency of response inhibition is measured as an estimate of the time required to successfully prevent a response, or the stop signal reaction time (SSRT). A prominent model of inhibitory control implicates right inferior frontal gyrus (rIFG), pre-supplementary motor area (pre-SMA), and motor cortex as essential cortical components of the inhibitory control system [17–19]. Cortical nodes of the inhibitory control system are linked with basal ganglia by anatomically and functionally distinct pathways. Two of these pathways are the hyperdirect and indirect pathways [20,21]. The hyperdirect pathway is well-situated for fast and cue-dependent inhibition, here called *reactive inhibition*, and is implicated in sudden termination of motor output that requires cognitive processes [22,23]. For example, if one suddenly notices one is about to step on a Lego, the ability to stop oneself depends on cognitive processes underlying identification of the threat and determination of an appropriate reaction (i. e., stopping) [17,24–27]. Reactive inhibition is postulated to be reflected in increased activity

in pre-frontal regions such as the rIFG and pre-SMA [28]. The specific roles rIFG and pre-SMA play in reactive inhibition are still unclear. Planned suppression of motor output without the need for cognitive control processes, such as stopping movement at the end of a dance is thought to recruit the indirect pathway and to be mediated primarily by motor cortex, without significant influence from rIFG and pre-SMA [29–32]. For example, in a study using an adaptation of the SST in which subjects were informed about the probability of a subsequent stop trial – ostensibly allowing them to plan to stop – increased activity was only observed over sensorimotor cortex and not over prefrontal regions [32].

Previous research suggests that substance use disorder may be associated with specific deficits in the prefrontal-basal ganglia circuits that mediate reactive inhibition and not necessarily those that mediate planned inhibition. For example, studies using functional magnetic resonance imaging (fMRI) reveal hypoactivation of rIFG during motoric inhibition tasks in individuals with an addiction [9]. An fMRI study of nicotine-dependent individuals also demonstrated that activity in right inferior frontal cortex was modulated by nicotine withdrawal during a motor inhibition task [8]. Interestingly, this study showed that pre-SMA was unaffected by nicotine. The authors suggest that nicotine prefer-entially affects attentional control aspects of inhibition which may be mediated by rIFG – a key node of the reactive inhibition network. Additionally, neural stimulation of rIFG improved performance on a motoric inhibition task in nicotine-dependent individuals [33].

Though the current literature supports disruption of the prefrontal circuits that mediate reactive inhibitory control processes in substance use disorders, the relationship between disorders of addiction, such as nicotine dependence, and planned inhibitory processes is unclear. The goal of the present study is to examine the extent to which reactive and planned inhibitory processes are differentially disrupted in nicotine-dependent individuals. To this aim, we employed a novel stop signal task that explicitly separates planned and reactive inhibitory processes and assessed (1) group differences in task performance between smokers and non-smokers and (2) the continuous relation between task performance and smoking behaviors within the smoking group. On the basis of the prior clinical literature reviewed above, we predicted deficits in reactive inhibitory control in smokers relative to non-smokers and a dose-dependent relationship such that greater reactive inhibitory control impairment would increase with nicotine exposure among smokers. The neurophysiological literature also supports a specificity hypothesis whereby the effects observed between and within groups on reactive control would not generalize to planned stopping. We also anticipated that individuals who smoked more recently (i.e., within the last 30 mins) would stop faster than those who last smoked longer ago (i.e., 24 h or more) given the previous literature demonstrating cognitive enhancements following acute consumption of nicotine and deficits following nicotine abstinence [5,34–36].

## 2. Method

This study was approved by the University of Oregon ethics board and took place entirely online. All subjects completed a demographic questionnaire and the Continuous Movement Stop Task (CMST), a simple motor inhibition task in which subjects terminated an ongoing movement under conditions that elicited either planned or reactive motor termination

processes ([37]; Fig. 1). In this task, participants moved a computer mouse (or used a trackpad) in a continuous circular motion while monitoring a countdown displayed on their screen. On the majority of trials (75 %), the countdown proceeded to “1” before the stop signal was displayed indicating that the participant should cease their movement (planned stop). In other words, participants could predict the onset of the stop signal and prepare to terminate their movement accordingly. On the remaining trials (25 %), and without warning to the participant, the stop signal was displayed before the countdown reached “1” (unplanned stop). Location data were collected from each participant’s mouse (or trackpad), allowing for identification of movement termination. The amount of time between the stop signal and full motor arrest, henceforth referred to as ‘stop time’, provided a measure of efficiency of the inhibitory control system. Because the arrival of the stop signal on planned stop trials was predictable, these trials assessed planned or prepared inhibitory processes whereas the unplanned stop trials elicited unplanned or reactive processes.

Subjects who identified as smokers also completed the (1) Fägerstrom Test of Nicotine Dependence (FTND) [38], a standard measure used to evaluate the intensity of physical addiction to nicotine through questions about smoking frequency and urge strength and (2) a brief nicotine product usage survey which identified other forms of nicotine consumption besides combustible cigarettes (e.g., e-cigarette, hookah, etc.).

### 2.1. Participants

Participants were recruited through Amazon’s Mechanical Turk (MTurk) and were paid upon completion of the experiment. All subjects provided a digital signature indicating their informed consent. Of the 653 participants that consented 422 identified as smokers, 229 identified as non-smokers, and 2 did not answer the question. Only 281 of the 422 participants who identified as a smoker and 164 of the 229 participants who identified as a non-smoker completed the demographics questionnaire and at least 100 trials of the CMST.

