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Effects of Nicotine Withdrawal on Motivation, Reward Sensitivity and Reward-Learning

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by

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Abstract

Research on addictive behavior has traditionally emphasized the role that primary reinforcing effects of drugs of abuse plays in the development and maintenance of dependence. However, contemporary behavioral economic theory and animal models of nicotine dependence suggest the need for greater attention to the impact that response to alternative rewards may have on smoking behavior. The present study sought to investigate the impact of nicotine withdrawal on self-report, behavioral and neural indices of motivation, immediate response to rewards and the capacity to learn and modify behavior in response to positive and negative feedback. Heavy smokers ($n = 48$) completed two laboratory sessions following overnight deprivation, during which they smoked either nicotinized or denicotinized cigarettes. At each session, they completed a reward prediction and feedback learning task while electro-encephalographic recordings were obtained, as well as resting state recordings which were used to extract global indices of motivational state. Results confirmed that nicotine withdrawal produced an avoidant motivational state. This effect was strongly related to numerous indices of smoking motivation. Exploratory analyses also revealed numerous moderators of these effects. Behavioral data from tasks provided some support for the impact of nicotine withdrawal on reward and feedback processing, though minimal impact was observed for neural indices. Together, results confirm the manifestation of a broad-spanning impact of nicotine withdrawal on motivational state, but effects on specific reward systems remains unknown. Future research should examine the impact of nicotine withdrawal on other reward-related constructs to better delineate these effects.

Introduction

Following the 1964 Surgeon General's report on smoking and health (U.S. Public Health Service, 1964), research on the health consequences of tobacco use began to grow rapidly. At present, strong evidence implicates a role for tobacco smoking in the development of several widespread health problems (Centers for Disease Control and Prevention, 2009). These health consequences lead to approximately 480,000 deaths in the United States alone each year (U.S. Department of Health and Human Services, 2014), with millions more worldwide (Ezzati & Lopez, 2003; Murray & Lopez, 1997). Despite monumental efforts to improve interventions and reduce the prevalence of smoking, recent estimates indicate that approximately 1 in 5 adults in the United States is a current smoker (Centers for Disease Control and Prevention, 2014). Although the majority of smokers are interested in quitting and amenable to treatment (Centers for Disease Control and Prevention, 2003; M. C. Fiore et al., 2004), even those who undergo intensive treatments are highly likely to relapse within 6 months (M.C. Fiore, Jaen, & Baker, 2008). Nicotine, the primary psychoactive constituent in tobacco, is thought to play a principal role in both ongoing smoking behavior and relapse (Benowitz, 1988). A better understanding of the role that nicotine plays in maintaining smoking behavior will aid in the development of novel interventions for smokers and has the potential to significantly boost cessation rates.

Traditional Views on Nicotine

Theories of smoking behavior in humans have routinely emphasized the role of the innate pleasurable effects derived from smoking (i.e. positive reinforcement) and the relief of aversive

withdrawal symptoms experienced during abstinence (i.e. negative reinforcement; Eissenberg, 2004; Glautier, 2004). Smoking cessation interventions have typically been developed and studied in concordance with these views. For example, pharmacotherapy development has focused on identifying medications capable of decreasing the value of nicotine by blocking these rewarding effects or mitigating withdrawal symptoms (Benowitz, 2008; Lerman et al., 2002). Interestingly, it has been noted that these "primary reinforcing" effects of nicotine are weak relative to other drugs of abuse (Henningfield & Goldberg, 1983), despite the fact that nicotine is generally considered to be highly addictive and to carry abuse potential comparable to that of other drugs (see J. H. Robinson & Pritchard, 1992; Stolerman & Jarvis, 1995). Traditional self-administration paradigms employed with other drugs (e.g. fixed ratio reinforcement schedules) do not reliably result in self-administration of nicotine in primates (Deneau & Inoki, 1967). Although rodent studies have produced responding using a fixed ratio schedule, these have generally required restricted access, pairing of the drug with other stimuli (i.e. second-order conditioning), or other modifications in order to prove successful (Rose & Corrigall, 1997). Thus, increases in the incentive value of nicotine (T. E. Robinson & Berridge, 1993, 2000, 2008) due to its reinforcing properties appear to offer an important, but incomplete understanding of the development and maintenance of smoking behavior. Recent evidence suggests that nicotine may generate and maintain addiction through very different mechanisms.

Alternative Views on Nicotine

A growing body of literature in rodent models of nicotine dependence suggests that self-administration of nicotine is maintained primarily via the influence of nicotine on other environmental rewards (i.e. "secondary reinforcement"; Chaudhri et al., 2006; Le Foll &

Goldberg, 2005), rather than due to the primary rewarding effects themselves. Expanding on early work documenting that nicotine self-administration is not always reliably induced with prototypical paradigms (as described above), research has revealed that reliable responding can be produced when nicotine is paired with other reinforcers. For instance, rodent studies demonstrate that when nicotine is paired with a brief cue light, followed by the cage lights being dimmed (which itself served as a reinforcer), rats will reliably respond for nicotine under fixed ratio conditions (Caggiula et al., 2002). In a related line of work, rodent models indicate that nicotine withdrawal reliably *increases* the neural reward threshold, resulting in the need for greater amounts of reward to activate reward pathways (Epping-Jordan, Watkins, Koob, & Markou, 1998). These deficits in reward processing are thought to produce a state akin to anhedonia, similar to that seen in depression (Paterson & Markou, 2007). It is characterized by an inability to experience pleasure and a resultant withdrawal from previously pleasurable activities (Loas, 1996). Indeed, the underlying neurobiology of depression and addiction appears to be strikingly similar (Balfour & Ridley, 2000; Markou, Kosten, & Koob, 1998). In light of evidence suggesting that smokers who show a blunted neural response to positive stimuli may be more prone to relapse following a quit attempt (Versace et al., 2012), it is plausible that nicotine motivates smoking behavior not only by increasing the incentive value of smoking, but by suppressing the value of alternative behaviors. Unfortunately, human research on this topic is limited, as reviewed below.

Nicotine Withdrawal and Anhedonia in Humans

In one line of research, nicotine withdrawal has produced consistent deficits on the Card Arrangement Reward Response Objective Task (CARROT), which measures the change in rate that participants perform a simple card-sorting task under conditions of reward and no-reward

(al-Adawi & Powell, 1997; Dawkins, Powell, West, Powell, & Pickering, 2006; Powell, Dawkins, & Davis, 2002). However, one study did find a general decline in performance not specific to reward trials, indicating that deficits may be due to generalized cognitive deficits and motor performance slowing, rather than blunted reward response per se (Kalamboka, Remington, & Glautier, 2009). Other studies have shown that nicotine withdrawal decreases affective response to pleasant (Dawkins, Acaster, & Powell, 2007) or both pleasant and unpleasant (Dawkins & Powell, 2011) images.

Whereas deficits in the immediate reward response during nicotine withdrawal may be inherently aversive and/or motivate smoking behavior during withdrawal episodes, it is equally important to understand how withdrawal might lead to changes in reward-seeking behavior over time due to learning deficits. This is particularly critical given that smoking cessation aids appear to mitigate the effects of withdrawal on immediate reward response (Cryan, Bruijnzeel, Skjei, & Markou, 2003). Nicotine withdrawal has a remarkably rapid onset, with many effects emerging within 30 minutes of smoking (Hendricks, Ditre, Drobes, & Brandon, 2006). Thus, even individuals smoking at regular intervals will likely experience frequent bouts of withdrawal throughout the day; potentially suppressing their ability to learn the rewarding properties of alternative behaviors. Although mixed findings have been observed for the acute effects of nicotine on these learning trajectories in humans (Barr, Pizzagalli, Culhane, Goff, & Evins, 2008; Perkins, Grottenthaler, & Wilson, 2009), we are aware of only one study examining withdrawal-induced deficits in reward-seeking (Pergadia et al., 2014). Thus, the need for human research on this topic is great.

Current Study

The primary goal of the current study is to investigate the effects of nicotine withdrawal on three closely related constructs: approach/avoidance motivational state, reward sensitivity, and reward-seeking and aversion-avoidance learning. This goal will be achieved through use of carefully selected self-report, behavioral, and neural indices assessing each of the above constructs. Given one long-term goal of the proposed study and broader research program will be to link human research to neurobiological effects observed primarily in rodent models, neural indices in humans may prove particularly useful for understanding the mechanisms involved. In addition, research in our laboratory has previously revealed that neural indices may be more sensitive than behavioral response on overnight abstinence procedures such as the one employed herein (e.g. Evans, Park, Maxfield, & Drobes, 2009).

Motivational State. Consistent with evidence suggesting similar neurobiological processes in nicotine withdrawal and depression (Markou et al., 1998), we will examine asymmetry in frontal cortical activity thought to index approach/avoidance motivational state (Harmon-Jones, Gable, & Peterson, 2010; van Honk & Schutter, 2006). This index has received significant attention as a potential endophenotype for depression and other internalizing disorders, and has been demonstrated to have a stable trait-like component, while still being modifiable by internal states (Thibodeau, Jorgensen, & Kim, 2006). There is limited work examining the effects of nicotine withdrawal on cortical asymmetry, particularly with carefully controlled experimental procedures. However, available evidence does provide some support for the notion that nicotine withdrawal results in a pattern of asymmetry consistent with a more avoidant state (Gilbert et al., 1999).

Reward Sensitivity. An established reward prediction task (Martin & Potts, 2004; Potts, Martin, Burton, & Montague, 2006) will be used to assess reward sensitivity. The task was modeled from tasks used to elicit dopamine response in the ventral tegmental area (VTA) in monkeys (Schultz, Dayan, & Montague, 1997). Prior research in humans has shown that the medial-frontal negativity (MFN) event-related potential (ERP) component operates consistent with VTA dopamine neurons (Potts et al., 2006). This component exhibits a pattern similar to the feedback-related negativity (FRN), which is thought to reflect monitoring of reward contingencies by the anterior cingulate cortex (Holroyd & Coles, 2002), an area that receives projections from the striatal dopaminergic systems implicated in both reward-learning (Nieuwenhuis, Holroyd, Mol, & Coles, 2004) and addiction (Di Chiara & Bassareo, 2007). Given ongoing research into the biological substrates of nicotine withdrawal in animal models (Johnson, Hollander, & Kenny, 2008), the insight that this task may provide into the neural substrates of nicotine withdrawal in humans may aid development of translational models of nicotine dependence.

Feedback Learning. This will be assessed using a well-established probabilistic learning task that has been used to study these processes across a range of neurological and psychiatric disorders (Chase et al., 2010; Frank, Seeberger, & O'Reilly R, 2004; Grundler, Cavanagh, Figueroa, Frank, & Allen, 2009; Waltz, Frank, Robinson, & Gold, 2007). Previous research has documented inhibited performance on this task following dopamine depletion via pharmacologic manipulation (Frank & O'Reilly, 2006). While nicotine withdrawal also depletes dopamine, the effects are far more diffuse than the targeted drugs that were used in prior research (Kenny & Markou, 2001). Thus, it will be important to confirm that nicotine withdrawal does indeed produce similar effects as these targeted agents. Genetic polymorphisms associated with

dopaminergic systems have also been shown to impact performance in healthy controls (Doll, Hutchison, & Frank, 2011; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Furthermore, this task allows for concurrent recording of ERPs, and previous research has shown that FRN amplitude predicts behavioral performance during this task (Frank, Woroch, & Curran, 2005). Hence, an extensive research literature documents the relationships between this task, and biological substrates involved in addictive behavior. As noted above, such tasks can provide a framework for the development and refinement of translational models of dependence, guiding further research on this topic in both humans and non-human animals.

A secondary goal of the proposed project will be to examine whether the outcomes of primary aims are moderated by any of several variables suggested by prior research, including sex (Perkins, Donny, & Caggiula, 1999), working memory capacity (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008; Frank & O'Reilly, 2006), as well as self-reported trait differences in nicotine dependence, approach/avoidance motivational tendencies and impulsivity/risk-taking. An additional exploratory goal will be to examine the convergent validity between primary outcome variables and select variables with more immediate clinical relevance (e.g. self-reported withdrawal, craving, mood, subjective value of smoking, smoking topography), in order to better understand the external validity of these tasks and inform future research aimed at developing interventions that are consistent with the proposed model.

Aims and Hypotheses. In accordance with the aforementioned goals, the following specific *a priori* hypotheses were made: 1) Nicotine withdrawal will produce a leftward shift in frontal alpha power, indicative of an avoidant motivational state; 2) Nicotine withdrawal will slow response times to initiate the next trials following a loss, result in decreased neural reactivity in response to unexpected rewards and increased neural reactivity in response to

unexpected non-rewards; and 3) Nicotine withdrawal will impair approach-based learning (indexed by a reduction in accuracy for approach trials during the testing phase of the probabilistic learning task), enhance avoidance-based learning (increased accuracy for avoidance trials during the testing phase of the probabilistic learning task) and enhance feedback-related negativity response during the training phase of the probabilistic learning task. Additional exploratory aims of the present study include: 1) testing whether the effects described in each of the above hypotheses are moderated by demographic, smoking or other individual difference characteristics; 2) examining convergent validity of primary outcome variables with behavioral and self-report indices of smoking motivation (e.g. smoking topography, craving, withdrawal, mood, ratings of cigarettes). We make no specific hypotheses regarding these effects.

Methods

Experimental Design and Overview

The present study employed a within-subjects design, wherein participants completed a baseline session followed by two counter-balanced experimental sessions in which they smoked either nicotine (0.60 mg nicotine yield) or placebo (0.05 mg nicotine yield) cigarettes (i.e. Quest 1 or Quest 3; Vector Tobacco, Inc.). Each experimental session was preceded by 12 hours of smoking abstinence and both participants and experimenters were blind to cigarette contents. Primary outcome measures included asymmetry in resting cortical activity (Hypothesis 1), as well as behavioral and neural (i.e. event-related potential) responses on two counter-balanced computer tasks (Hypotheses 2 and 3). A wide variety of potentially relevant variables were collected at baseline for exploratory analyses aimed at determining whether they moderate any of the primary outcomes (Exploratory Aim 1). Self-report and behavioral indices of smoking motivation were also collected at the experimental sessions to confirm the success of the experimental manipulation and determine the extent to which results from primary outcome measures converge with established indicators of smoking motivation (Exploratory Aim 2). Participants were compensated approximately $110 apiece for completing the study, with the exact amount varying across participants and sessions due to the use of task-based incentives, as described below.

Participants

A total of 75 smokers were recruited from the community via online and newspaper advertisements, flyers, and an existing participant database. The initial eligibility determination

was made via telephone based on the criteria outlined below, followed by a more detailed assessment during their baseline session at the laboratory. Of the 75 smokers who presented for the initial appointment, 27 either failed to attend any of the experimental sessions or were determined to be ineligible based on the following criteria. Individuals were required to be English-speaking, 18-65 years of age, have smoked $\geq$ 15 cigarettes per day for at least one year, and not be actively attempting to quit at the time of study. Participants completed a urine drug screen to ensure freedom from medications/drugs with the potential to impact study outcomes (e.g. benzodiazepines, opiates, cocaine, amphetamines, halluncinogens). Female participants were also tested for pregnancy, and confirmed that they were not currently breast-feeding or planning to become pregnant during the course of their participation. Participants who reported significant medical comorbidities (e.g. asthma, high blood pressure, significant head injury involving loss of consciousness, Parkinson's disease, cancer, kidney disease), disabilities (e.g. significant visual or hearing impairment), or use of medications (e.g. psychotropic medications, beta blockers) that would compromise either the participants' safety or the validity of the results were excluded. Participants were also asked to report if they had ever been diagnosed with a mental health disorder and underwent additional testing to confirm they were free from active psychopathology at the baseline session.

