Published in final edited form as:

Drug Alcohol Depend. 2014 November 1; 144: 245–253. doi:10.1016/j.drugalcdep.2014.09.773.

Neural Reward and Punishment Sensitivity in Cigarette Smokers

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Abstract

Background—Nicotine addiction remains a major public health problem but the neural substrates of addictive behavior remain unknown. One characteristic of smoking behavior is impulsive choice, selecting the immediate reward of smoking despite the potential long-term negative consequences. This suggests that drug users, including cigarette smokers, may be more sensitive to rewards and less sensitive to punishment.

Methods—We used event-related potentials (ERPs) to test the hypothesis that smokers are more responsive to reward signals and less responsive to punishment, potentially predisposing them to risky behavior. We conducted two experiments, one using a reward prediction design to elicit a Medial Frontal Negativity (MFN) and one using a reward- and punishment-motivated flanker task to elicit an Error Related Negativity (ERN), ERP components thought to index activity in the cortical projection of the dopaminergic reward system.

Results and Conclusions—The smokers had a greater MFN response to unpredicted rewards, and non-smokers, but not smokers, had a larger ERN on punishment motivated trials indicating that smokers are more reward sensitive and less punishment sensitive than nonsmokers, overestimating the appetitive value and underestimating aversive outcomes of stimuli and actions.

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Contributors

Authors Potts and Drobes designed the study and implemented the design. Potts was primarily responsible for the writeup. Author Bloom supervised the data collection, analyzed the behavioral, clinical symptom, and demographic data, performed much of the literature review, contributed to the experimental design, and wrote the patients descriptive portions of the manuscript. Evans contributed to data acquisition and analysis, study design, and manuscript preparation. All authors have read and approved the final version of the manuscript.

Conflict of Interest

None.

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Keywords

Event-Related Potentials; Medial Frontal Negativity; Error Related Negativity; Addiction; Reward; Punishment

1. INTRODUCTION

Diseases related to cigarette smoking are prevalent causes of death and disability (CDC, 2008). Estimates place the number of deaths per year due to smoking-related illnesses in the US at 440,000 and the annual cost of smoking related health care at \$167 billion (Centers for Disease Control and Prevention, 2005). Understanding the neural systems involved in smoking motivation might allow improved screening, prevention, and targeted intervention.

Early addiction models proposed that nicotine addiction was a consequence of the impact of an addictive substance on neurophysiology. Under these models an individual would initially use a potentially addictive substance due to choice or circumstance, changing brain function, then engage in addictive use either to experience the pleasurable feelings provided by the drug (positive incentive) or to avoid the negative experience of withdrawal symptoms (e.g., negative incentive; Watkins et al., 2000). However, these models do not explain the continued use of a drug even when the pleasure derived from that drug has been reduced through tolerance, or the repetitive relapse behavior of detoxified addicts when the threat of withdrawal is removed. These models also fail to address why some individuals appear more susceptible to developing addiction (Shiffman and Paton, 1999).

Most neural models of addiction focus on the brain's reward pathway, the mesotelencephalic dopamine (DA) system. This pathway has been described in detail in the animal model (Rolls, 1999), and involves dopaminergic projections from the tegmentum (the ventral tegmental area: VTA) to multiple telencephalic targets, including the basal ganglia (ventral striatum/nucleus accumbens), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (VMPFC; Cools, 1988; Schultz et al., 1997). The mesotelencephalic DA system appears to mediate the primary reinforcing characteristics of natural stimuli, such as food and sex (Hikida et al., 2003), as well as the reinforcing properties of drugs of abuse, including nicotine (Brautbur, 1996; Volkow et al., 1999; Wise, 1999). Early conceptions of this DA system related it to the hedonic value or positive reinforcement properties of items with adaptive approach value, however, this conception has changed as a result of recent research showing that reward system neurons may be conditioned (Schultz et al., 1997).

Single-unit studies in monkeys have found that the reward system is not sensitive just to the presence of reward but rather to reward expectation (Schultz et al., 1997; Tremblay and Schultz, 1999). Schultz et al. (1997) showed that when monkeys received an unpredicted juice reward, neural activity in the VTA increased at the time of the reward, responding to reward delivery. However, once the animal was trained that a cue (such as a light or sound) reliably predicted reward delivery, VTA activity increased at the time of the reward predicting cue but no longer to the actual rewarding stimulus. Following conditioning, when a predicted reward was not delivered, VTA activity again increased to the reward-predictive

cue but was then suppressed when the predicted reward was not delivered. This response pattern demonstrates that VTA neurons do not simply code reward but rather code whether the delivered reward meets expectation (Schultz et al., 1997).