Given the possibility that excessively long response times indicated a lapse in attention, trials in which subjects took more than 1 s to respond to the GO signal or the STOP signal were removed from analysis. After removal of these trials, subjects who had fewer than 30 trials of either trial type were removed from all analyses. 161 smokers and 33 non-smokers were excluded from analysis for this reason. Of the subjects included in the analyses, 11 % of trials were excluded on average in the smoker group (range = 0–44 %) and 3 % of trials were excluded on average in the non-smoker group (range = 0–46 %). To qualify as a smoker, participants needed to identify as a smoker and consume an average of at least 2 mg of nicotine (~1 cigarette) per day. 29 self-identified smokers did not meet this criterion and were excluded from analysis. Inclusion in the non-smoker group required that subjects identified as a non-smoker and, if a former smoker, had quit one year or more before completing the experiment. 25 participants who identified as a non-smoker indicated that they quit smoking within the last year and were excluded from analysis.

Participants were asked to indicate their age, the sex they were assigned at birth, their racial identity, if they had a neurological diagnosis, and if they take neurological medications (Table 1). We did not specify examples of neurological diagnoses or neurological medications, thus it is possible participants with psychiatric diagnoses or who are taking

psychiatric medications answered in the affirmative to these questions. Participants were not excluded on the basis of neurological disease or medication but this information was included in the statistical models as a covariate. After exclusion, 91 smokers and 106 non-smokers remained for analysis.

Participants in the smoker group consisted of 91 individuals who identified as a smoker and reported consuming a daily average of at least 2 mg of nicotine (~1 cigarette/day). 89 subjects reported smoking cigarettes, 54 of these 89 subjects reported smoking e-cigarettes in addition to combustible cigarettes, and 2 reported smoking only e-cigarettes. One of the 56 subjects who reported smoking e-cigarettes did not report level of nicotine content, so we cannot confirm the e-cigarettes this subject used contained nicotine. Information regarding nicotine consumption can be found in Table 2.

Although the chemical composition of e-cigarette liquid is different than that of combustible cigarettes and the dependence-related effects of the two products may differ somewhat [39], we consider consumption of either product to merit inclusion in the smoker group because the pharmacokinetics of the two are comparable due to their identical administration route (i.e inhalation) [40]. Additionally, total plasma nicotine concentration produced by e-cigarettes has been shown to reach similar levels as that produced by combustible cigarettes [41].

Participants in the non-smoker group consisted of 106 individuals who identified as a non-smoker and reported that they had not formerly been a smoker who quit within the last year.

A one-way ANOVA showed that there was not a significant difference in age between the smoking and non-smoking groups; $F(1195) = .017$, $p = 0.896$. A chi-squared test of sex indicated that there was not a significant difference between groups; $X^2(1, N = 196) = 0.19$, $p = .66$.

## 2.2. Behavioral measures

**2.2.1. Reaction times—**Reaction times following the stop signal (Stop Time) were calculated for each subject using location data from their mouse (or trackpad). Location data were recorded using a Java Script event listener as XY coordinates in pixel space defined by the display parameters of the computer each subject used. Reaction time to the go signal (RT) was defined as the time point at which subjects moved at least one pixel from their starting location. Stop time was defined as the time from the onset of the stop signal to the point at which change in XY coordinates was 0. We hypothesized that on planned stop trials participants would attempt to stop as close to the stop signal as possible – in line with the task instructions. This could result in participants stopping very close to the time of stop signal onset or even just before the stop signal. Thus, we included in our analysis trials where participants stopped moving any-where from 200 ms before to 1 s after the stop signal. Trials where participants stopped (no more than 200 ms) prior to the stop signal were given a negative value, trials where participants stopped at the time of the stop signal were recorded as a 0 ms stopping time, and trials where participants stopped (no more than 1 s) after the stop signal were given a positive stopping time. Variability in response times to the

stop signal and the go signal were also evaluated by calculating the coefficient of variability (CV) for each measure.

**2.2.2. Heaviness of smoking—**Heaviness of smoking was measured as the estimated average amount of nicotine consumed daily. Participants who used tobacco were asked to report the average number of cigarettes they smoked per day, if they used e-cigarettes and, if so, the range of nicotine levels in the cartridges they use and how many puffs per day they take (Table 2). Nicotine levels for cartridges were divided into low (<8 mg), medium (8–16 mg), and high (>16 mg).

According to the National Institute on Drug Abuse [1], a smoker will consume between 1 and 2 mg of nicotine per cigarette. Previous research on e-cigarettes shows that, on average, smokers will consume approximately 0.2 % of the total nicotine content per puff [42]. To estimate daily nicotine consumption from cigarettes, we multiplied the number of cigarettes smoked per day by 1.5 mg (the middle of the range reported by NIDA). Nicotine consumption from e-cigarettes was estimated by finding the median of the range of nicotine levels reported, taking 0.2 % of this number and multiplying the product by the number of puffs reported. We determined the range to be 1–8 mg for low levels and the range was 16–24 for high levels [42]. Estimated nicotine from cigarettes and e-cigarettes were then added together (when participants used both) to produce an estimate of daily average nicotine consumption.

**2.2.3. Dependence—**Nicotine dependence was derived from the FTND [38]. This test consists of 6 questions pertaining to nicotine consumption habits and compulsion to smoke. There are 3 yes/no items scored 0 (no) and 1 (yes) and 3 multiple choice items scored 0–3. These items are then summed to produce a score of 0–10. These scores are then categorized in different classes of nicotine dependence including very low (0–2), low (3–4), moderate (5), high (6–7), and very high (8–10).