Procedures

Baseline sessions began with informed consent procedures, followed by breath samples to confirm sobriety (BrAC = .000) and smoking status (CO $\geq$ 10 ppm). Next, urine samples were collected to confirm drug abstinence and negative pregnancy status (females). Participants then completed a battery of baseline questionnaires consisting of measures described in detail below. Afterwards, a brief structured interview (Sheehan et al., 1998) was administered to assess for the

presence of exclusionary psychopathology (i.e. depression, mania, psychosis, alcohol/drug dependence). Assuming all eligibility criteria were met, participants also completed a brief working memory task, and a behavioral task to assess risk-taking propensity. They were then paid, scheduled for their experimental session, given abstinence instructions and dismissed.

Experimental sessions began with breath samples to once again confirm sobriety (BrAC = .000), and compliance with abstinence procedures (CO < 10 or ≤ 50% of the value obtained at the baseline session). Initial measures of smoking motivation were obtained and then participants were allotted 10 minutes to smoke their first nicotine or placebo cigarette of the session via a CReSS topography device (Borgwaldt, Inc.; Hamburg, Germany). Measures of smoking motivation were completed again after smoking, as well as ratings of the cigarette and its effects. Participants were then fitted with an EEG cap and afterwards completed a second bout of smoking, followed by measures of smoking motivation and cigarette ratings. Immediately after completing the measures, EEG was recorded at rest for later extraction of frontal asymmetry indices. This was immediately followed by either the reward sensitivity or feedback learning tasks (counterbalanced across participants). Once the task was completed, a final round of smoking occurred followed by the same battery of measures as with previous bouts with the addition of a self-report measure of hedonic capacity/anhedonia. Lastly, participants completed another bout of resting EEG and the remaining task.

Primary Outcome Measures

Motivational State. Eight minutes of resting EEG activity was obtained at each recording (two per session) for extraction of frontal asymmetry indices. Each recording was divided into eight one-minute segments of eyes-open or eyes-closed recording that occurred in one of two

different counterbalanced orders (OCCOCOOC or COOCOCCO). Participants were seated and instructed to fixate their eyes at a spot on the wall during eyes open recording.

Reward Sensitivity. An established reward prediction task was used to assess reward processing/sensitivity (Potts et al., 2006). In this task, participants are presented with a sequence of stimuli that includes a predictor stimulus (S1), a reward-determining stimulus (S2), and the amount of the reward from the present trial plus current bankroll. Stimuli consist of lemons (representing no reward) and gold bars (representing reward). On 80% of trials, S1 and S2 are identical (i.e. S1 predicts S2). On the remaining trials, prediction is violated by the presentation of a different stimulus. Thus, there are a total of four trial types: (1) Expected Reward (S1 = Gold Bar; S2 = Gold Bar); (2) Unexpected Reward (S1 = Lemon; S2 = Gold Bar); (3) Expected No-Reward (S1 = Lemon; S2 = Lemon); and (4) Unexpected No-Reward (S1 = Gold Bar; S2 = Lemon). A reward ($0.25) occurs if S2 is a gold bar, regardless of S1. Participants "spend" $0.05 for each trial. Both the S1 and S2 stimulus were presented for 500 ms. Feedback remained on the screen until the next trial was initiated. A 300 ms black fixation cross occurred immediately prior to both the stimuli and feedback. Participants were presented with a total of 480 trials divided into 8 blocks. The task is self-paced, with individuals initiating each trial via button press. They begin each block with $1 in the bankroll, and at the end of the task draw a number between 1 and 8 and are paid their winnings for that block (averaging $5.50). EEG was recorded throughout, as was the time taken to initiate the next trial following presentation of the reward/bankroll.

Feedback Learning. An established feedback learning task was used to assess participants approach and avoidance learning tendencies (Frank et al., 2004). The task consists of two phases. During the first phase (training), participants are repeatedly presented with three different pairs

of stimuli (see Table 1). Each stimulus has a certain probability of resulting in reward, and participants have up to 4 seconds per trial to select between them, learning their relative contingencies over the duration of the training phase. After each trial, participants are presented with feedback regarding whether the stimulus was correct on that particular trial, consisting of the word "Correct!" in blue font or "Incorrect!" in red font. Each trial began with a green fixation cross presented for a random interval between 250-750 ms. Stimuli were then presented for up 4000 ms. If no response was made during that window, the phrase "No response detected" was presented as feedback. After the selection was made or the 4000 ms expired, a blank screen was presented for 350 ms, followed by feedback for 600 ms. A blank screen was presented for 500 ms between trials. Each of the stimulus pairs occurred 20 times within each of four blocks of training. After the fourth block and any subsequent blocks (up to a maximum of 6), participants were evaluated to determine if they met a minimum criterion for optimal responding (65% A in AB, 60% C in CD, 50% E in EF). Once meeting this criterion or after reaching 6 blocks, participants transitioned to the testing phase of the task. During this phase, stimuli are recombined so that all 15 possible combinations are presented eight times each across 120 trials. No feedback occurs during this phase, but the timing and sequence are otherwise identical to the training phase. Participants were paid $0.10 for each correct response during the testing phase in order to motivate effort. Approach and avoidance learning are determined by measuring the degree to which participants select A (the most-frequently rewarded stimulus overall) vs. avoid B (the least-frequently rewarded stimulus) in novel pairings. Novel stimuli were used at each session to avoid carryover effects and stimulus assignment to reward probabilities was counterbalanced across participants. As with the reward prediction task, EEG was recorded throughout the task.

Table 1. *Sample stimuli for probabilistic learning task*

Name	Stimulus	Reward Probability %	Name	Stimulus	Reward Probability %
A	や	80%	**B**	ぬ	20%
C	す	70%	**D**	ん	30%
E	せ	60%	**F**	そ	40%

Hedonic Capacity. In addition to the above, self-reported anhedonia/hedonic capacity was assessed with the *Snaith-Hamilton Pleasure Scale* (SHAPS) to determine if the effects are captured by self-report. The SHAPS assesses consists of 14 common activities and participants rate their capacity to experience pleasure from each of them (Snaith et al., 1995).

Baseline Measures/Moderators

Demographic information, including sex, age, race, ethnicity, education, and income level, along with a brief medical history were assessed with a series of single item questions. Female participants also reported the date their last menstrual cycle began and the anticipated start date of their next cycle (this information was updated at each experimental session). The *Chapman Handedness Inventory* (CHI) was used a measure of hand dominance, which is believed to influence EEG asymmetry. It consists of 13 items and has high internal consistency and test-retest reliability (Chapman & Chapman, 1987). Two measures of nicotine dependence were employed in the present study. The *Fagerström Test for Nicotine Dependence* (FTND) is a brief, well-established, unidimensional measure of nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The *Wisconsin Inventory of Smoking Dependence Motives* (WISDM) is a 68-item multidimensional measure that includes 13 subscales (Piper et al., 2004). A brief smoking history was obtained, including single item measures to assess age at initiation

and duration of smoking, as well as any history of cessation attempts. The *Contemplation Ladder*, an 11-point continuous measure of cessation motivation (Biener & Abrams, 1991), was included as part of this history and participants also reported their confidence they would succeed if they tried to quit smoking along a 5-point scale (ranging from not at all confident to completely confident).

Several other individual difference measures were obtained as potential moderators of experimental effects. These included the *Big Five Inventory* (BFI), a widely used 44-item measure of five dimensions of personality: Extraversion, Neuroticism, Agreeableness, Conscientiousness, and Openness (John, Naumann, & Soto, 2008). Analyses for the present study focused on only the first two dimensions, which have theoretically tenable links to motivational systems. Trait differences in motivational systems were also directly assayed using the *Behavioral Inhibition System/Behavioral Activation System* (BIS/BAS) scale (Carver & White, 1994). It includes three subscales for Behavioral Activation System (Reward Responsiveness, Drive and Fun-Seeking), with a separate scale for the Behavioral Inhibition System. It has adequate reliability, and previous research has documented its relation to other measures of approach/avoidance motivation, including those employed in the present study (Sutton & Davidson, 1997). The *Barratt Impulsiveness Scale – Version 11* (BIS-11) was used to assess impulsivity. It consists of 30 items that provide a composite score of multiple dimensions (Patton, Stanford, & Barratt, 1995). A cognitive measure was also included; the *Cognitive Failures Questionnaire* (CFQ) is a 25-item self-report measure of commonplace cognitive errors, that includes items of memory, distractibility and physical errors (Broadbent, Cooper, FitzGerald, & Parkes, 1982).

At the end of the baseline session, participants also completed two tasks under the supervision of an experimenter. The first was the *Reading Span* task (Daneman & Carpenter, 1980), a brief test of working memory. In the task, participants are presented with simple sentences of 6-10 words to read aloud and must retain the last word from each sentence while reading. After completing a designated number of sentences (ranging from 2 to 5), participants are asked to recall as many of the last words as they can. The second was a computerized measure of risk-taking, the *Balloon Analogue Risk Task* (BART; Lejuez et al., 2007). The youth version of this task was used due to its relative brevity and ease of determining compensation for task performance relative to the version designed for adults. In the task, participants are shown a balloon on screen and may earn points displayed in a bank via "pumping" that balloon by clicking on a button. However, the balloon increases in size with each pump and has a greater risk of popping (no points are awarded if the balloon pops). Thus, each pump results in both greater reward and greater risk of losing that reward. Participants must elect to either further pump the balloon or collect the points earned for that trial. The number of presses prior to the balloon exploding varies randomly across 30 task trials, though increases with each press. Compensation for this task was based on the total number of points collected across all trials divided amongst four possible categories. These are labeled small, medium, large and bonus and corresponded to payments of $1, $3, $5 and $7 respectively. The primary score used to measure performance is the average number of pumps on unexploded balloons.

Smoking Motivation Measures

Three core constructs thought to play a key role in smoking motivation were measured: withdrawal, craving and mood. Withdrawal was measured using the *Minnesota Nicotine Withdrawal Scale-Revised* (MNWS-R), which assesses 15 common symptoms of tobacco

withdrawal (Hughes & Hatsukami, 1986, 1998). Craving was measured using the *Questionnaire on Smoking Urges – Brief* (QSU-B), a 10-item measure that includes two separate factors – one assessing the desire to smoke for pleasurable effects and one assessing desire to smoke to alleviate aversive symptoms (Cox, Tiffany, & Christen, 2001). The *Mood Form* (MF; Diener & Emmons, 1984), which consists of 9 items that span both positive and negative moods, was used to assess current mood.

Cigarette Rating Measures

Cigarettes were rated using the *Modified Cigarette Evaluation Questionnaire* (mCEQ; Cappelleri et al., 2007). The mCEQ is a 12-item measure of the subjective rewarding effects derived from smoking, consisting of 3 subscales (Smoking Satisfaction, Psychological Reward, and Aversion) plus 2 single-item measures (Enjoyment of Respiratory Tract Sensations, and Craving Reduction).

Smoking Topography Measures

A Clinical Research Support System (CReSS) desktop device was used to measure smoking topography. The device allowed for the direct assessment of numerous components of smoking behavior, including puffs per cigarette, puff volume, puff duration, inter-puff interval and peak flow rate. It is both highly reliable and concordant with other measures of smoking topography (Blank, Disharoon, & Eissenberg, 2009).

Cortical Data Acquisition

Participants were fitted with a 64-channel electroencephalogram (EEG) cap for measurement of resting EEG, and event-related potentials during the computer tasks. The caps used (Compumedics; Charlotte, NC) include a standard 10-20 electrode montage, two mastoid channels and separate bipolar channels for the monitoring of vertical and horizontal eye

movements and blinks. Electrode impedances were kept under 50kΩ. A Neuroscan Synamps[2] system was used for signal amplification. Data was recorded in AC mode at 1000 Hz with an online bandpass filter of .05-200 Hz. A vertex reference was used during acquisition, but re-referenced to the average of the two mastoid electrodes offline.

Data Processing

Smoking Topography. Puff data was processed separately for each cigarette using the *Puff CleanUp Utility* (Borgwaldt, Inc.; Hamburg, Germany). A puff was collapsed into the preceding puff if the inter-puff interval was less than 300 ms. Puffs with volumes below 5.0 ml or durations below 200 ms were removed. Indices were then averaged across puffs, with the exception of number of puffs and total puff volume (which was a sum of individual puff volumes for a given cigarette).

Cortical Data. All data was visually inspected for paroxysmal artifact and problematic sections were flagged for removal. Data processing was done using a set of custom Matlab scripts and existing toolboxes (details as follows). Bad channels were replaced using a spherical spline interpolation procedure (Srinivasan, Nunez, Tucker, Silberstein, & Cadusch, 1996) and channels with non-standard locations (i.e. CB1, CB2) were removed from the dataset. Data was down-sampled to 500 Hz and an optimal finite impulse response filter was generated (Cook & Miller, 1992) for the application of lowpass filters (Resting EEG: 50 Hz; Task-Based EEG: 30 Hz) to the continuous data. Resting EEG was then divided into 2000ms epochs with 1500 ms overlaps. Task-Based EEG was epoched from 200 ms prior to the relevant event to 1000 ms following it. Both resting and task data were then subjected to (separate) Independent Components Analyses (ICAs; Jung et al., 1998) to identify and parse eye movements, eyeblinks and other artifacts using *runica* within the EEGlab toolbox (Delorme & Makeig, 2004).

Artifactual components were identified using the ADJUST plugin (Mognon, Jovicich, Bruzzone, & Buiatti, 2011) and removed, with the remaining components being back-projected to the scalp. Residual artifacts were then identified according to criteria set forth by Foti et al. (2009) and offending epochs were flagged for removal. All channels were then re-referenced to the average of the two mastoid electrodes.

Frontal asymmetry of resting EEG was calculated according to standard procedures (Coan & Allen, 2004). A fast Fourier Transformation (FFT) using a Hamming window was conducted on each epoch. Power in the alpha frequency band (8-13 Hz) was then extracted, averaged across epochs and log transformed. Difference scores were computed for frontal electrodes (i.e. F2-F1; F4-F3; F6-F5; F8-F7). It was these scores that were targeted for analysis. For event-related potentials, epochs time-locked to the stimulus of interest (S2 on reward prediction task, feedback on probabilistic learning task) were extracted. Epochs were all baseline corrected to the 200 ms pre-stimulus interval. Signals within the time window of interest were then averaged across epochs and electrodes based on regions of interest identified in prior research using each task (Frank et al., 2005; Martin, Potts, Burton, & Montague, 2009) and visual inspection of the waveforms. In the case of the MFN on the reward prediction task, this corresponded to the signal from electrodes FP1, FPz, FP2, AF3, AF4, F1, Fz, F2, FC1, FCz and FC2 occurring 250-350 ms following S2 onset. The same set of electrodes was used for extraction of the FRN on the probabilistic learning task with the exception of FP1, FPz and FP2, which exhibited minimal variance as a function of trial type and were thus excluded. Signals were extracted from these electrodes from the 220-320 ms window following feedback onset.

Data Analysis

Except where otherwise noted, all analyses employed a mixed model framework with a random intercept for subject. A restricted maximum likelihood approach was used for variance component estimation. An initial model was run for each outcome with only relevant experimental variables entered to determine overall effects. Moderator variables were grand-mean centered before being separately introduced into the model to determine their overall influence and potential interaction with all possible combination of experimental effects. A comparable approach was used for testing the concordance of primary outcomes with smoking motivation variables. The most temporally proximal value was used for each comparison (i.e. the third craving assessment for the first resting EEG, the fourth craving assessment for the second resting EEG, the third craving assessment for the reward prediction on sessions where it was administered first, etc.). Owing to the large number of moderators and smoking motivation variables examined, the Benjamini-Hochberg approach was used to control the false discovery rate (FDR; Benjamini & Hochberg, 1995) for each series of analyses.

Results

Sample Characteristics

A total of 41 participants completed the baseline session and both experimental sessions.

An additional 7 participants completed the baseline session and one experimental session.

Demographic and smoking characteristics of the sample are presented in Table 2. The

prototypical participant was a relatively heavy smoker with a moderate level of nicotine

dependence, in their mid-late 30's and with relatively low educational attainment. Completers

and non-completers did not differ on any of these variables (all p's > .05).