**2.2.4. Time since last cigarette—**We attempted to identify nicotine state (i.e., sated or in withdrawal) by asking participants to report the approximate amount of time that had elapsed between the time they were participating in the experiment and the time they smoked a cigarette. Considering that participants may not be likely to remember the precise time at which they last smoked a cigarette, we asked them to simply report whether their last cigarette was (a) less than 30 min ago, (b) about an hour ago, (c) 3 or more hours ago today, or (d) more than 24 h ago.

## 2.3. Data analysis

Data were compiled using custom MATLAB (2019a) scripts and all statistical tests were performed using JASP [43]. Distributions of variables were evaluated for normality using the Shapiro-Wilk test. In cases where the assumption of normality was violated, non-parametric tests were used.

**2.3.1. Between groups—**Between-group differences in average stop times for planned and unplanned stop trials, coefficients of variation (CV) for planned and unplanned stop times, average go-signal reaction times (RT) and the CV of RTs were all evaluated using a

one-way ANOVA. Neurological diagnosis and/or the use of neurological medication were examined as covariates using ANCOVA. Participants reported if they had a neurological diagnosis and/or if they take neurological medication.

**2.3.2. Within groups—**A one-way ANOVA was used to assess within-group differences in average planned and unplanned stop times and differences in stop time variability between planned and unplanned stop trials. Pearson's correlations were used to evaluate the relations between variables in all cases except for instances when the assumptions of pair-wise normality were violated as determined by the Shapiro-Wilk test for bivariate normality. Instances in which Spearman's correlations were used are noted in the results section.

## 3. Results

### 3.1. Between groups

Smokers stopped significantly more slowly than non-smokers on planned stop trials ($F(1195) = 48.17$, $p < 0.001$, $d = .997$; $M_{smokers} = 465.942$ ms, $SD_{smokers} = 158$ ms; $M_{non\text{-}smokers} = 329.93$ ms, $SD_{non\text{-}smokers} = 116.86$ ms; Fig. 2a) and unplanned stop trials ($F(1195) = 67.27$, $p < 0.001$, $d = 1.178$; $M_{smokers} = 610.86$ ms, $SD_{smokers} = 156.24$ ms; $M_{non\text{-}smokers} = 467.7$ ms, $SD_{non\text{-}smokers} = 107.53$ ms; Fig. 2b). Surprisingly, we found that the non-smoker group expressed greater variability in stop times on planned stop trials than the smoker group, $F(1195) = 9.97$, p = .002, $d = .454$; $M_{smokers} = .485$, $SD_{smokers} = .204$; $M_{non\text{-}smokers} = .591$, $SD_{non\text{-}smokers} = .263$ (Fig. 3a). There was not a difference between groups in the CV of stop times for unplanned stop trials ($M_{smokers} = .277$, $SD_{smokers} = .131$; $M_{non\text{-}smokers} = .304$, $SD_{non\text{-}smokers} = .11$), $F(1195) = 2.38$, $p = .125$ (Fig. 3b).

We did not find a difference in average RT between smokers ($M = 364.76$, $SD = .24$) and non-smokers ($M = 328.03$, $SD = 110.36$), $F(1195) = 3.27$, $p = .072$. We did, however, find that the smoker group expressed significantly greater variability in RT ($M = .749$, $SD = .423$) than the non-smoker group ($M = .566$, $SD = .24$), $F(1195) = 14.384$, $p < .001$, $d = .545$.

An ANCOVA showed no interaction effect between neurological diagnosis and group ($F(1193) = 2.07$, $p = 0.152$) or neurological medications and group ($F(1193) = 3.842$, $p = .051$) for planned stops or for unplanned stops ($F(1193) = 1.25$, $p = .265$ and $F(1193) = 3.86$, $p = .051$).

### 3.2. Within groups

**3.2.1. Non-smokers—**The non-smoker group stopped significantly more slowly on unplanned ($M = 467.702$ $SD = 107.531$) compared to planned ($M = 329.925$, $SD = 116.862$) stop trials, $F(1210) = 79.785$, $p < .001$, $d = 1.23$ (Fig. 2c). To control for the possibility of confounding variables such as age, neurological diagnosis, and neurological medication, we estimated a post hoc linear model with stop times as the dependent variable, trial type as a fixed factor, and the afore mentioned variables as covariates. The effect of trial type remained significant in this model ($F(1207) = 81.266$, $p < .001$, $d = 1.244$). Additionally, we found that there was less variability in stop times on unplanned stop trials ($M = .304$, $SD$

=.11) compared to planned stop trials ($M$ =.591, $SD$ =.263), $F$(1210) = 107.86, $p$ < .001, $d$ = 1.433 (Fig. 3c).

**3.2.2. Smokers—**Like the non-smoker group, the smoker group took significantly longer to stop on unplanned ($M$ = 610.86, $SD$ = 156.24) compared to planned ($M$ = 465.94, $SD$ = 610.86) stop trials, $F$(1180) = 38.713, $p$ < .001, $d$ = .928 (Fig. 2d). We found that smokers also demonstrated significantly less variability in stop times for unplanned ($M$ =.277, $SD$ =.131) compared to planned stop trials ($M$ =.485, $SD$ =.131), $F$(1180) = 65.411, $p$ < .001, $d$ = 1.206 (Fig. 3d). To control for the possible mediating influence of variables such as age, neurological diagnosis and neurological medications, and dependence as well as nicotine use measures including cigarettes per day and estimated daily nicotine consumption, we estimated a post hoc linear model with stop time as the dependent variable, trial type as a fixed factor, and all of the above mentioned variables as covariates. The effect of trial type remained significant in this model ($F$(1170) = 47.25, $p$ < .001, $d$ = 1.025).