Table 2. *Sample Characteristics*

	Completers Only Mean (SD) or %	All Participants Mean (SD) or %
Demographic Variables		
Age	38.2 (10.4)	37.9 (9.8)
Sex (% female)	36.6%	35.4%
Race (% non-white)	26.8%	29.2%
Ethnicity (% Hispanic)	12.2%	12.5%
Education Level (% ≤ HS Degree)	51.2%	54.2%
Handedness (% Right-handed)	68.3%	68.8%
Smoking Variables		
Cigarettes Per Day	20.4 (10.7)	20.3 (10.3)
FTND	4.9 (1.9)	5.1 (1.9)
Contemplation Ladder	4.4 (2.7)	4.5 (2.5)
Baseline CO Level	32.4 (15.9)	31.9 (15.0)
Age Became Regular Smoker	17.9 (4.3)	18.0 (4.6)
# Past Quit Attempts	1.6 (2.4)	1.6 (2.3)
Preferred Cigarette Type (% Menthol)	41.5%	43.8%

Note. HS = High School; FTND = Fagerström Test for Nicotine Dependence;
CO = Carbon Monoxide. Owing to the small number of left-handed individuals
(< 5%), this category was collapsed with ambidextrous for analysis.

Exposure Biomarkers

The expected decrease in CO level from baseline to experimental sessions was observed,

F (1, 89.0) = 387.28, $p < .001$. This decrease did not differ as a function of nicotine contents, F

(1, 96.2) = 0.56, $p = .457$. Initial CO levels at experimental sessions also did not differ as a

function of nicotine contents, $F (1, 41.8) = 1.59$, $p = .214$. At experimental sessions, a significant main effect of cigarette number was observed, indicating that the CO boost increased across the cigarettes, $F (2, 212.7) = 3.46$, $p = .033$. Post-hoc testing revealed a trend-level increase in the size of the CO boost from the first to the second cigarette ($p = .064$) and a significant increase from the first to the third cigarette ($p = .012$). A significant main effect of withdrawal status indicated that CO boosts were larger overall for sessions with nicotine cigarettes, $F (1, 220.2) = 5.77$, $p = .017$. However, the interaction between withdrawal status and cigarette number was not significant, $F (2, 212.7) = 1.25$, $p = .290$. Means and standard deviations for all CO levels are presented in Table 3.

Table 3. *Carbon monoxide level means and standard deviations*

Status	Baseline	Experimental						
	CO	Pre-Cig 1	Post-Cig 1	Pre-Cig 2	Post-Cig 2	Pre-Cig 3	Post-Cig 3	
	M (SD)	M (SD	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	
Placebo	31.9 (15.0)	9.8 (6.0)	15.3 (7.2)	13.0 (6.2)	19.3 (7.5)	16.5 (6.6)	22.7 (7.7)	
Nicotine		10.7 (6.6)	16.8 (7.8)	13.9 (6.9)	20.3 (8.2)	16.9 (7.0)	24.0 (8.9)	

Note. CO = Carbon Monoxide.

Smoking Motivation

There was no evidence to suggest there were differences in the initial (pre-smoking) scores for craving [$F (1, 41.2) = 0.42$, $p = .519$] or negative mood [$F (1, 41.8) = 2.41$, $p = .128$] as a function of the nicotine content of the sessions. There were weak trend-level effects indicating participants reported slightly higher levels of both withdrawal [$F (1, 42.4 = 2.96$, $p = .093$] and positive mood [$F (1, 41.4) = 3.03$, $p = .089$] at nicotine sessions prior to smoking. In an abundance of caution, pre-smoking scores for all available variables were included as covariates in the subsequent analyses examining scores on these measures administered after each bout of smoking. Table 4 depicts the mean values for each internal state across time points separately as a function of session type (i.e. nicotine contents).

Craving. After adjusting for baseline craving, results revealed a significant main effect of nicotine on QSUB total scores, $F(1, 215) = 8.65$, $p = .004$, with participants in placebo sessions reporting higher craving across time points. A significant main effect for cigarette number was also observed, $F(2, 210.3) = 12.59$, $p < .001$. Post-hoc testing revealed craving was significantly higher following the first cigarette, relative to the second ($p = .002$) and third ($p < .001$) cigarettes, with only a small trend-level differences between the second and third cigarettes ($p = .085$). The interaction between nicotine and cigarette number was not significant, $F(2, 210.3) = 0.46$, $p = .955$.

Table 4. *Internal state means and standard deviations*

Variable	Range	Session	Baseline M (SD	Post-Cig 1 M (SD)	Post-Cig 2 M (SD)	Post-Cig 3 M (SD)
Craving	10-70	Placebo	40.20 (14.37)	23.09 (11.99)	20.13 (12.14)	18.40 (10.90)
		Nicotine	42.03 (16.90)	21.02 (12.75)	18.23 (11.14)	16.86 (11.07)
Withdrawal	0-32	Placebo	8.11 (5.35)	3.67 (3.38)	2.47 (2.53)	2.76 (2.63)
		Nicotine	9.39 (5.72)	3.18 (3.19)	2.37 (2.92)	2.34 (2.59)
Positive Mood	0-6	Placebo	2.54 (1.50)	2.76 (1.51)	2.79 (1.61)	2.74 (1.53)
		Nicotine	2.69 (1.57)	3.19 (1.46)	3.05 (1.50)	2.97 (1.57)
Negative Mood	0-6	Placebo	0.75 (1.03)	0.37 (0.68)	0.23 (0.47)	0.25 (0.47)
		Nicotine	0.96 (1.34)	0.27 (0.46)	0.17 (0.39)	0.22 (0.50)

Note. Range depicts the full range of possible scores for the scale. Craving and withdrawal use summed scores, mood measure uses mean scores.

Withdrawal. Although participants reported greater withdrawal across time points in the placebo session, this effect did not reach significance, $F(1, 224.6) = 3.38$, $p = .067$. A significant effect of cigarette number was observed, $F(2, 209.7) = 7.77$, $p = .001$. Post-hoc tests revealed significant differences from the first to the second ($p = .000$) and third ($p = .002$) third cigarettes, with no differences between the second and third cigarettes ($p = .637$). As with craving, the nicotine x cigarette number interaction was not significant, $F(1, 209.7) = 0.27$, p .762.

Positive Mood. Participants reported higher levels of positive mood across time points during the nicotine session, $F(1, 223.5) = 8.86$, $p = .003$. The effect of cigarette number was not significant, $F(2, 205.7) = 0.95$, $p = .388$, nor was the nicotine x cigarette number interaction, F

$(2, 205.7) = 0.72$, $p = .487$.

Negative Mood. Participants reported lower levels of negative mood across time points during the nicotine sessions, $F (1, 220.1) = 6.02$, $p = .015$. A significant effect of cigarette number was also found, $F (2, 209.6) = 5.33$, $p = .006$. Consistent with prior results, post-hoc tests indicated this was driven by significant differences between the first and the second ($p = .002$) and third ($p = .025$) cigarettes, with no difference between the second and third cigarettes ($p = .367$). The nicotine x cigarette number interaction was not significant, $F (2, 209.6) = 0.56$, $p = .572$.

Cigarette Ratings

Means and standard deviations of each mCEQ subscale as a function of nicotine contents (i.e. withdrawal status) are presented below in Table 5.

Table 5. *Cigarette rating scale means and standard deviations*

Variable	Range	Session	Cig 1 M (SD)	Cig 2 M (SD)	Cig 3 M (SD)
Smoking Satisfaction	1-7	Placebo	3.81 (1.41)	3.61 (1.52)	3.49 (1.45)
		Nicotine	4.65 (1.41)	4.11 (1.65)	3.98 (1.68)
Psychological Reward	1-7	Placebo	2.79 (1.39)	2.32 (1.25)	2.33 (1.27)
		Nicotine	3.36 (1.49)	2.67 (1.48)	2.64 (1.40)
Craving Reduction	1-7	Placebo	4.11 (2.00)	3.82 (1.89)	3.96 (1.87)
		Nicotine	4.93 (1.76)	4.16 (2.08)	3.64 (1.98)
Enjoyment of Respiratory Sensations	1-7	Placebo	2.93 (1.66)	2.80 (1.75)	2.62 (1.57)
		Nicotine	3.91 (1.84)	3.43 (1.90)	3.25 (1.94)
Aversion	1-7	Placebo	1.70 (0.89)	1.38 (0.61)	1.26 (0.59)
		Nicotine	2.16 (1.04)	1.52 (0.75)	1.50 (0.69)

Note. Range depicts the full range of possible scores for the subscale.

Smoking Satisfaction. A significant main effect of nicotine on satisfaction derived from smoking was found, $F (1, 218.0) = 27.34$, $p < .001$, with nicotine cigarettes being rated as more satisfying overall. A significant main effect of cigarette number was also present, $F (2, 214.3) = 9.53$, $p < .001$. Post-hoc tests revealed a pattern of findings similar to what was observed for internal state indices, with ratings of the first cigarette significantly higher than both the second

($p = .002$) and third ($p < .001$) cigarettes, but no difference between the second and third

cigarettes ($p = .293$). The nicotine x cigarette number interaction was not significant, F (2, 214.3)

$= 1.42$, $p = .243$.

Psychological Reward. Nicotine also had a significant effect on the psychological reward

derived from smoking, F (1, 217.60) $= 13.66$, $p < .001$, with nicotine cigarettes being rated as

more rewarding overall. As above, a significant main effect of cigarette number was also

observed, F (2, 214.0) $= 20.37$, $p < .001$. Post-hoc tests again indicated differences between both

the first and the second cigarette ($p < .001$), as well as the first and the third cigarette ($p < .001$),

with no difference between the second and third cigarette ($p = .897$). The nicotine x cigarette

number interaction was not significant, F (2, 214.0) $= 0.93$, $p = .398$.

Craving Reduction. A trend-level finding indicated nicotine cigarettes were rated as being

slightly more effective for reducing craving, F (1, 220.5) $= 3.27$, $p = .072$. A significant main

effect of cigarette number was observed, F (2, 214.3) $= 8.17$, $p < .001$. Post-hoc tests indicated

the presence of significant differences in ratings of craving reduction between the first and both

the second ($p = .005$) and third ($p < .001$) cigarettes, with no difference between the second and

third cigarettes ($p = .296$). However, all of these findings were qualified by a significant nicotine

x cigarette number interaction, F 2, 214.3) $= 4.74$, $p = .010$. When broken down, this interaction

indicated that only the first cigarette was rated as more effective for reducing craving based on

its nicotine content ($p = .006$), with no statistically significant differences for the second ($p =$

.227) or third ($p = .161$) cigarettes.

Respiratory Sensation Enjoyment. Nicotine cigarettes were rated as producing

significantly more enjoyable respiratory tract sensations, F (1, 217.9) $= 26.59$, $p < .001$. A

significant effect of cigarette number was also observed, F (2, 214.1) = 6.28, p = .002. Post-hoc testing revealed that ratings of the first cigarette differed from both the second (p = .028) and third (p = .001) cigarettes, but that ratings of the second and third cigarette were comparable (p = .195). The nicotine x cigarette number interaction was not significant, F 2, 214.1) = 1.04, p = .355.

Aversion. Nicotine cigarettes were also rated as producing significantly more aversive sensations overall, F (1, 220.8) = 21.31, p < .001. As with other indices, a significant main effect of cigarette number was observed, F (2, 212.7) = 25.59, p < .001. As above, post-hoc tests revealed indicated the first cigarette was rated as significantly more aversive than the second (p < .001) or the third (p < .001) cigarettes, but the second and third cigarettes did not differ from one another (p = .388). The nicotine x cigarette number interaction was not significant, F (2, 212.7) = 1.83, p = .162.

Smoking Topography

Due to technical problems, topography data was unavailable for the first cigarette of a placebo session for one participant, the first cigarette of a nicotine session for one participant and for the third cigarette of a placebo session for one participant. Additionally, all topography indices were screened for values outlying from the grand mean and values more than 3 SDs from the mean were excluded from analyses. This resulted in the exclusion of additional values for: Average Interpuff Interval (1 value), Average Puff Duration (2 values), Average Puff Volume (1 value) and Total Puff Volume (6 values). Values were also screened for their deviation from subject-specific means, but no additional outlying values were identified. Means and standard deviations of topography indices are presented in Table 6.

Table 6. *Smoking topography means and standard deviations*

Variable	Session	Cig 1 M (SD)	Cig 2 M (SD)	Cig 3 M (SD)
Total Puff Volume	Placebo	1163.12 (399.95)	1051.00 (286.63)	1135.42 (379.97)
	Nicotine	1114.55 (331.45)	1035.77 (267.16)	1017.31 (284.10)
Average Puff Volume	Placebo	98.61 (29.93)	96.66 (32.37)	93.33 (27.91)
	Nicotine	92.54 (32.06)	87.78 (26.77)	85.28 (28.36)
Average Flow Rate	Placebo	58.67 (15.92)	56.11 (14.93)	56.52 (16.65)
	Nicotine	59.05 (16.73)	55.79 (15.39)	53.18 (13.78)
Average Inter-Puff Interval	Placebo	14.70 (5.56)	15.21 (5.83)	14.10 (5.06)
	Nicotine	16.28 (6.16)	16.18 (5.54)	14.85 (5.58)
Average Puff Duration	Placebo	2.14 (0.62)	2.21 (0.61)	2.20 (0.72)
	Nicotine	2.00 (0.65)	2.05 (0.70)	1.98 (0.63)
Number of Puffs	Placebo	12.68 (3.37)	11.89 (2.90)	12.70 (3.10)
	Nicotine	12.58 (3.11)	12.36 (3.26)	12.55 (3.27)

Note. Puff volume is in milliliters. Flow rate is in milliliters per second. Inter-puff interval is in seconds. Puff duration is in seconds.

Total Puff Volume. Results revealed a weak trend-level main effect of nicotine content on total puff volume, $F (1,216.5) = 3.07$, $p = .081$, indicating higher total puff volume across cigarettes during placebo sessions. A similarly weak trend-level finding was observed for cigarette number [$F (2, 206.9) = 2.51$ $p = .083$]. Post-hoc tests revealed a trend suggesting significantly higher puff volume for the first cigarette relative to the third ($p = .055$), with no differences between the first and second cigarette ($p = .300$) nor the second and third cigarettes ($p = .366$). The cigarette number x nicotine content interaction was not significant [$F (2, 209.1) = 0.16$, $p = .851$.

Average Puff Volume. Results revealed a significant main effect of nicotine content on average puff volume, $F (1,214.2) = 7.00$, $p = .009$, indicating that participants' puff volume was significantly higher for placebo cigarettes. No main effect of cigarette number was observed [$F (2, 209.1) = 1.87$, $p = .157$], nor was there a significant interaction between cigarette number and nicotine contents [$F (2, 209.1) = 0.16$, $p = .851$.

Average Peak Flow Rate. There was a significant effect of cigarette number for average flow rate [$F (2, 211.3) = 4.26$, $p = .015$] indicating higher flow rates for the first relative to the

second ($p = .037$) and third ($p = .005$) cigarettes, with no difference between the second and third

cigarettes ($p = .473$). There was no main effect of nicotine content [$F(1, 216.1) = 0.09, p = .765$]

nor was there evidence of a nicotine contents x cigarette number interaction [$F(2, 211.3) = 1.19,$

$p = .307$].

Average Inter-puff Interval. A significant main effect of nicotine content was found for

inter-puff interval [$F(1, 212.8) = 15.22, p < .001$] indicating inter-puff intervals were shorter for

placebo cigarettes than nicotine cigarettes. A significant main effect of cigarette number was also

found [$F(2, 209.8) = 6.940, p = .002$]. Post-hoc tests revealed this was driven by a significantly

shorter inter-puff interval at the third cigarette relative to the first ($p = .006$) and second ($p =$

$.001$) cigarettes, with no difference between the first and second cigarettes ($p = .592$). The

nicotine content x cigarette number interaction was not significant [$F(2, 209.8) = 0.63, p =$

$.532$].