Number of cigarettes smoked per day was inversely and significantly related to stop times for both planned ($r$ = 0.219, $p$ = .039) and unplanned ($r$ = .237, $p$ = .025) stop trials. Among smokers, more cigarettes per day related to faster stopping on both trial types. To rule out the possibility of age as a confounding factor, we conducted a post-hoc analysis evaluating the relation between age and number of cigarettes smoked per day. A spearman correlation revealed that age is not significantly related to number of cigarettes smoked per day ($r$ = .19, $p$ = .076).

Estimated daily average nicotine consumption (in milligrams) was also inversely and significantly related to stop times for both planned ($r$ = −.212, $p$ = .044) and unplanned ($r$ = −.236, $p$ = .024) stop trials. That is, greater daily average nicotine intake related to faster stopping on both trial types. To rule out the possibility of age as a confounding factor, we conducted a post-hoc analysis evaluating the relation between daily average nicotine consumption and age. A spearman correlation indicated that age is not related to average nicotine consumption ($r$ = .173, $p$ = .102).

Dependence was significantly and positively related to stop times for planned stop trials ($r$ = .221, $p$ = .035) but was unrelated to stop times on unplanned stop trials ($r$ = .14, $p$ = .187; Fig. 4).

Recency of last cigarette was not significantly related to stop times for planned ($r$ = −.036, $p$ = .735) or unplanned ($r$ = −.042, $p$ = .692) stop trials.

Mean RT and the CV of planned stop times, unplanned stop times, and RT did not significantly relate to any measures of nicotine consumption or dependence.

## 4. Discussion

In this study we used the CMST to investigate group differences between smokers and non-smokers in prepared (i.e. planned) and reactive (i.e. unplanned) movement termination. We found that smokers stopped significantly more slowly than non-smokers when movement cessation was planned than when it was unplanned (Fig. 2). We also found that stop

times were significantly more variable for planned than for unplanned stop trials for both groups and that stop times for planned stop trials were significantly more variable in the non-smoker group compared to the smoker group (Fig. 3). There was not a difference in average RT between groups. However, variability in RT was significantly greater for smokers than for non-smokers. The measure of dependence derived from the FTND was significantly related to stop times on planned but not those on unplanned stop trials. Further investigation of the relationship between nicotine consumption and both types of inhibitory processes revealed that estimated daily nicotine consumption and average number of cigarettes smoked per day were significantly negatively related to stop times for both planned and unplanned stop trials. Recency of the last cigarette smoked was not related to either planned or unplanned stop times. We did not identify any relations between average RT or the CVs of planned stop times, unplanned stop times, and RT and any measure of nicotine consumption.

## 4.1. Between group differences

**4.1.1. Reaction times—**Our finding that smokers stopped significantly more slowly than non-smokers supports a model of nicotine addiction characterized by inhibitory control deficits in smoking. Furthermore, it extends this model to include disruptions in both reactive and prepared inhibitory processes. Our observation of group differences is in line with findings in some previous studies [9–11], but not others ([44] for review). It is possible that the CMST offers a more sensitive measure of inhibitory control processes than other inhibition tasks, such as the stop signal task, that provide only a single estimate of inhibitory efficiency for each subject. Additionally, the CMST may elicit inhibitory processes critically involved with nicotine addiction that cannot be measured with other standard tasks.

We observed a discrepancy in the exclusion rate of trials and of subjects between groups. 11 % of trials in the smoker group and 3% of trials in the non-smoker group were excluded as a result of excessively long reaction times. Additionally, 57 % of all respondents who identified as a smoker and 21 % of non-smokers were removed from analysis due to an insufficient number of acceptable trials following removal of trials with excessively long reaction times. We suspect this is in part a reflection of the tendency for smokers to take longer to stop than non-smokers. That is, because stop times for smokers are longer overall, they are more likely to reach and exceed our stop time cutoff of 1000 ms. This finding may also be a reflection of lapses in attention that are hypothesized to be more common among chronic smokers than non-smokers [45].

**4.1.2. Variability—**Stop times for planned stop trials were significantly more variable than stop times for unplanned stop trials for both smokers and non-smokers. We take this to suggest that the processes underlying reactive stopping are more stereotyped than those underlying prepared stopping. Additionally, we found that stop time variability for planned stop trials was significantly greater for non-smokers than for smokers. This may reflect attentional lapses in the smoker group that resulted in reactive stopping on some planned stop trials. If individuals in the smoker group lost focus toward the end of the countdown to the stop signal, they may react to the stop signal on planned stop trials in a similar way they would on unplanned stop trials – with reduced variability. Though acute nicotine

administration can improve attention, chronic exposure to nicotine can impair attention by disrupting cholinergic signaling in pre-frontal cortex through desensitization of nicotinic acetylcholine receptors ([45] for review). Fluctuations in attention within the smoker group may also explain the observed increase in RT variability with respect to the non-smoker group.

## 4.2. Smokers

**4.2.1. Dependence—**The observed correlation between dependence and inhibitory control is in line with previous research showing a relationship between dependence (as measured by the FTND) and reductions in performance on various measures of inhibitory control [12,46,47]. Interestingly, the present study reveals this relationship is specific to prepared inhibitory control processes as opposed to reactive inhibitory processes.