Average Puff Duration. A main effect of nicotine content [$F(1, 211.0) = 17.32, p < .001$]

indicated participants took significantly longer puffs on placebo relative to nicotine cigarettes.

There was no effect of cigarette number [$F(2, 208.7) = 0.76, p = .471$], nor was there a nicotine

contents x cigarette number interaction [$F(2, 208.7) = 0.01, p = .992$].

Number of Puffs. A trend-level finding suggested number of puffs taken differed across

cigarettes [$F(2, 211.0) = 2.71, p = .069$], with post-hoc testing suggesting slightly fewer puffs

being taken on the second cigarette relative to both the first ($p = .048$) and third ($p = .043$)

cigarette, with no difference between the first and third cigarette ($p = .968$). No effect of nicotine

content was observed [$F(1, 214.7) = 0.21, p = .646$], nor was there evidence of a nicotine

content x cigarette number interaction [$F(2, 211.0)\ 1.01, p = .367$].

Hedonic Capacity

Anhedonia scores ranged from 14-56. Participants did report greater capacity to experience pleasure in the nicotine condition ($M_{Placebo}$ = 44.56, $SD_{Placebo}$ = 5.61; $M_{Nicotine}$ = 46.11, $SD_{Nicotine}$ = 7.15), but this effect did not reach statistical significance, F (1, 43.0) = 3.00, p = .090.

Motivational State

Frontal Asymmetry. Results revealed a significant main effect of nicotine content [F (1, 670.85) = 11.20, p < .001] with significantly lower scores during placebo sessions than nicotine sessions (indicative of greater left hemisphere alpha). Neither session order, nor recording instance within session were associated with asymmetry scores and did not interact with the nicotine effect (all p's > .05). A significant main effect for electrode sites was found [F (1, 653.252) = 4.90, p = .002], indicating overall asymmetry scores differed across the homologous electrode pairs. However, this finding did not interact with nicotine content [F (3, 653.25) = 0.21, p = .889]. When broken down across specific electrode pairs, results indicated the nicotine effect was significant for F1-F2 [F (1, 134.93) = 4.52, p = .035] and the F3-F4 pair [F (1, 133.44) = 7.86, p = .006]. Although similar in size and direction, effects did not reach significance for either the F5-F6 pair [F (1, 133.68) = 2.26, p = .136] or the F7-F8 pair [F (1, 134.31) = 2.88, p = .092]. Results are presented in Figure 1.

Moderators. For all moderator analyses, a main effect of electrode site was retained as a covariate. The relevant moderator variable was then introduced to determine its association with overall asymmetry scores and whether it interacted with nicotine. All moderators were tested individually in separate models. Results are presented in Table 7. Examination of these moderator effects indicated the above effects of frontal asymmetry were present in men (p <

.001), but not women ($p = .506$). The effect was present among those who had *not* made a quit

attempt in the past ($p < .001$) but not among those who *had* tried to quit previously ($p = .631$).

Individuals with greater motivation to quit exhibited smaller withdrawal-induced shifts towards

left frontal alpha asymmetry ($B = 0.00426$, 95% CI [0.00173, 0.00678], $p < .001$). Individuals

who were menthol smokers ($p < .001$) exhibited larger effects than those who were non-menthol

smokers ($p = .364$). Lastly, participants with relatively greater activation system scores (i.e.

approach-driven motivational tendencies) exhibited larger shifts towards left frontal alpha

asymmetry. This finding converged across the Reward Response ($B = -0.0256$, 95% CI [-0.0362,

-0.0150], $p < .001$), Drive ($B = -0.0193$, 95% CI [- 0.0302, - 0.0083], $p < .001$) and Fun-Seeking

subscales ($B = -0.0243$, 95% CI [-0.0366, -0.0119], $p < .001$) of the BIS/BAS measure.

Association with Smoking Motivation. Results are presented in Table 8. As above,

electrode site was retained as a covariate for all analyses. Following the FDR correction

procedure, five indices of smoking motivation retained a significant overall association with

frontal asymmetry (i.e. craving, negative mood, craving reduction in response to the cigarette,

average puff volume and average inter-puff interval). No interactions with nicotine content were

observed after correction, thus these associations do not appear to be strictly dependent on

withdrawal state. Greater craving was associated with lower asymmetry difference scores ($B = -$

0.00080, 95% CI [-0.00135, -0.00026], $p = .004$) and relatedly greater reductions in craving

following smoking were associated with higher asymmetry difference scores ($B = 0.00495$, 95%

CI [0.00193, 0.00798], $p = .001$). Greater negative mood was associated with higher asymmetry

difference scores ($B = 0.02118$, 95% CI [0.00584, 0.03651], $p = .007$). Greater puff volume was

associated with lower asymmetry scores ($B = -0.00031$, 95% CI [-0.00051, -0.00010], $p = .004$)

and longer inter-puff intervals were associated with higher asymmetry scores ($B = 0.00186$, 95% CI [0.00070, 0.00301], $p = .002$).

Reward Sensitivity

Behavioral. Trials with response times < 100 ms or $> \pm 3$ SDs from the grand mean or the individual's trial-type mean for a given session were removed (7.5% of trials). To account for this missing data, mixed models examining response times were analyzed directly at the trial level rather than averaging them together prior to analysis. One nicotine session and one placebo session were outliers with regards to the number of trials eliminated due to the response time cleaning procedures, so were excluded from all response time analyses presented below. Among the remaining sessions, a significant nicotine content x prediction x reward interaction was observed [$F (1, 38565.99) = 8.70, p = .003$]. When broken down, this interaction indicated the presence of slowed response times to both unpredicted rewards ($p < .001$) and unpredicted non-rewards ($p < .001$) relative to their predicted counterparts during placebo sessions. In contrast, during nicotine sessions slowed response times were observed in response to unpredicted rewards relative to predicted rewards ($p < .001$), but not unpredicted non-rewards relative to predicted non-rewards ($p = .355$). These findings are displayed in Figure 2.

Neural. Visual inspection of the waveforms confirmed the presence of a robust MFN peaking 285 ms after onset of the S2 stimulus, with the largest variability observed at the Fz electrode. Results confirmed the presence of the anticipated prediction x reward interaction [$F (1, 299.80) = 31.74, p < .001$], indicating prediction errors resulted in a more positive deflection for reward trials and a more negative deflection for non-reward trials. A significant main effect of nicotine contents was found [$F (1, 303.72) = 13.12, p < .001$], revealing that the MFN was more negative during placebo sessions. However, nicotine contents did not interact with

prediction or reward trial types, nor was the hypothesized nicotine contents x reward x prediction interaction significant (all p's > .170). Findings are displayed in Figure 3 and waveform at electrode Fz is presented in Figure 4.

Moderators. Results of moderator analyses for behavior are presented in Table 9. These indicated that heavier smokers (i.e. higher CPD) had larger increases in response time in response to unpredicted trials relative to predicted trials (B = 2.39, 95% CI [1.30, 3.49], p < .001). Individuals who did not initiate smoking until they were older (B = 3.29, 95% CI [-5.20, 1.38], p = .001) or who were high in behavioral inhibition (B = -39.24, 95% CI [, -57.73, -20.76], p < .001) had smaller increases in response time in response to reward trials relative to non-reward trials. With regards to the effects of nicotine on response to reward trials, a significant Sex x Nicotine x Reward interaction was observed (B = 48.84, 95% CI [11.47, 86.21], p = .010). Breaking down this effect indicated it was driven by trend-level findings in opposite directions, suggesting nicotine had opposing effects in men and women. Men exhibited longer response times to rewards relative to non-rewards when receiving nicotine (p = .069), whereas women exhibited shorter response times to rewards relative to non-rewards when receiving nicotine. An Ethnicity x Nicotine x Reward interaction was also observed (B = -116.63, 95% CI [-171.44, -61.83], p < .001). This interaction indicated that nicotine had minimal effect on response to rewards among individuals not of Hispanic ethnicity (p = .304), but individuals of Hispanic ethnicity had faster response times to reward relative to non-reward trials during placebo sessions (p < .001), but slower response times to reward relative to non-reward trials during nicotine sessions (p = .013). A significant Nicotine Dependence (WISDM) x Nicotine x Reward interaction (B = -2.61, 95% CI [-3.90, -1.31], p < .001) indicated that withdrawal slowed response times on reward trials the most for highly dependent individuals. A Neuroticism x

Nicotine x Reward interaction (B = -39.89, 95% CI [-66.83, -12.95], p = .004), with response times to rewards being slowest for individuals with high levels of neuroticism. In contrast, a significant Extraversion x Drug x Reward interaction (B = 46.65, 95% CI [20.71, 72.60], $p <$ .001) indicated that higher extraversion was relatively protective of withdrawal-induced reward-processing deficits. Lastly, a Behavioral Inhibition x Drug x Reward (B = 82.39, 95% CI [45.43, 119.34], $p <$ .001) indicated those low in behavioral inhibition exhibited a robust increase in response time to reward trials during placebo sessions, whereas those high in behavioral inhibition had faster responses to rewards during placebo sessions.

No moderators of MFN amplitude on the reward prediction task remained significant following FDR correction (see Table 10).

Association with Smoking Motivation. Results for smoking motivation and response time are presented in Table 11. A number of moderators exhibited moderate to strong positive (craving, withdrawal, positive mood, cigarette satisfaction, cigarette psychological reward, cigarette respiratory tract sensations, CO boost, total puff volume, average puff volume, average flow rate, average puff duration) or negative (cigarette craving reduction, cigarette aversive effects, number of total puffs) relationships with response time. A Psychological Reward x Prediction interaction indicated those with higher levels of psychological reward from the most proximal cigarette had reduced response times to unpredicted trials (B = -14.38, 95% CI [-22.75, -6.01], $p <$ .001). A significant Negative Mood x Reward interaction (B = 33.16, 95% CI [15.12, 51.21], $p <$ .001) indicated those with a more negative mood had slowed response times on reward trials. A CO Boost x Reward interaction (B = 5.20, 95% CI [2.27, 8.12], $p <$ .001) suggested those with a larger CO boost from the most proximal cigarette also had slowed

response times on reward trials.

  With regards to nicotine, a number of motivational variables were associated with the effect of nicotine on both prediction and reward trial response times. The increase in response time on unpredicted trials was significantly greater during placebo sessions amongst those reporting higher levels of negative mood, as evidenced by a Negative Mood x Nicotine x Prediction Type interaction (B = -67.25, 95% CI [-112.12, -22.38], p = .003). This increase was also observed among those with low inter-puff intervals, as evidenced by an Inter-puff Interval x Nicotine x Prediction Type interaction (B = 5.56, 95% CI [1.60, 9.52], p = .006). A significant Craving x Nicotine x Reward Type interaction (B = -3.06, 95% CI [-4.69, -1.42], p < .001) indicated a strong positive relationship between craving and response time following reward trials during placebo sessions. Comparable interaction effects were observed for nicotine withdrawal (B = -10.71, 95% CI [-17.40, -4.04], p = .002), negative mood (B = -63.18, 95% CI [-99.27, -27.08], p = .001), smoking satisfaction (B = -24.06, 95% CI [-35.27, -12.85], p < .001), psychological reward from smoking (B = -18.12, 95% CI [-31.66, -4.58], p = .009), reduction in craving from smoking (B = -16.38, 95% CI [-25.40, -7.36], p < .001). However, an opposing effect was found for enjoyment of respiratory tract sensations from smoking (B = -13.62, 95% CI [-23.88, -3.36], p = .009), which indicated a weaker relationship between this variable and response time following reward trials during placebo sessions. Lastly, a significant four-way Positive Mood x Nicotine x Prediction x Reward interaction was found (B = 57.96, 95% CI [28.63, 87.28], p < .001), indicating positive mood was most strongly associated with response time for unpredicted rewards during placebo sessions.

  Results of analyses examining associations between MFN amplitude and smoking

motivation variables are presented in Table 12. As shown, several variables were associated with MFN amplitude across all trial types (i.e. moderator main effects). MFN amplitude was positively associated with positive mood ($B = 0.45$, 95% CI [0.09, 0.81], $p = .015$), satisfaction from smoking ($B = 0.37$, 95% CI [0.07, 0.68], $p = .016$), psychological reward from smoking ($B = 0.62$, 95% CI [0.27, 0.98], $p = .001$), boost in carbon monoxide level ($B = 0.17$, 95% CI [0.06, 0.29], $p = .003$) and inter-puff interval ($B = 0.10$, 95% CI [0.02, 0.18], $p = .010$). In contrast, a negative association was observed between MFN amplitude and total puff volume ($B = -0.001$, 95% CI [-0.002, -0.001], $p = .002$). However, there were no significant interactions between any of the smoking motivation variables and either nicotine contents or the trial conditions (i.e. reward, prediction).

Feedback Learning

Behavioral. For 11 placebo sessions and 10 nicotine sessions, participants did not choose stimulus A over B during the testing phase on at least 50% of trials. To maintain consistency with prior research these sessions are excluded from the analyses presented below, though it should be noted that the pattern of findings for primary outcomes did not differ substantially when analyses were repeated with all sessions included. Limited variability precluded estimation of random effects for numerous analyses conducted on this task, so population-averaged models with a compound symmetry covariance matrix (analogous to repeated measures ANOVA) were employed throughout. There was no effect of trial type [$F (1, 97.29) = 0.35$, $p = .555$], nicotine content [$F (1, 124.47) = 0.06$, $p = .807$], nor was there evidence of a nicotine content x trial type interaction [$F (1, 97.29) = 0.68$, $p = .411$]. Separate analyses confirmed that nicotine content did not impact either Choose A ($p = .186$) or Avoid B ($p = .565$) performance. Results are presented

in Figure 5.

Neural. Visual inspection of the topographic plots revealed the presence of a robust FRN in the form of a negative-going wave peaking 300 ms after the onset of feedback. As with the MFN, maximum variability and the strongest trial type effects were observed at the Fz electrode. Results confirmed the presence of a robust effect of feedback type [F (1, 126.08) = 28.45, p = .003], with incorrect feedback producing a more negative FRN than correct feedback. Similar to results on the reward prediction task, a significant main effect of nicotine content emerged [F (1,129.9) = 9.20, p = .003) indicating that independent of trial type, waveforms were more negative during placebo sessions relative to nicotine sessions. However, there was no evidence of a nicotine content x feedback type interaction [F (1, 126.08) = 0.20, p = .659]. These effects are illustrated in Figure 6. The waveform at the Fz electrode is depicted in Figure 7.

Moderators. Results of moderator analyses for accuracy on the testing phase of the task are presented in Table 13. Moderator analyses of FRN amplitude during the training phase are presented in Table 14. No moderators remained significant following FDR correction.