It is important to note that this finding does not necessarily contradict studies such as that conducted by Billieux et al. [12], which showed a correlation between dependence and performance on a Go/No Go task – a task that requires unanticipated inhibition of a prepotent response. As a result of the requirement that participants intend to move on every trial (which precludes the option to provide foreknowledge of an impending stop signal) reactive inhibition cannot be cleanly separated from prepared inhibition on that task. That is, knowing with certainty that a stop signal is about to appear on the Go/No-Go task would permit participants simply to plan to not respond, as opposed to reactively withhold a response. Previous research has shown that proactive inhibitory mechanisms, or “breaking” mechanisms that are employed prior to movement onset, facilitate reactive mechanisms in inhibitory control tasks such as the Go/No Go or the Stop Signal Task [48–50]. Proactive inhibitory control is commonly observed as a slowing of go-signal reaction time. For example, when provided with information about the probability of a stop signal during a standard stop signal task, participants proactively engage inhibitory mechanisms to facilitate movement suppression. On trials in which participants are erroneously expecting a stop signal, preparatory engagement of inhibitory control manifests as a delayed response to the go signal. Although proactive inhibition as measured using the stop signal task may differ from preparatory mechanisms recruited in the present experiment, it is possible that the slowing in reactive inhibitory processes observed by Billieux et al. [12] was influenced by deficits in preparatory response inhibition.

A key advantage of the CMST used in the present study is that the planned stop condition removes reactive processes from stopping, allowing for differentiation between the two. Because participants are aware that at some point in every trial they will be instructed to stop, we do not assert that the unplanned stop condition in the CMST recruits exclusively reactive inhibitory processes and that there is no involvement of prepared inhibitory mechanisms. In other words, preparatory inhibitory mechanisms may always be engaged to some extent in anticipation of the stop signal. However, it is unlikely that the planned stop condition elicits reactive processes to the same degree as the unplanned stop condition. Thus, the contrast between the unplanned and planned conditions allows us to quantitatively separate the processes.

It is important to note that the observed correlation was relatively weak and may not reflect a useful relation between dependence measures and inhibitory control. Additionally, it is possible that our measure of dependence was not sufficiently sensitive to provide an accurate picture of the relation between nicotine dependence and inhibitory control. Further research into the relation between prepared inhibitory control deficits and nicotine abuse is needed.

**4.2.2. Heaviness of smoking—**Surprisingly, we found an inverse relationship between nicotine consumption and stop times for both planned and unplanned stop trials. Despite the overall reduction in performance of smokers compared to non-smokers, smokers who consumed more nicotine daily expressed greater inhibitory capacity relative to those who consumed less. This is in contrast to work showing that diminished inhibitory capacity was associated with quantity of cigarettes consumed daily [12]. Previous work has shown a decline in inhibitory control capacity following bouts of nicotine abstinence [35]. It is possible that smokers who smoke more often are more consistently sated and less likely to express abstinence-related deficits than smokers who smoke less often. However, future inquiry into this possibility is needed. Additionally, the correlational values obtained were small and may not reflect a relation that is meaningful.

It is important to note that this finding is not necessarily inconsistent with the observed relation between dependence and inhibitory control. Though dependence and smoking frequency are often correlated, they measure different aspects of nicotine use. Dependence may reflect the psychological aspects of nicotine use to a greater degree than smoking behavior per se. For instance, separate genes have been identified for nicotine dependence, on the one hand, and smoking behavior, on the other [51].

**4.2.3. Time since last cigarette—**Given the previous work demonstrating the short-term cognitive enhancement following acute nicotine use and the deficits following nicotine abstinence [5,34–36], we anticipated that individuals who smoked more recently (i.e., within the last 30 mins) and were presumably in a more sated nicotine state would stop faster than those who last smoked longer ago (i.e., 24 h or more) and were possibly closer to a withdrawal state. Thus, our finding that recency of the last cigarette smoked was not correlated with stop times from either trial type was unexpected. Although the cognitive benefits of nicotine consumption are well-documented, inhibitory control deficits in abstinent smokers are not always observed [46,52–54]. Additionally, it is possible that this lack of observed relation was a product of how the data were collected rather than a true representation of reality. Time since last cigarette was reported as a categorical variable (i.e., less than 30 min ago, about an hour ago, etc) rather than as a continuous variable. The categorical nature of this variable may have reduced sensitivity enough to obscure an existing relation.

### 4.3. Limitations

Though the present study represents an exciting contribution to the nicotine addiction literature, there are limitations that should be addressed in future research. First, our sample consisted predominantly of light to moderately dependent smokers with only 2 subjects falling into the very highly dependent category. As previous work has shown differences in

inhibitory control capacity between moderately and heavily dependent smokers [46], future research including a more representative sample would provide an important addition to this line of inquiry.

Additionally, subjects were not asked to report the duration of their nicotine use (i.e., how long since they started smoking) or any previous attempts at quitting. Specifics regarding preferred cigarette brand were also not collected, which would have provided a more accurate assessment of the total quantity of nicotine consumed daily. Furthermore, nicotine content in e-cigarette cartridges is extremely variable and not always accurately identified on product labels [42,55,56]. Variability in puff topography (puff duration, velocity, inter-puff interval, number of puffs) and device features such as heating element design and voltage also affect total nicotine yield per bout of smoking [57]. These variables obscure actual nicotine consumption when estimated based on number of puffs and nicotine concentration alone, thus our estimate of daily nicotine consumption is an approximation of actual consumption. Our measure of nicotine state is also imprecise. To estimate nicotine state we asked subjects to report approximately when they last consumed a cigarette. Subjects provided a ballpark estimate that was collected as a categorical variable and thus may not be sensitive enough to accurately reflect possible relationships with our behavioral measures. Additionally, subjects may smoke during the task, after they have answered the cigarette recency question, in which case their answer would be irrelevant. In future research, a precise quantification of nicotine consumption could be provided by evaluating plasma nicotine levels following a smoking session.

Lastly, we did not collect information regarding alcohol use, a potentially confounding factor known to commonly co-occur with nicotine use and to influence response inhibition. Future research should include investigation of the possibility that alcohol use mediates the relationship between nicotine use and stopping behavior.

## 5. Conclusion

The present study revealed group differences between smokers and non-smokers on a novel measure of prepared and reactive inhibitory control. Additionally, we found task performance to be weakly related to dependence and heaviness of smoking. This study provides an exciting contribution to the existing literature, but future research addressing the present limitations is needed to provide important insight into mechanisms of nicotine addiction and potential treatment options.

## Funding

This study was supported by the National Cancer Institute of the National Institutes of Health (R01 CA240452) and the Reńee James Seed Grant to Accelerate Scientific Research.

## Data availability

All data and materials used during the current study are available in the Open Science Framework (OSF) repository, https://osf.io/ds3pa/.

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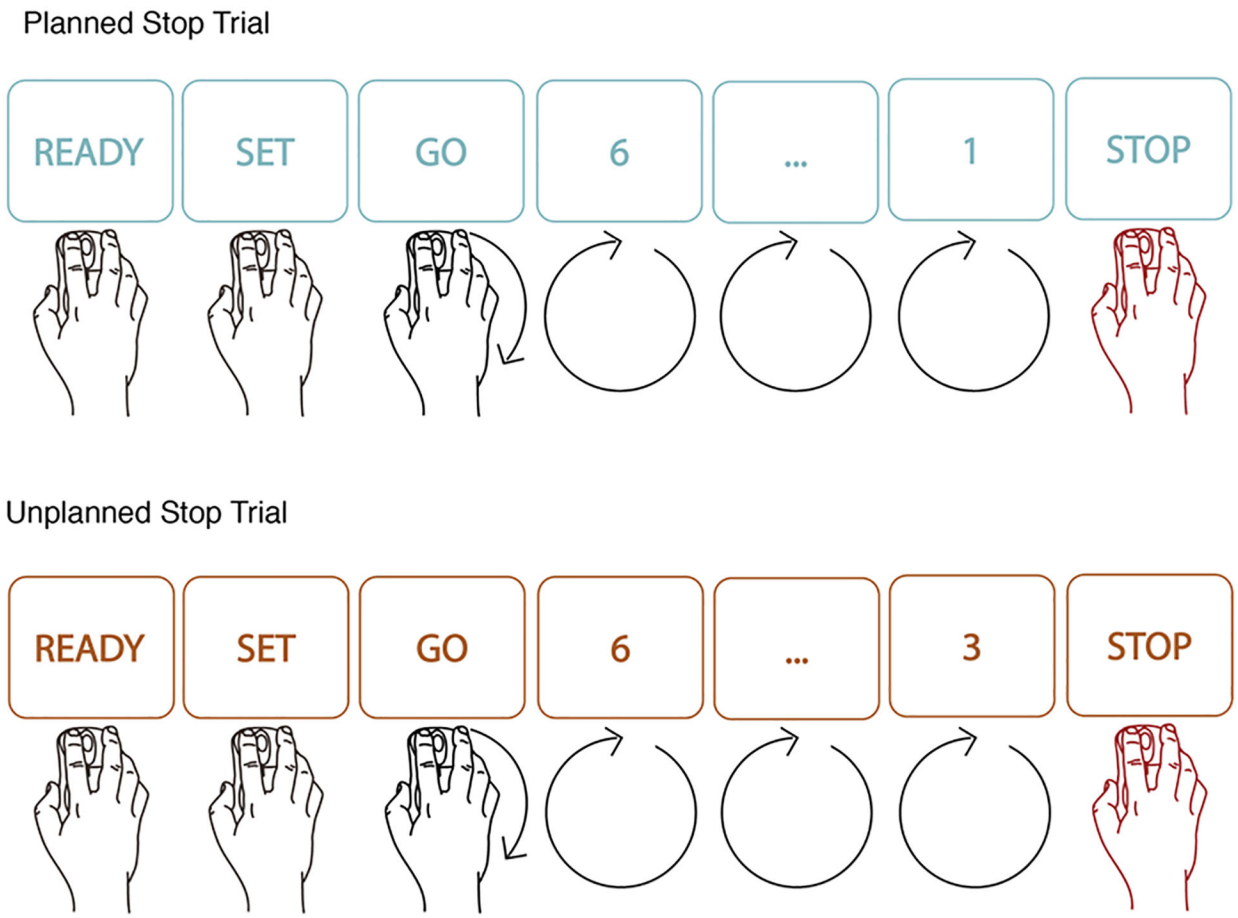