Association with Smoking Motivation. Only one effect for probabilistic learning accuracy remained significant following FDR correction, a Withdrawal x Nicotine Content x Learning Type interaction (B = -0.11, 95% CI [-0.18, -0.04], p = .002). This effect indicated the presence of a positive relationship between Avoid B performance and withdrawal symptoms during placebo sessions, but a negative association during nicotine sessions. A significant negative relationship was observed between average peak flow rate and FRN amplitude (B = -0.08, 95% CI [-0.14, -0.03], p = .001). No other effects reached significance after FDR correction.
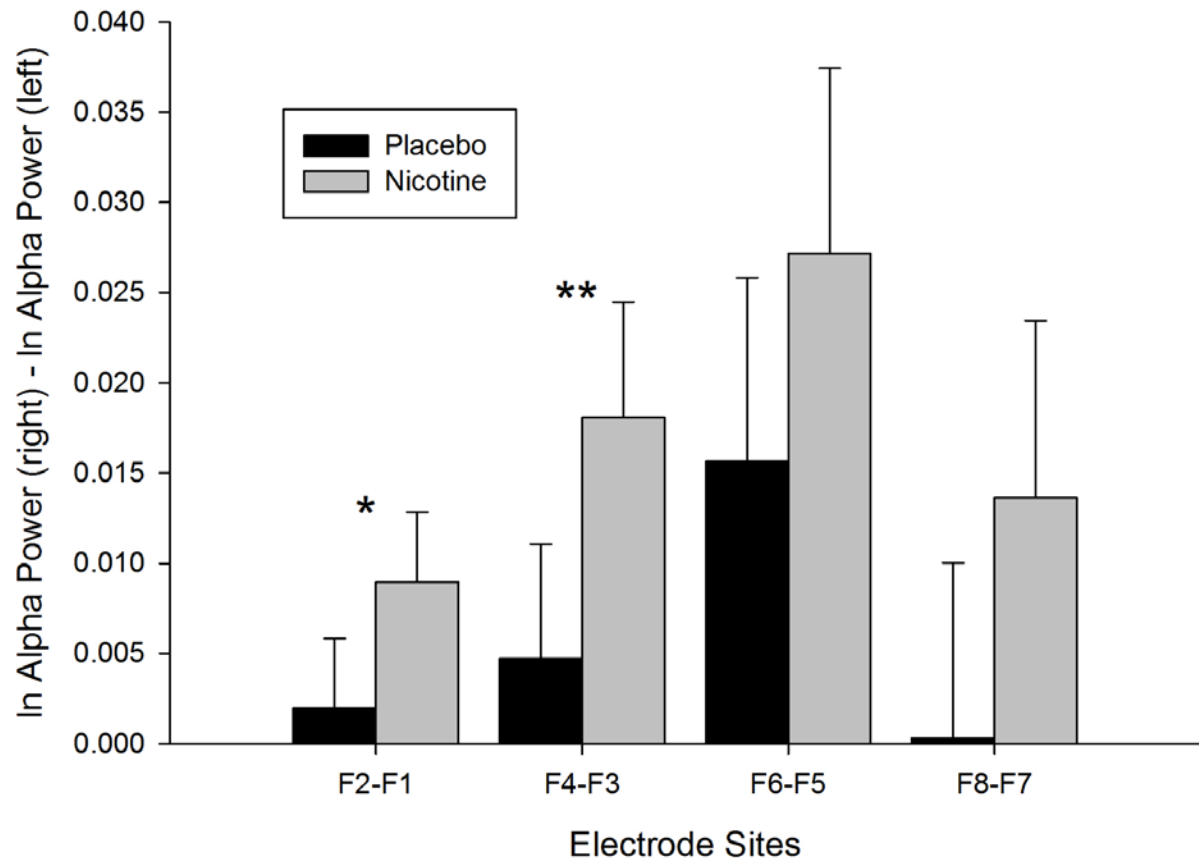
Figure 1. *Effects of nicotine on frontal alpha asymmetry*

Note. Bars represent standard error of the mean. * $p < .05$; ** $p < .01$
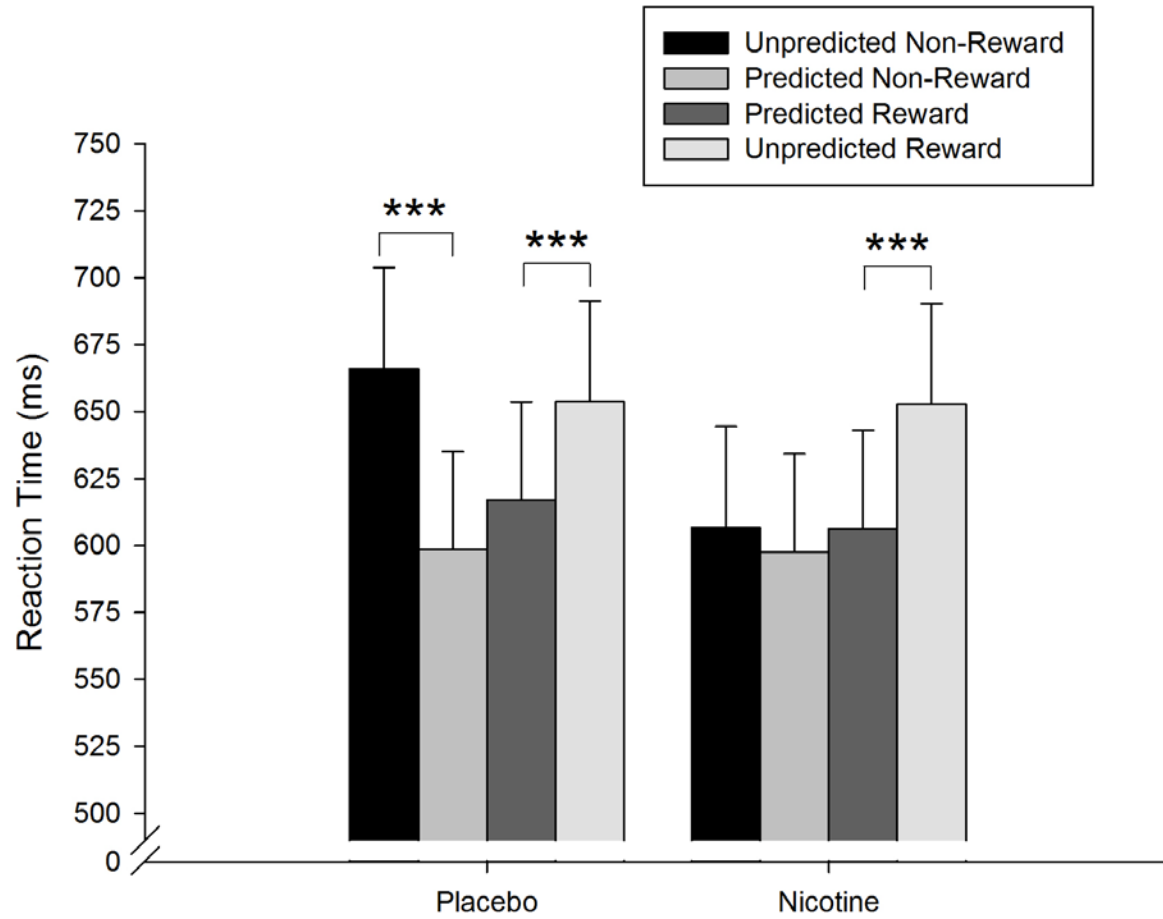
Figure 2. *Mean response times on reward prediction task*

Note. Bars represent standard error of the mean. *** $p < .001$
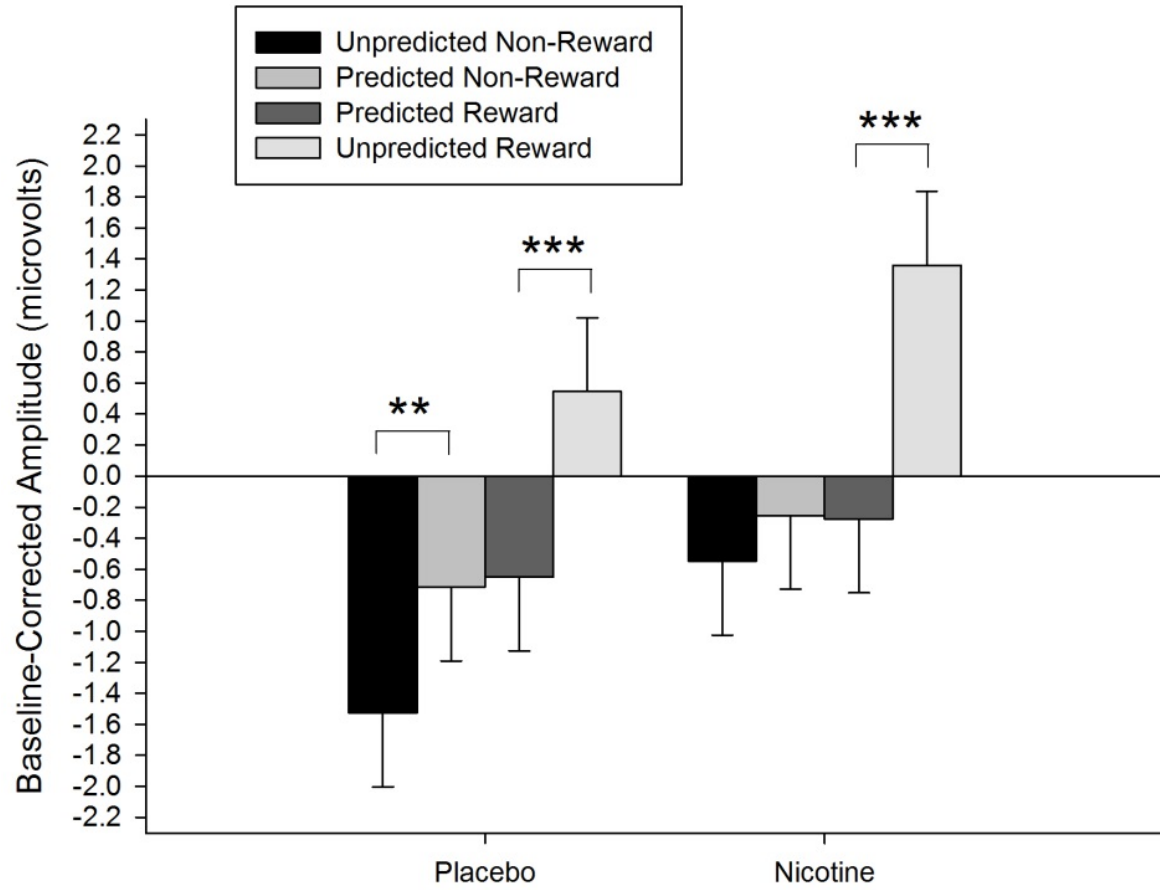
Figure 3. *Mean MFN amplitude on reward prediction task*

Note. Bars represent standard error of the mean
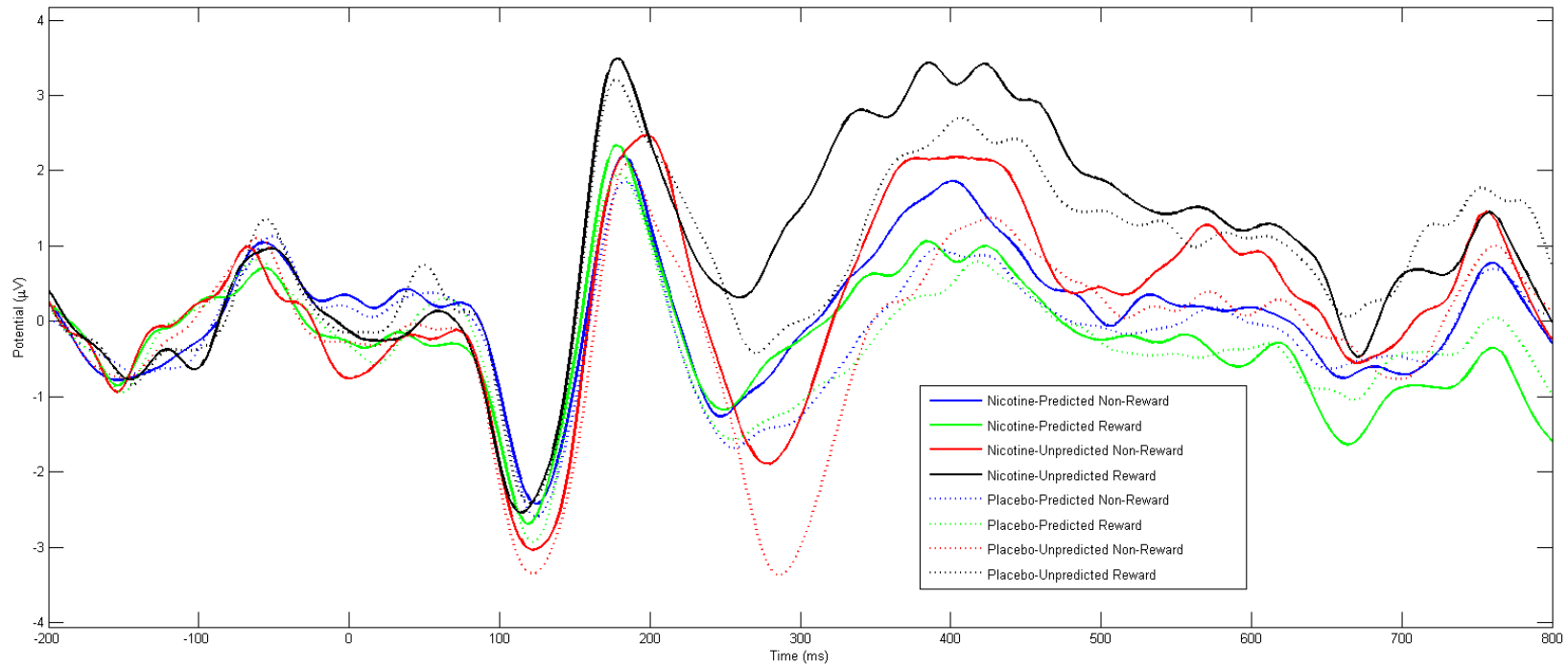
Figure 4. *Neural response to S2 stimuli on reward prediction task at Fz electrode.*
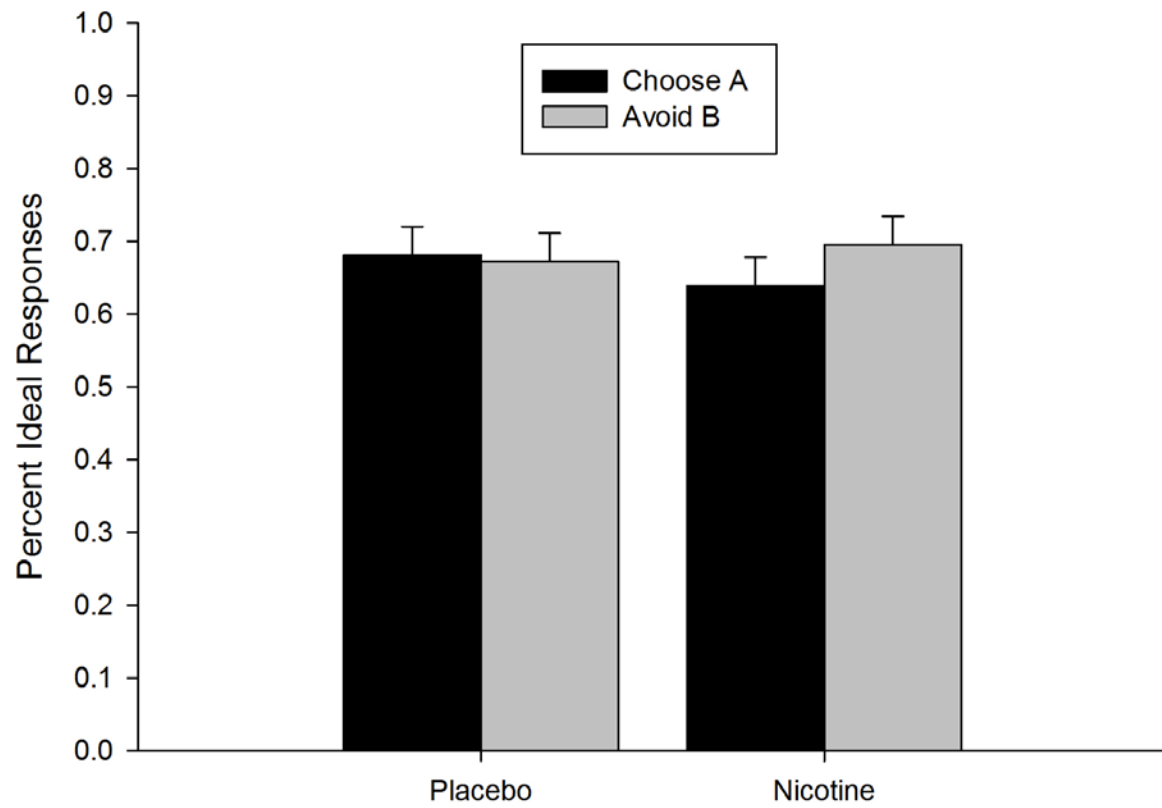
Figure 5. *Testing outcomes on probabilistic learning task*

Note. Bars represent standard error of the mean.
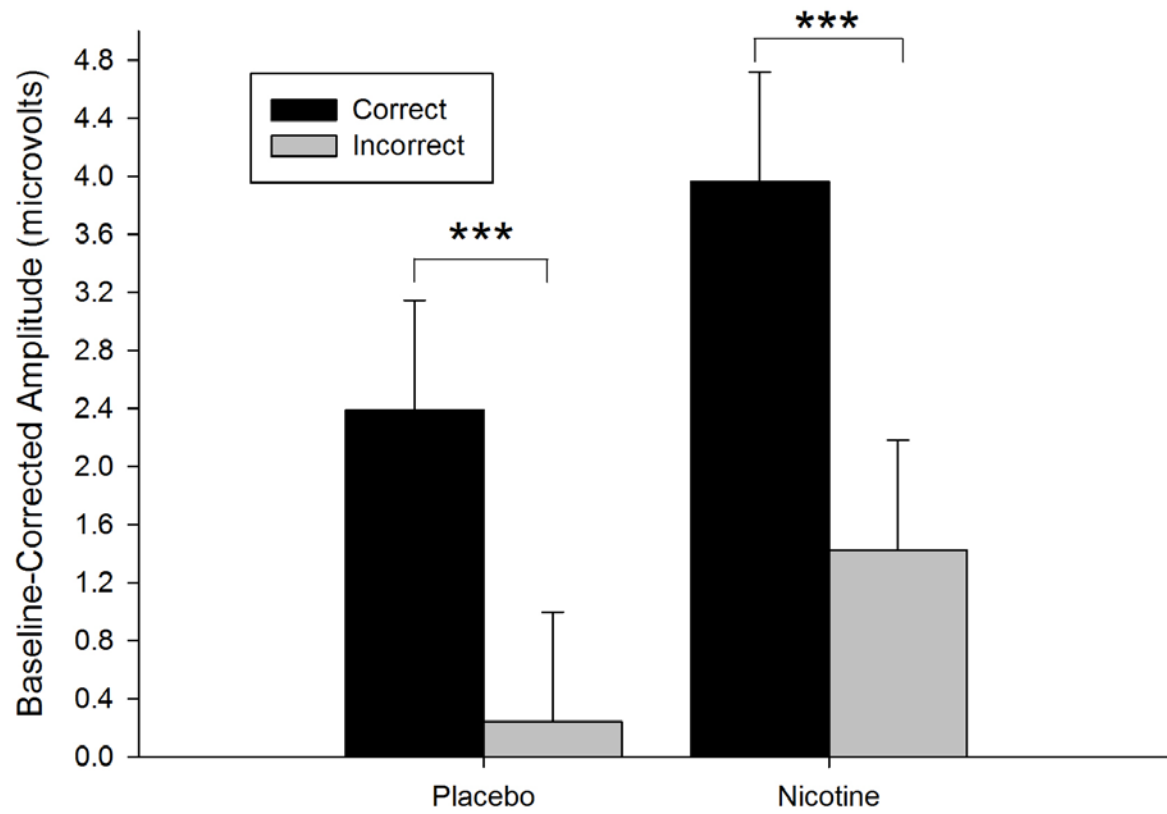
Figure 6. Mean FRN amplitude during training phase of probabilistic learning

Note. Bars represent standard error of the mean. *** *p* < .001
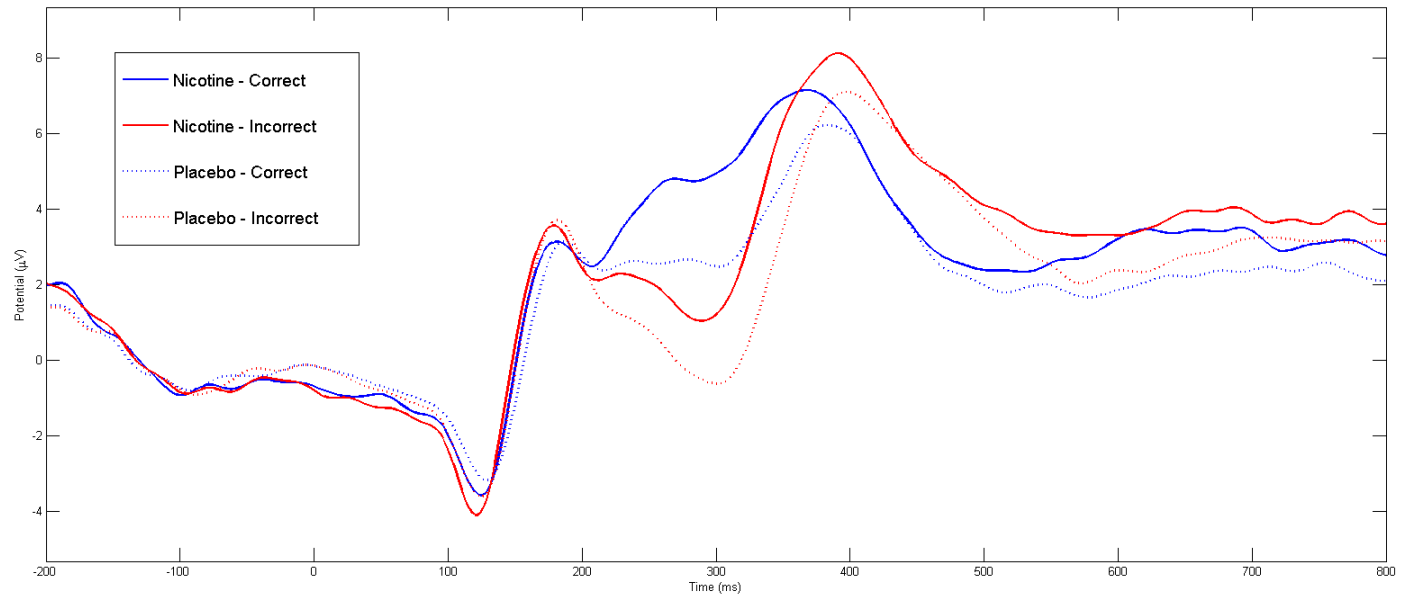
Figure 7. *Neural responses to feedback on probabilistic learning task at Fz electrode.*

Table 7. *Moderators of frontal asymmetry*

|	Main Effect		Interaction	
	F	*P-value*	*F*	*P-value*
Demographic				
Sex	0.01	.942	**11.29**	**< .001**
Race	0.53	.469	0.15	.698
Ethnicity	3.64	.063	1.62	.203
Education Level	0.87	.355	0.00	.962
Age	3.08	.086	0.06	.803
Handedness	0.24	.627	1.99	.159
Smoking				
Cigarettes per day	0.07	.795	0.08	.779
Age at first cigarette	0.07	.791	1.22	.271
Motivation to quit	0.04	.848	**11.15**	**< .001**
Menthol smoker	0.18	.670	**7.00**	**.008**
Quit History	0.02	.897	**17.55**	**< .001**
Quit Confidence	0.33	.567	0.04	.847
Nicotine Dependence (FTND)	0.79	.380	1.52	.218
Nicotine Dependence (WISDM)	1.38	.246	3.56	.060
Personality				
Neuroticism (Big Five)	3.22	.079	0.09	.759
Extraversion (Big Five)	0.10	.751	3.27	.071
Impulsivity				
Global Impulsivity (Barratt)	6.76	.012	1.01	.314
Risk-Taking Propensity (BART)	1.30	.260	1.18	.278
Trait Motivation				
Behavioral Inhibition (BISBAS)	3.44	.070	0.57	.452
Reward Response (BISBAS)	0.00	.973	**22.40**	**< .001**
Drive (BISBAS)	1.54	.221	**11.92**	**< .001**
Fun Seeking (BISBAS)	1.26	.267	**14.87**	**< .001**
Cognitive				
Cognitive Control (CFQ)	1.46	.233	3.80	.052
Working Memory (RS Trial)	0.00	.984	0.01	.926

Note. Effects that remain significant following FDR correction (done separately by column) are bolded. FTND = Fagerström Test for Nicotine Dependence; WISDM = Wisconsin Inventory of Smoking Dependence Motives; BART = Balloon Analogue Risk Task; BISBAS = Behavioral Inhibition Systems/Behavioral Activation Systems; CFQ = Cognitive Failures Questionnaire; RS = Reading Span

Table 8. *Associations between frontal asymmetry and smoking motivation*

	Main Effect		Interaction	
	F	*P-value*	*F*	*P-value*
Internal State				
Craving	**7.02**	**.008**	2.81	.094
Withdrawal	0.00	.987	5.77	.017
Positive Mood	0.60	.439	0.20	.657
Negative Mood	**6.50**	**.011**	2.68	.102
Cigarette Ratings				
Satisfaction	2.90	.089	0.03	.859
Psychological Reward	5.59	.019	2.83	.093
Craving Reduction	**10.74**	**.001**	0.54	.461
Respiratory Tract Sensations	3.40	.066	1.12	.290
Aversion	0.59	.441	0.13	.723
Exposure				
CO Boost	3.90	.049	4.64	.032
Smoking Topography				
Total Puff Volume	0.35	.556	1.45	.229
Average Puff Volume	**7.40**	**.007**	1.45	.229
Average Peak Flow Rate	3.49	.062	0.75	.388
Average Inter-puff Interval	**9.88**	**.002**	0.00	.990
Average Puff Duration	2.73	.099	0.51	.474
Number of Puffs	0.91	.340	2.16	.142

Note. Effects that remain significant following FDR correction are bolded.

Table 9. *Moderators of response time on reward prediction task*

Moderator	Moderator Main Effect		Moderator x Prediction		Moderator x Reward		Moderator x Prediction x Reward		Moderator x Nicotine x Prediction		Moderator x Nicotine x Reward		Moderator x Nicotine x Prediction x Reward	
	F	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*
Demographic														
Sex	0.31	.579	0.33	.563	6.30	.012	5.71	.017	1.65	.199	**6.56**	**.010**	0.05	.819
Race	0.24	.237	3.69	.055	4.31	.038	0.03	.865	2.92	.088	0.01	.917	0.16	.693
Ethnicity	0.00	.984	2.19	.139	1.00	.318	0.41	.520	0.00	.964	**17.40**	**< .001**	0.00	.950
Education Level	0.04	.838	0.06	.797	0.88	.347	0.11	.740	0.01	.942	2.26	.133	0.59	.443
Age	0.83	.386	1.77	.184	0.43	.514	0.21	.650	0.04	.851	0.13	.720	1.91	.167
Handedness	0.00	.992	0.83	.363	0.05	.820	0.38	.540	2.58	.108	0.14	.705	1.76	.185
Smoking														
Cigarettes per day	0.60	.442	**18.40**	**< .001**	0.40	.529	2.44	.118	2.79	.095	3.26	.071	0.14	.713
Age at first cigarette	0.35	.555	4.89	.027	**11.41**	**.001**	1.09	.297	6.77	.009	4.76	.029	0.03	.853
Motivation to quit	0.43	.514	0.23	.630	3.63	.057	0.19	.666	0.18	.668	0.66	.417	0.24	.625
Menthol smoker	0.00	.951	0.05	.827	5.87	.015	5.56	.018	6.70	.010	0.81	.367	3.51	.061
Quit History	0.30	.585	0.81	.369	1.84	.175	1.05	.306	0.37	.544	0.84	.359	1.86	.173
Quit Confidence	0.00	.961	0.05	.822	0.24	.624	0.03	.864	1.26	.262	0.80	.372	1.44	.230
Nicotine Dependence (FTND)	0.89	.350	2.18	.140	0.02	.691	0.00	.999	0.67	.413	3.04	.081	5.56	.018
Nicotine Dependence (WISDM)	0.54	.468	1.03	.310	0.77	.380	0.00	.982	0.31	.581	**15.58**	**< .001**	2.40	.121
Personality														
Neuroticism (Big Five)	1.31	.259	0.17	.683	5.98	.015	0.48	.488	0.27	.607	**8.42**	**.004**	1.23	.268
Extraversion (Big Five)	0.89	.352	0.29	.592	2.59	.108	5.57	.018	0.45	.503	**12.42**	**< .001**	0.12	.726
Impulsivity														
Global Impulsivity (Barratt)	0.93	.340	0.07	.793	2.34	.126	0.60	.439	0.15	.701	2.76	.097	1.71	.191
Risk-Taking Propensity (BART)	0.13	.719	6.19	.013	6.87	.009	1.32	.251	0.47	.495	4.00	.046	0.02	.897
Trait Motivation														
Behavioral Inhibition (BISBAS)	0.62	.434	3.24	.072	**17.32**	**< .001**	2.30	.130	0.59	.444	**19.09**	**< .001**	0.96	.328
Reward Response (BISBAS)	0.08	.778	3.12	.077	0.02	.876	1.43	.232	0.30	.585	0.39	.534	0.61	.437
Drive (BISBAS)	0.05	.822	2.16	.142	0.68	.410	0.13	.722	0.17	.681	0.40	.526	0.90	.342
Fun Seeking (BISBAS)	3.66	.062	0.36	.549	1.31	.252	0.40	.528	3.71	.054	0.06	.808	2.78	.095
Cognitive														
Cognitive Control (CFQ)	0.02	.884	1.02	.312	3.42	.064	0.22	.639	0.08	.781	2.59	.108	0.95	.329
Working Memory (RS Trial)	1.54	.220	0.03	.871	0..41	.521	4.01	.045	0.12	.728	0.44	.507	1.58	.209

Note. Effects that remained significant following FDR correction (done separately by column) are bolded.

Table 10. *Moderators of MFN amplitude on reward prediction task*

Moderator	Moderator Main Effect		Moderator x Prediction		Moderator x Reward		Moderator x Prediction x Reward		Moderator x Nicotine x Prediction		Moderator x Nicotine x Reward		Moderator x Nicotine x Prediction x Reward	
	F	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*
Demographic														
Sex	1.69	.200	7.34	.007	0.70	.404	2.74	.099	1.49	.223	0.51	.478	0.75	.388
Race	0.10	.749	3.12	.078	0.89	.345	0.01	.936	2.84	.093	0.75	.388	1.29	.258
Ethnicity	0.30	.590	3.71	.055	0.21	.646	0.13	.722	0.97	.326	0.10	.751	0.09	.765
Education Level	0.60	.442	0.92	.340	0.11	.741	8.88	.003	0.56	.457	0.75	.387	2.89	.090
Age	1.83	.184	6.28	.013	0.07	.785	1.63	.202	0.54	.461	0.15	.703	0.35	.553
Handedness	0.34	.563	3.12	.078	0.72	.398	0.01	.943	0.37	.543	0.00	.994	0.07	.786
Smoking														
Cigarettes per day	0.81	.374	0.03	.875	0.47	.495	0.01	.906	0.16	.694	0.05	.820	0.00	.993
Age at first cigarette	0.42	.523	0.01	.924	0.48	.488	1.86	.174	0.00	.955	1.52	.219	0.15	.704
Motivation to quit	0.12	.732	1.97	.162	0.54	.464	2.31	.130	0.85	.357	1.19	.275	0.23	.630
Menthol smoker	0.00	.982	0.94	.333	0.69	.406	3.28	.071	0.48	.490	2.34	.127	0.87	.353
Quit History	0.41	.528	1.65	.199	0.00	.959	0.32	.573	0.25	.616	0.02	.897	0.20	.655
Quit Confidence	0.00	.976	0.01	.907	2.38	.124	3.06	.081	0.02	.890	1.64	.201	0.90	.344
Nicotine Dependence (FTND)	1.48	.230	0.22	.641	0.00	.966	3.04	.083	0.02	.877	0.01	.931	0.54	.463
Nicotine Dependence (WISDM)	0.53	.472	0.02	.885	0.00	.977	0.32	.574	0.01	.904	0.05	.819	0.56	.457
Personality														
Neuroticism (Big Five)	0.01	.922	0.52	.473	0.58	.449	0.29	.590	0.11	.739	0.06	.806	0.13	.715
Extraversion (Big Five)	0.14	.708	0.80	.373	0.37	.546	2.10	.149	0.02	.882	0.00	.988	0.12	.733
Impulsivity														
Global Impulsivity (Barratt)	0.01	.915	2.13	.146	0.02	.897	0.92	.337	0.02	.901	0.58	.448	0.56	.457
Risk-Taking Propensity (BART)	0.00	.972	0.90	.345	0.98	.323	0.33	.565	0.32	.573	0.10	.758	0.00	.952
Trait Motivation														
Behavioral Inhibition (BISBAS)	0.00	.990	4.04	.045	1.08	.301	0.85	.358	1.36	.244	1.26	.262	0.15	.704
Reward Response (BISBAS)	0.03	.875	3.60	.059	0.00	.947	0.67	.413	0.44	.509	0.04	.851	0.03	.872
Drive (BISBAS)	1.19	.281	0.07	.789	1.31	.254	0.03	.869	0.14	.713	0.16	.691	0.48	.489
Fun Seeking (BISBAS)	1.68	.201	2.52	.113	0.25	.616	1.22	.271	0.01	.917	0.13	.723	0.23	.633
Cognitive														
Cognitive Control (CFQ)	0.45	.507	3.00	.084	0.39	.532	0.62	.430	0.57	.453	1.30	.255	0.43	.510
Working Memory (RS Trial)	0.50	.482	0.92	.339	0.29	.591	0.05	.816	0.15	.703	0.04	.840	0.06	.803

Note. No effects reached significance following FDR correction (done separately by column).