**Fig. 1.**
Depiction of planned and unplanned stop trials in CMST.

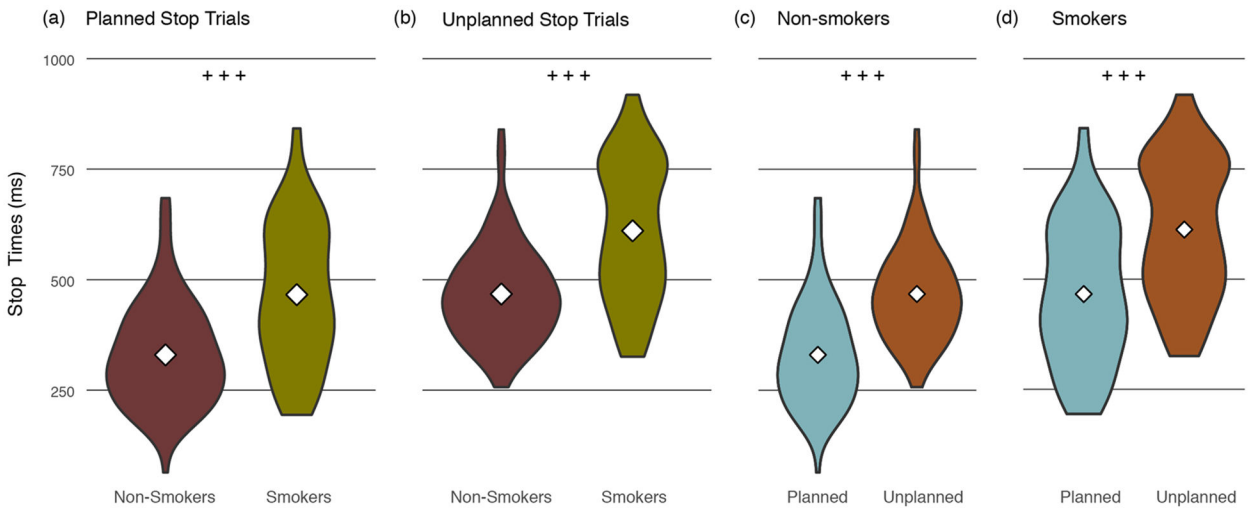


**Fig. 2.**

Stop times by trial type and group. White diamond indicates group mean. + ++ = p < .001 (a) Stop times on planned stop trials for non-smokers (M=329.9, SD=107.5) and smokers (M=466.2, SD=157.1). (b) Stop times on unplanned stop trials for non-smokers (M=467.7, SD=107.5) and smokers (M=612.4, SD=156). (c) Stop times for planned and unplanned stop trials for the non-smoker group only. (d) Stop times for planned and unplanned stop trials for the smoker group only.

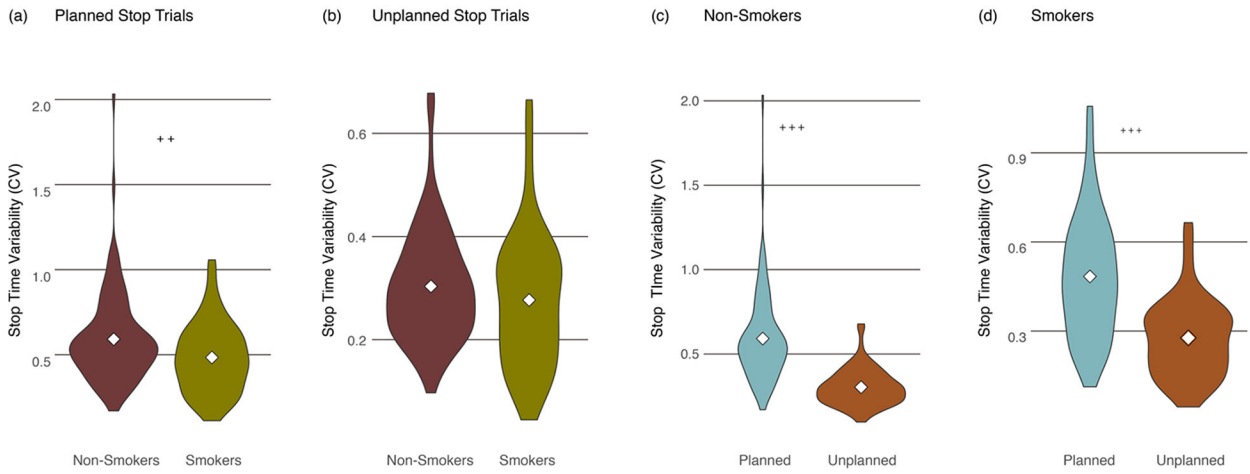


**Fig. 3.**

Variability in stopping. White diamond indicates group mean. + + = p < .05, + ++ = p < .001 (a) The CV of stop times on planned stop trials is greater for non-smokers (*M*=.6, *SD*=.3) compared to smokers (*M*=.5, *SD*=.2), *p* = .002. (b) The CV of stop times on unplanned stop trials is not significantly different between smokers (*M* =.3, *SD* =.1) and non-smokers *(M*=.3, *SD*=.1) *p* = .125. (c) The CV of stop times on planned stop trials is greater than the CV of stop times for unplanned stop trials among non-smokers, *p < .001.* (d) The CV of stop times on planned stop trials is greater than the CV of stop times for unplanned stop trials among smokers, *p < .001.*