Table 11. *Associations between response time on the reward prediction task and smoking motivation*

Moderator	Moderator Main Effect		Moderator x Prediction		Moderator x Reward		Moderator x Prediction x Reward		Moderator x Nicotine x Prediction		Moderator x Nicotine x Reward		Moderator x Nicotine x Prediction x Reward	
	F	P-value	F	P-value	F	P-value	F	P-value	F	P-value	F	P-value	F	P-value
Internal States														
Craving	**5.75**	**.016**	2.61	.106	0.01	.932	0.00	.958	1.23	.268	**13.47**	**< .001**	0.83	.362
Withdrawal	**15.48**	**< .001**	0.29	.593	3.56	.058	0.20	.656	0.45	.502	**9.88**	**.002**	0.33	.566
Positive Mood	**17.58**	**< .001**	2.67	.102	0.91	.341	0.20	.658	0.40	.526	0.65	.419	**15.00**	**< .001**
Negative Mood	3.44	.064	2.80	.095	**12.98**	**< .001**	1.19	.275	**8.63**	**.003**	**11.77**	**.001**	0.05	.830
Cigarette Ratings														
Satisfaction	**263.52**	**< .001**	2.29	.130	0.27	.603	1.60	.205	1.45	.228	**17.69**	**< .001**	2.02	.156
Psychological Reward	**29.21**	**< .001**	**11.34**	**< .001**	1.07	.302	0.35	.555	0.00	.975	**6.88**	**.009**	0.03	.862
Craving Reduction	**11.09**	**.001**	1.98	.159	2.98	.085	0.85	.355	1.73	.189	**12.67**	**< .001**	0.60	.437
Respiratory Tract Sensations	**19.66**	**< .001**	7.20	.007	1.72	.190	0.02	.887	0.00	.963	**6.77**	**.009**	0.85	.356
Aversion	**37.20**	**< .001**	3.18	.074	0.37	.543	3.10	.078	2.69	.101	0.41	.522	0.01	.941
Exposure														
CO Boost	**26.11**	**< .001**	0.46	.496	**12.13**	**< .001**	0.17	.678	0.02	.886	0.10	.752	0.75	.388
Smoking Topography														
Total Puff Volume	**169.32**	**< .001**	3.53	.060	2.06	.151	0.62	.431	2.90	.089	0.00	.997	3.99	.046
Average Puff Volume	**298.21**	**< .001**	3.37	.066	0.70	.404	0.92	.338	2.49	.114	0.85	.358	3.62	.057
Average Peak Flow Rate	**164.04**	**< .001**	1.10	.293	1.51	.220	0.79	.375	0.01	.910	0.22	.638	5.48	.019
Average Inter-Puff Interval	2.79	.095	5.44	.020	0.62	.430	0.03	.855	**7.58**	**.006**	3.28	.070	1.28	.258
Average Puff Duration	**148.50**	**< .001**	1.14	.285	3.58	.059	0.09	.767	2.26	.133	0.54	.461	0.05	.820
Total Puffs	**63.29**	**< .001**	0.31	.575	0.24	.623	0.01	.945	1.27	.259	1.75	.186	0.95	.329

Note. Effects that remained significant following FDR correction (done separately by column) are bolded.

Table 12. *Associations between MFN amplitude on the reward prediction task and smoking motivation*

Moderator	Moderator Main Effect		Moderator x Prediction		Moderator x Reward		Moderator x Prediction x Reward		Moderator x Nicotine x Prediction		Moderator x Nicotine x Reward		Moderator x Nicotine x Prediction x Reward	
	F	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*
Internal States														
Craving	0.03	.864	0.08	.778	0.43	.511	0.10	.753	0.64	.425	0.04	.839	1.71	.193
Withdrawal	0.39	.535	0.13	.720	2.10	.148	0.01	.930	0.52	.472	0.00	.992	1.56	.209
Positive Mood	**6.03**	**.015**	2.51	.115	0.29	.591	2.94	.088	2.91	.089	0.05	.824	3.38	.067
Negative Mood	2.95	.087	1.02	.313	0.07	.788	1.03	.312	0.07	.793	0.22	.642	1.34	.248
Cigarette Ratings														
Satisfaction	**5.87**	**.016**	0.00	.967	0.24	.628	2.43	.120	0.02	.885	0.60	.440	1.45	.229
Psychological Reward	**11.71**	**.001**	0.52	.473	0.84	.361	0.16	.687	0.49	.483	0.56	.455	1.97	.162
Craving Reduction	0.86	.353	0.00	.957	0.18	.669	0.18	.672	0.02	.888	0.10	.748	1.07	.302
Respiratory Tract Sensations	4.09	.044	0.08	.782	0.06	.804	1.53	.217	0.44	.509	0.02	.900	4.08	.044
Aversion	1.60	.206	0.55	.461	0.55	.458	0.36	.552	0.71	.400	0.14	.711	0.34	.561
Exposure														
CO Boost	**8.72**	**.003**	0.40	.526	0.43	.515	1.34	.249	0.27	.603	1.27	.261	0.16	.691
Smoking Topography														
Total Puff Volume	**9.49**	**.002**	1.05	.306	1.10	.295	0.06	.814	0.70	.404	0.26	.609	0.75	.386
Average Puff Volume	4.97	.026	0.56	.453	0.06	.807	0.07	.794	1.17	.280	0.06	.810	0.08	.777
Average Peak Flow Rate	2.62	.106	1.38	.241	0.56	.457	0.32	.571	0.06	.809	0.53	.466	0.92	.339
Average Inter-Puff Interval	**6.76**	**.010**	0.92	.337	0.32	.570	0.04	.835	0.35	.552	0.02	.892	0.07	.788
Average Puff Duration	1.37	.243	0.01	.916	0.46	.498	0.10	.748	1.01	.315	0.15	.696	0.68	.409
Total Puffs	2.60	.108	0.05	.831	0.00	.968	0.00	.948	0.56	.453	0.18	.676	0.34	.561

Note. Effects that remained significant following FDR correction (done separately by column) are bolded.

Table 13. *Moderators of accuracy on probabilistic learning task*

Moderator	Moderator Main Effect		Moderator x Trial Type		Choose A Moderator x Nicotine		Avoid B Moderator x Nicotine		Moderator x Nicotine x Trial Type	
	F	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*	*F*	*P-value*
Demographic										
Sex	4.86	.033	0.00	.959	0.08	.776	0.33	.572	0.03	.875
Race	0.91	.344	1.43	.235	0.00	.979	2.46	.125	0.62	.432
Ethnicity	1.38	.247	0.44	.510	0.39	.537	0.00	.959	0.21	.645
Education Level	0.00	.994	0.88	.350	6.68	.015	1.92	.174	6.18	.015
Age	1.74	.195	0.70	.404	0.03	.862	0.04	.847	0.00	.956
Handedness	0.23	.633	0.08	.774	0.74	.397	0.74	.396	1.33	.253
Smoking										
Cigarettes per day	1.50	.224	0.31	.579	0.00	.973	0.11	.747	0.01	.938
Age at first cigarette	7.38	.010	0.25	.617	0.03	.870	7.23	.012	2.50	.117
Motivation to quit	0.17	.687	0.32	.574	0.04	.840	0.01	.933	0.01	.915
Menthol smoker	1.72	.197	0.08	.784	0.01	.915	0.80	.375	0.10	.752
Quit History	0.02	.891	2.79	.098	2.86	.102	0.16	.692	0.51	.477
Quit Confidence	0.10	.753	6.35	.013	0.40	.549	2.87	.099	0.57	.451
Nicotine Dependence (FTND)	0.25	.622	2.95	.089	4.27	.048	8.18	.007	9.26	.003
Nicotine Dependence (WISDM)	0.34	.562	0.78	.380	1.71	.204	1.31	.261	2.33	.131
Personality										
Neuroticism (Big Five)	0.18	.675	2.64	.107	0.39	.537	0.51	.480	0.46	.499
Extraversion (Big Five)	0.92	.343	4.34	.040	0.14	.710	0.54	.465	0.46	.497
Impulsivity										
Global Impulsivity (Barratt)	0.04	.853	4.90	.029	1.58	.218	0.01	.908	0.45	.502
Risk-Taking Propensity (BART)	0.00	.988	0.64	.426	0.15	.701	0.43	.515	0.12	.728
Trait Motivation										
Behavioral Inhibition (BISBAS)	0.18	.723	2.77	.099	0.78	.383	2.25	.142	0.09	.763
Reward Response (BISBAS)	1.22	.277	7.29	.008	0.19	.669	0.95	.337	0.16	.690
Drive (BISBAS)	0.21	.652	1.70	.196	0.00	.995	2.43	.130	0.52	.474
Fun Seeking (BISBAS)	0.21	.653	0.18	.669	0.72	.407	0.04	.854	0.16	.687
Cognitive										
Cognitive Control (CFQ)	1.20	.278	6.53	.012	0.05	.823	0.00	.963	0.02	.893
Working Memory (RS Trial)	0.00	.967	0.40	.526	6.34	.017	3.40	.073	7.64	.007

Note. No effects remained significant following FDR correction

Table 14. *Moderators of FRN amplitude on probabilistic learning task*

Moderator	Moderator Main Effect		Moderator x Feedback		Moderator x Nicotine		Moderator x Nicotine x Feedback	
	F	P-value	F	P-value	F	P-value	F	P-value
Demographic								
Sex	0.14	.706	0.11	.737	1.31	.255	0.02	.887
Race	0.08	.778	0.17	.681	1.28	.259	0.01	.927
Ethnicity	4.19	.047	0.25	.617	8.44	.004	0.16	.688
Education Level	1.04	.313	0.31	.581	0.07	.792	0.06	.802
Age	0.01	.915	2.75	.100	1.02	.315	0.21	.652
Handedness	0.04	.843	0.01	.906	0.93	.337	0.00	.971
Smoking								
Cigarettes per day	0.42	.521	0.09	.762	0.62	.432	0.15	.698
Age at first cigarette	3.08	.086	0.13	.715	5.19	.024	0.01	.906
Motivation to quit	0.15	.706	0.15	.697	0.39	.532	0.00	.976
Menthol smoker	0.50	.485	1.54	.217	2.42	.122	0.05	.827
Quit History	1.06	.309	0.32	.575	0.04	.846	0.15	.697
Quit Confidence	0.36	.551	0.50	.480	0.00	.956	0.06	.810
Nicotine Dependence (FTND)	3.41	.071	0.76	.385	1.50	.223	0.02	.883
Nicotine Dependence (WISDM)	2.11	.154	0.72	.398	0.37	.542	0.00	.959
Personality								
Neuroticism (Big Five)	0.02	.897	1.06	.305	0.00	.959	0.42	.521
Extraversion (Big Five)	0.01	.924	0.70	.405	0.00	.998	0.00	.985
Impulsivity								
Global Impulsivity (Barratt)	1.18	.283	0.32	.571	1.08	.301	0.01	.913
Risk-Taking Propensity (BART)	0.01	.907	0.14	.714	5.52	.020	0.31	.581
Trait Motivation								
Behavioral Inhibition (BISBAS)	0.01	.916	0.11	.744	2.09	.151	0.24	.623
Reward Response (BISBAS)	0.19	.666	1.34	.249	0.29	.588	0.13	.717
Drive (BISBAS)	0.00	.953	0.01	.914	0.45	.505	0.00	.950
Fun Seeking (BISBAS)	0.75	.392	0.37	.542	0.01	.942	0.00	.980
Cognitive								
Cognitive Control (CFQ)	0.57	.456	0.06	.810	0.55	.460	0.00	.998
Working Memory (RS Trial)	0.04	.850	0.80	.373	0.20	.656	0.01	.905

Note. No effects remained significant following FDR correction

Table 15. *Associations between accuracy on the probabilistic learning task and smoking motivation*

Moderator	Moderator Main Effect		Moderator x Trial Type		Choose A Moderator x Nicotine		Avoid B Moderator x Nicotine		Moderator x Nicotine x Trial Type	
	F	P-value	F	P-value	F	P-value	F	P-value	F	P-value
Internal States										
Craving	2.28	.137	0.03	.864	5.64	.022	1.43	.238	5.41	.022
Withdrawal	2.16	.148	0.68	.411	4.38	.043	6.05	.018	**10.54**	**.002**
Positive Mood	0.18	.671	0.45	.504	0.09	.765	0.01	.913	0.02	.903
Negative Mood	0.58	.451	1.88	.174	0.38	.542	0.06	.807	0.00	.956
Cigarette Ratings										
Satisfaction	0.13	.720	0.36	.552	6.21	.021	4.30	.046	6.36	.013
Psychological Reward	0.45	.506	0.12	.728	3.58	.069	0.51	.480	1.68	.199
Craving Reduction	0.59	.444	0.04	.849	0.43	.516	0.60	.442	0.91	.342
Respiratory Tract Sensations	0.08	.775	0.15	.704	4.00	.056	0.40	.533	1.32	.254
Aversion	1.66	.204	0.54	.462	2.15	.153	1.60	.213	2.50	.117
Exposure										
CO Boost	3.32	.074	1.64	.204	0.75	.392	0.94	.337	0.01	.934
Smoking Topography										
Total Puff Volume	0.03	.863	1.23	.271	0.01	.943	1.26	.267	0.05	.817
Average Puff Volume	0.03	.871	2.90	.092	0.56	.460	2.05	.159	1.28	.261
Average Peak Flow Rate	4.88	.034	3.77	.055	0.05	.817	1.14	.291	0.31	.579
Average Inter-Puff Interval	0.01	.909	1.73	.192	1.27	.270	1.38	.248	2.17	.145
Average Puff Duration	1.21	.276	0.04	.848	0.35	.559	0.42	.518	0.17	.685
Total Puffs	0.00	.958	2.33	.130	0.15	.700	0.02	.894	0.03	.862

Note. Effects that remained significant following FDR correction (done separately by column) are bolded.

Table 16. *Associations between FRN amplitude and smoking motivation*

Moderator	Moderator Main Effect		Moderator x Feedback		Moderator x Nicotine		Moderator x Feedback x Nicotine	
	F	P-value	F	P-value	F	P-value	F	P-value
Internal States								
Craving	0.72	.396	0.07	.792	2.31	.131	0.20	.655
Withdrawal	0.02	.885	0.15	.697	1.97	.161	0.06	.807
Positive Mood	2.16	.145	0.03	.859	0.71	.400	0.01	.913
Negative Mood	0.01	.933	0.19	.663	1.25	.265	0.03	.854
Cigarette Ratings								
Satisfaction	6.43	.013	0.45	.506	0.02	.898	0.21	.651
Psychological Reward	7.49	.007	0.82	.368	6.74	.011	0.04	.850
Craving Reduction	4.73	.031	0.01	.916	0.02	.895	0.25	.617
Respiratory Tract Sensations	1.40	.239	0.44	.508	0.07	.792	0.09	.764
Aversion	5.94	.016	0.16	.694	2.45	.120	0.11	.740
Exposure								
CO Boost	0.04	.844	0.12	.732	0.05	.820	0.16	.692
Smoking Topography								
Total Puff Volume	1.28	.260	0.86	.356	0.26	.612	0.06	.810
Average Puff Volume	0.22	.637	2.56	.110	0.01	.945	0.05	.821
Average Peak Flow Rate	**10.68**	**.001**	0.79	.375	2.46	.119	0.87	.353
Average Inter-Puff Interval	0.10	.752	0.42	.518	1.29	.259	0.00	.970
Average Puff Duration	0.64	.426	0.62	.434	0.04	.849	0.02	.894
Total Puffs	0.87	.353	0.73	.394	0.01	.931	0.03	.866

Note. No effects remained significant following FDR correction.

Discussion

Overall, results of the present study support the notion that nicotine withdrawal impacts motivational and reward systems in humans. A detailed discussion of results for each of the primary outcome variables is presented in separate sections below. However, generally speaking, hypotheses regard the effects of nicotine withdrawal on frontal asymmetry were confirmed and numerous moderators were identified, providing a framework to guide future research on the role of individual differences in the experience of nicotine withdrawal. Critically, frontal asymmetry was also strongly related to indices of smoking motivation, suggesting that broad shifts in motivational state as indexed by frontal asymmetry may play an important role in driving behavior. However, results from the reward prediction and probabilistic learning task were significantly more convoluted and generally did not support *a priori* hypotheses. Nicotine withdrawal produced a robust decrease in MFN amplitude, but this effect was comparable across all trial types. Thus, its significance is largely unknown. However, significant effects on behavior during the task (i.e. time to initiate next trial following feedback) were observed, indicating that nicotine withdrawal may indeed impact reward processing, just not via traditional pathways studied using this task. Nicotine withdrawal did not appear to impact behavior during the testing phase of the probabilistic learning task. As with the MFN, a robust effect of withdrawal on FRN amplitude during the training phase was observed, but the lack of an interaction with trial type diminishes its interpretive meaning. Regardless, results suggest that whatever impact nicotine

withdrawal may have on feedback learning may be transient and unlikely to lead to significant

adaptations in future behavior.

Motivational State

As noted above, frontal asymmetry results from the present study were largely consistent

with hypotheses. Nicotine withdrawal produced a leftward shift in frontal alpha power (or

alternatively, a rightward shift in cortical activation). This is consistent with well-established

findings for depression (e.g. Allen & Cohen, 2010; Allen & Kline, 2004; Coan & Allen, 2004)

and provides some evidence to suggest that the neurobiological similarities between nicotine

withdrawal and depression observed in animals can justifiably be extended to human research

(Markou et al., 1998). Given the increased emphasis on transdiagnostic models of

psychopathology and identifying links between disorders, such as the Research Domain Criteria

(RDoC) put forth by the National Institutes of Health (Cuthbert & Insel, 2013; Insel et al., 2010;

Woody & Gibb, 2015), further exploration of this finding as a potential mechanism linking

nicotine dependence and depression is warranted. Numerous moderators of this effect were also

present. The effect was present among men but not women, which could plausibly be attributed

to the oft-repeated assertion that smoking among men is driven principally by physiological (vs.

social) factors (Perkins et al., 1999). However, other explanations remain equally plausible, as

sex may merely be associated with a host of other variables that have a more direct relationship

with frontal asymmetry effects. Thus, caution is urged regarding interpretation of this effect at

the present time.

The fact that nicotine withdrawal produced a more robust leftward shift in frontal alpha

among those who report higher trait approach motivation suggests this is a potentially critical

risk factor. Prior research indicates frontal asymmetry correlates with trait approach motivation

(Coan & Allen, 2003; Sutton & Davidson, 1997) and that high approach motivation renders individuals more likely to engage in smoking or other drug use behaviors (O'Connor, Stewart, & Watt, 2009). As results from the present study indicate high approach motivation also renders individuals more susceptible to a potentially adverse effect of withdrawal (perhaps due to having "more to lose" from a motivational standpoint), this construct of approach motivation may indeed play a profound role in the onset and maintenance of smoking behavior. Also noteworthy is that the effects of nicotine withdrawal on frontal asymmetry was strongest among those who had never before attempted to quit and had relatively lower levels of motivation to quit. If withdrawal truly induces a state of cortical activation similar to depression, it is plausible that it may include feelings of helplessness/hopelessness and a corresponding reduction in effort to modify behavior. Alternatively, the shift observed in response to nicotine withdrawal could represent an underlying vulnerability to depression – a view that is consistent with the capability model of frontal asymmetry to the degree that one assumes nicotine withdrawal reflects a neurobiological "challenge" to emotional systems (Coan, Allen, & McKnight, 2006). Regardless, results support the notion that nicotine withdrawal has a robust impact on global motivational indices such as frontal alpha wave asymmetry. Further exploration of these findings and the role they may play in smoking behavior may inform the development of novel interventions and our understanding of the neural mechanisms responsible for smoking motivation.

Reward Sensitivity

Findings for the reward prediction task were somewhat consistent with the notion that nicotine withdrawal impacts immediate reward processing. As noted above, a main effect of nicotine withdrawal on MFN amplitude was observed. However, the absence of a significant trial type interaction renders the meaning of this effect difficult to interpret. To the degree one

assumes MFN amplitude does reflect dopaminergic response within the VTA, these results may reflect a global blunting of dopaminergic activity within this region that is relatively independent of whatever active processing may be occurring. Though not precisely how the impact of nicotine withdrawal has traditionally been conceptualized in animal models, it is nonetheless consistent with the results of some prior research (Kenny & Markou, 2001). The significant associations between MFN amplitude (independent of trial type) and several indices of smoking motivation also provide some support for this viewpoint.

Despite the above findings, nicotine withdrawal did appear to have meaningful and specific effects on behavior during the task. Individuals were slower to initiate the next trial following presentation of an unexpected non-reward during periods of nicotine withdrawal, potentially reflecting heightened frustration in response to an expected reward not being delivered and/or a potential reluctance to reengage in reward-seeking behavior following a loss. Responses following unexpected reward trials were slowed relative to other trial types regardless of withdrawal status. These results are generally consistent with other research documenting differences in reward-seeking and decision-making brain activation among smokers undergoing nicotine withdrawal (Addicott et al., 2012) and are particularly noteworthy since, to the best of our knowledge, no previous research using this task has examined response time. Present results suggest it may be a more sensitive index than neural measures on this task, at least with regards to the effects of nicotine withdrawal.

A number of moderators of response time effects were present. In contrast to frontal asymmetry results, withdrawal facilitated (speeded) responses following reward trials for men, but slowed responses to these trials for women. However, this effect for men may have been driven largely by individuals of Hispanic descent who exhibited very robust facilitation of

responding during placebo sessions. Unfortunately, there were no women of Hispanic descent in the present sample so this intersection cannot be explored statistically. Regardless, these effects should be interpreted cautiously given the relatively limited sample size of each subgroup. In addition to findings for demographic variables, high levels of nicotine dependence or neuroticism appeared to be risk factors for exhibiting slowed response times on reward trials during nicotine withdrawal, whereas high levels of extraversion or behavioral inhibition were relatively protective. Individuals with higher levels of nicotine dependence or neuroticism appeared to be at greatest risk of experiencing these effects, whereas the opposite pattern was observed for individuals with high levels of extraversion or behavioral inhibition.

Together, the above findings indicate a significant role for individual differences in reward processing/behavioral response to rewards. The well-established association between smoking and negative affect (Kassel, Stroud, & Paronis, 2003) may be partially explained by a linkage of the reward processing deficits within this population. When coupled with numerous robust associations between indices of smoking motivation and response time following reward trials during placebo sessions, this suggests that alterations in reward processing may play a pronounced role in motivating smoking behavior. As smoking offers a reliable reward from a neurobiological perspective (Benowitz, 2008), it seems logical that it would prove a more attractive option during times when nicotine withdrawal precluded normal reward processing and interfered with the processing of alternate rewards.

Feedback Learning

Unlike findings for frontal asymmetry and reward processing, there was only minimal evidence to suggest that nicotine withdrawal affected performance on the feedback learning task. As with the MFN, we did observe a main effect of withdrawal on the FRN with participants

exhibiting more negative FRNs to both correct and incorrect feedback during withdrawal. Again, this is generally consistent with a global reduction in dopaminergic activity during withdrawal, though relies heavily on a number of assumptions and theories regarding the neural generators of the FRN that itself remains an evolving area of research (Hauser et al., 2014). None of the moderators tested appeared to impact this effect, nor was there any evidence to support an association between FRN amplitude and smoking motivation.

There was also only minimal evidence to support any effects of nicotine withdrawal on behavioral performance during the testing phase of the task. No moderators of behavioral performance on this task survived FDR correction. However, it should be noted that several variables of substantial theoretical importance (i.e. nicotine dependence, education, working memory) narrowly missed this threshold and did have significant uncorrected p-values. Also cause for some level of optimism was the significant interaction between self-reported withdrawal, nicotine contents and testing trial type, as the hypothesized effects did appear to be present among those with higher levels of self-reported withdrawal. Thus, it seems premature to definitively conclude that nicotine withdrawal does not impact approach and avoidance learning. Rather, these effects may merely be weaker or more highly dependent on individual differences. It should be noted that much of the prior research using this task has been done on individuals with substantially higher levels of educational attainment than the sample of the present study (e.g. Frank et al., 2004). Limited understanding of the task or frustration with performance on the task may have obscured effects. Given the relative complexity of the task and the sheer number of cognitive processes involved in feedback learning relative to the other constructs assessed in this study, it seems reasonable to assume that greater noise would be present in behavioral performance on this task, thus rendering experimental effects more difficult to observe. Future

research should take this into account either by recruiting larger samples, employing a more robust manipulation of withdrawal or using alternative tasks. Lastly, it should be noted that although the focus of the present study was on neural responses to feedback during training and testing performance, this task allows for extraction of numerous other indices (e.g. learning trajectories during training, high-conflict vs. low-conflict learning, win-stay vs. lose-shift learning strategies) that may warrant further exploration.

Limitations

Foremost among the limitations of the present study are the relatively small sample size. Although the *n* of the present study was equal or larger than most studies of this type (e.g. Barr et al., 2008; Dawkins et al., 2007; Potts, Bloom, Evans, & Drobes, 2014) and power was further enhanced through the use of a within-subjects design, the stability of the parameter estimates and generalizability to the broader population of smokers is nonetheless a limitation. This concern is multiplied for analyses that examined individual differences variables (i.e. moderators of experimental effects, association of experimental effects with smoking motivation variables) and replication within larger samples is needed before any firm conclusions are drawn. Also noteworthy is that the present study employed careful screening procedures that significantly restricted the sample (e.g. eliminating potential participants with the most commonly comorbid psychopathologies). Though arguably appropriate for the current stage of research, this again raises questions about the generalizability of the results observed herein. Results could differ significantly when comorbid psychopathologies are included, as competing effects or interactions may overwhelm any direct effects of nicotine withdrawal.

The double-blind smoking procedure that was employed for studying nicotine withdrawal carries advantages for internal validity, but also precluded a refined assessment of the temporal

course of nicotine withdrawal. Evidence suggests that some withdrawal symptoms emerge within 30 minutes (Hendricks et al., 2006) and can last for several weeks to several months (Hughes, Higgins, & Bickel, 1994). The effects in the present study clearly emerged overnight, but it is unknown the degree to which similar effects would be observed earlier or later in the withdrawal process. Although a number of associations between motivational state, reward sensitivity and smoking motivation were observed, it is unknown whether these findings actually extend to impact actual smoking behavior. In light of recent criticisms levied at other areas of study within the tobacco use field (Perkins, 2009), it is acknowledged that the clinical relevance of the present findings hinges on the assumption that these effects are predictive of ongoing smoking behavior or relapse following a quit attempt. Though associations with numerous indices of motivation were observed, it is premature to assume that this extends to actual smoking behavior and this remains an open empirical question. An immediate future direction based on present findings includes examining the ability of these effects to prospectively predict smoking behavior from indices of reward processing during nicotine withdrawal, both within a laboratory context and in ecologically valid settings.

Conclusions

Overall, results of the present study support the notion that nicotine withdrawal has a profound impact on reward processes, while providing some clarity as to the specificity of these effects across diverse relevant systems. Changes in neural systems consistent with a global change in motivational state were observed (i.e. frontal asymmetry findings), while other results pointed to specific deficits in reward processing. Although there was minimal evidence for an effect of nicotine withdrawal on reward learning, it is nonetheless possible that these effects may impact behavioral choices. Looking back to the role of secondary reinforcement in driving

smoking behavior, results of the present study begin to illustrate how nicotine withdrawal may impact this process. Elevations in avoidance motivation and reward processing deficits may make individuals less inclined to pursue non-smoking rewards in their environment during bouts of withdrawal. Over time this behavior may become a pattern, exacerbating smoking and diminishing the relative value ascribed to unrelated activities. This process could well occur in conjunction with enhanced incentive value of nicotine (Robinson & Berridge, 2008), with an aggregated effect of dramatically increasing the likelihood of engaging in smoking behavior.

As noted by others (Leventhal, 2015), motivation to engage in a behavior cannot be understood in isolation. The impact that smoking and nicotine withdrawal may have on motivation and the processing of alternative rewards is critical for understanding why individuals may be motivated to smoke…whether it is due to the expected reward to be derived from smoking or the relative *lack* of reward that can be derived from alternate sources. The study provides an initial foray into this topic within humans, but it nonetheless remains a relatively understudied area. Studies across neurobiological, pharmacological, behavioral and sociological levels of analysis are needed to derive the maximal clinical utility from this line of research.

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Appendix A:

Initial Approval Letter from Institutional Review Board (IRB)

DIVISION OF RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX (813) 974-5618

August 28, 2012

Jason Oliver, M.A.
H Lee Moffitt Cancer Center
Tobacco Research and Intervention Program
4115 E. Fowler
Ave. Tampa, FL
33617

RE: **Expedited Approval** for Initial Review
        IRB#: Pro00008695
        Title: Effects of Nicotine Withdrawal on Motivation, Reward Sensitivity and
                Reward- Learning

Dear Mr. Oliver:

On 8/24/2012 the Institutional Review Board (IRB) reviewed and **APPROVED** the above referenced protocol**.** Please note that your approval for this study will expire on 8/24/2013.

Approved Items:
Protocol Document:
17163_2012.08.03_protocolV2.doc

Consent Document:
OliverDissertation
IC.docx.pdf
Please use only the official, IRB- stamped consent/assent document(s) found under the

"Attachment Tab" in the recruitment of participants. Please note that these documents are only valid during the approval period indicated on the stamped document.

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR56.110. The research proposed in this study is categorized under the following expedited review categories:

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(6) Collection of data from voice, video, digital, or image recordings made for research

purposes. (7) Research on individual or group characteristics or behavior (including, but not

limited to,
research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have
any questions regarding this matter, please call 813-974-

5638. Sincerely,

John A. Schinka, Ph.D., Chairperson
USF Institutional Review Board