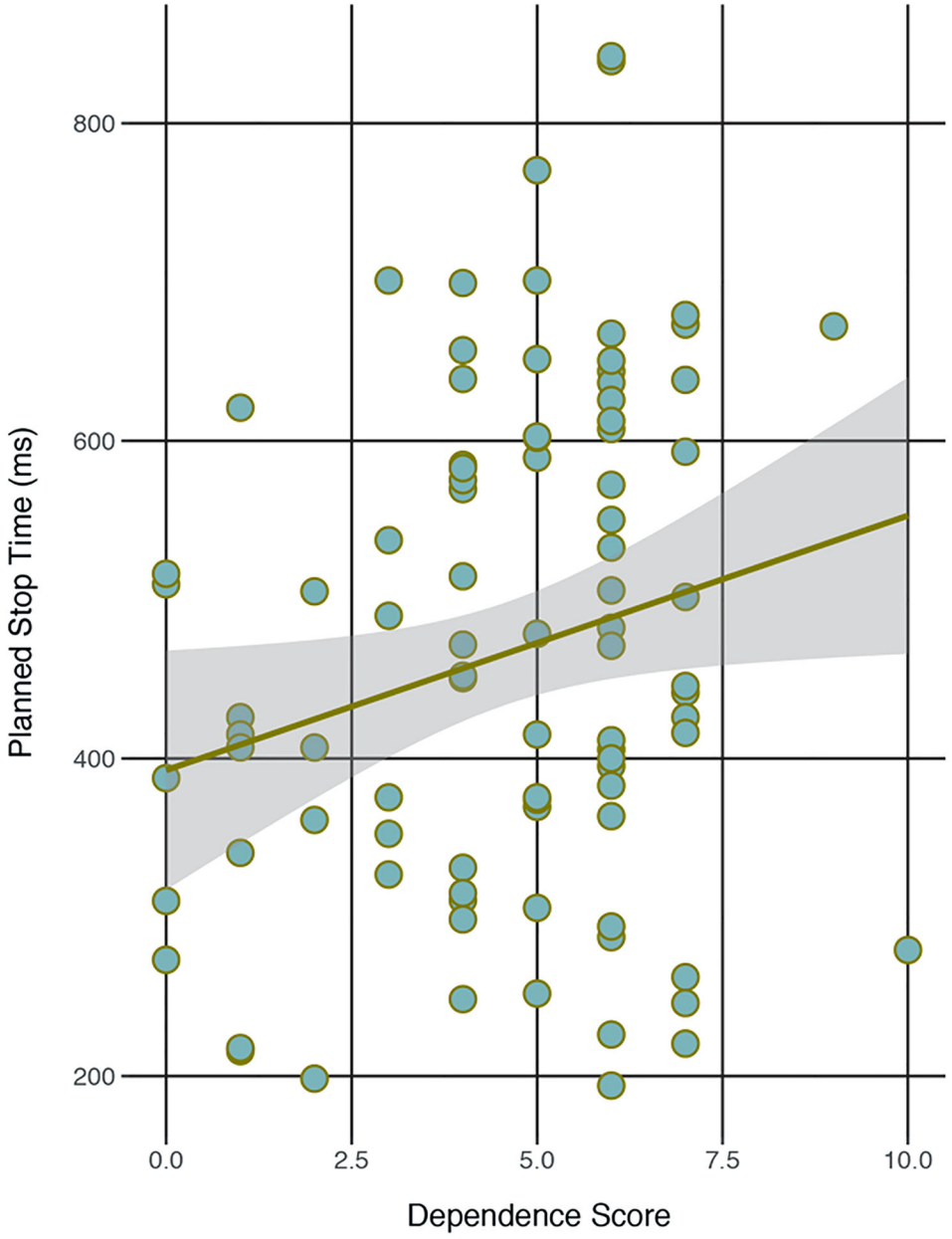


**Fig. 4.**

Dependence score was significantly and positively related to stop times for planned stop trials (r = 0.217, p = 0.038). Green line indicates line of best fit. Gray shadow is the 95% confidence interval.

## Table 1

Demographic information for both the smoking and non-smoking groups.

| Demographic information | | Smokers | Non-smokers |
|---|---|---|---|
| **Age (years)** | *Range* | 25–65 | 21–66 |
| | *Mean* | 38.1 | 37.92 |
| | *SD* | 9.15 | 10.31 |
| **Sex** | *Male* | 56 (62%) | 61 (57%) |
| | *Female* | 34 (37%) | 45 (42%) |
| | *Intersex* | 0 | 0 |
| **Racial Identity** | *White* | 74 (81%) | 82 (77%) |
| | *Black/ African American* | 9 (10%) | 10 (9%) |
| | *Asian* | 5 (5%) | 12 (11%) |
| | *Native American/ Native Alaskan* | 3 (3%) | 1 (1%) |
| **Neurological** | *Diagnosis* | 28 (31%) | 9 (8%) |
| | *Medication* | 31 (34%) | 10 (9%) |

**Table 2**

Nicotine consumption information.

| | Mean | SD | Range | Number of Responses |
|---|---|---|---|---|
| **Cigarettes/Day** | 9 | 6.5 | 2–35 | 89 |
| **Cigarette Nicotine Consumption (Cigarettes/Day * 1.5)** | 13.48 | 9.73 | 3–52.5 | 90 |
| **E-Cig puffs/day** | 18.86 | 37.4 | 1–200 | 56 |
| **E-Cig Nicotine Consumption (Nicotine level * puffs/day)** | 0.48 | 1.25 | .01–8 | 54 |
| **Total Nicotine Consumption** | 13.52 | 9.79 | 3–52.5 | 91 |
| **Dependence Score** | 4.54 | 2.18 | 0–10 | 91 |