A common view of the reward system in addiction hypothesizes hyposensitivity to reward such that naturally occurring rewards are insufficient to engender positive affect, motivating individuals with reward hyposensitivity to seek activities, including drug use, that provide greater stimulation to the reward system (Blum et al., 2000). However, other models propose that reward hypersensitivity better describes addictive behavior by biasing decisions toward immediate reward at the cost of long-term negative outcomes, (Bechara, 2003; Clark and Robbins, 2002). Other models are more complex, involving multiple neuromodulators (e.g., serotonin) and neural structures (e.g., amygdala, thalamus), contributing to dysregulation of the DA reward system, causing it to be hyposensitive in some situations and hypersensitive in others (Bardo et al., 1996; Epping-Jordan et al., 1998; Vallone et al., 2000). Additionally, it is unknown if reward system differences in addicted individuals reflect traits rendering the individual more addiction susceptible or homeostatic response to chronic drug use. For example, nicotine can induce both acute and chronic hypersensitivity of the DA reward system (Kenny and Markou, 2006) while nicotine withdrawal produces DA hyposensitivity (Epping-Jordan et al., 1998).

The majority of work describing the reward system is based on animal models. However, recent studies have used functional imaging and event-related potentials (ERPs) to study the neural substrates of reward and the role these neural systems may play in addiction (Elliott et al., 2000; Estruch et al., 1998; Liddle, 1997; Logan, 1996; Luu et al., 2000; Rogers et al., 1999; Weinstein, 1995). Reward expectation appears to be related to mesotelencephalic activity in humans as well as monkeys. For example, a study using fMRI showed that humans given predictable or unpredictable squirts of juice or water showed a larger increase in activity of the nucleus accumbens, thalamus, and medial OFC when the reward was unpredictable, compared to predictable, attributed to DA input from the VTA to these reward processing regions (Berns et al., 2001). Increased activation in the VTA and its telencephalic targets has also been shown in response to monetary rewards in humans (Delgado et al., 2000; Knutson et al., 2000; Thut et al., 1997; Warren et al., 1984). Both the VTA (Knutson et al., 2000) and the striatum (Delgado et al., 2000) respond to monetary rewards as well as punishments. Delgado et al. (2000) found sustained hemodynamic activation of the striatum following a reward and a decrease in activation following a punishment in a guessing task, illustrating that some parts of the reward system differentiate between monetary reward and punishment.

Two ERP components, the error related negativity (ERN) and medial frontal negativity (MFN) are hypothesized to index the cortical projection of the reward system to medial frontal cortex, particularly anterior cingulate cortex (ACC; Dehaene et al., 1994; Holroyd and Coles, 2002). The ERN is elicited to behavioral errors and the MFN to stimuli informing the participant that their response was an error. The ERN is seen over medial frontal electrodes and peaks about 100 ms after the execution of an erroneous response (Gehring et al., 1993). Source modeling has localized the ERN to ACC and surrounding neocortex (Dehaene et al., 1994; Gehring et al., 2000; van Veen and Carter, 2002). Recently the MFN

has been generalized to actions that, while not explicitly incorrect, result in motivationally negative outcomes, e.g. losses in gambling designs (Gehring and Willoughby, 2002), suggesting that the MFN may reflect motivational evaluation of actions rather than simple error detection (Gehring and Willoughby, 2002; Hajcak et al., 2005; Holroyd and Coles, 2002; Luu et al., 2000). Holroyd and Coles (2002) have presented a model that links the MFN to the DA input to the ACC in comparing the expected reinforcing value of an action with the reward actually acquired for behavioral correction. Studies in our lab using predicted and unpredicted delivered and withheld rewards found that the MFN responded consistently with the response of VTA DA neurons, being positive to unpredicted rewards and negative when a predicted reward was withheld, consistent with an index of the VTA projection to MFC (Potts et al., 2006).

The current experiments used the MFN and ERN to test the hypothesis that dysregulation of the reward system in cigarette smokers causes hypersensitivity to reward signals, creating an overestimation of the immediate appetitive value of potential choice options, and hyposensitivity to punishment, contributing to an underestimation of the potential negative consequences of risky choices. Experiment 1 employed a reward prediction violation design we developed previously based on experimental designs used to elicit a reward system response in the monkey to elicit the MFN (Potts et al., 2006). In the current study, we expected that smokers would have a more positive MFN to unpredicted rewards than control participants, indicating neural reward hypersensitivity. Experiment 2 employed a flanker task with punishment and reward motivated trials to elicit an ERN. We predicted that non-smokers would have a larger ERN on punishment motivated trials, signaling loss aversion, consistent with our prior work (Potts, 2011), but that the smokers would not, indicating reduced punishment sensitivity. The two experiments were performed on the same participants, with experiment order counterbalanced across subjects. Some participants performed both experiments on the same day, some on two different days within two weeks of each other.

2. METHODS AND RESULTS

The study was approved by the Institutional Review Board at the University of South Florida.

2.1 Participants

We recruited potential participants using ads on Craigslist and screened respondents by self-report and by Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2001), excluding for current psychosis, major depressive episode, manic episode, panic disorder, frequent panic attacks, and psychoactive substance use (for smokers, non-nicotine, lifetime substance dependence, history of neurologic illness or injury, and current use of medications that affect physiological responses, e.g., SSRIs, beta blockers). This yielded a sample of 23 smokers and 22 non-smoking controls. Data from one smoker was excluded from the Reward Prediction analysis for excessive EEG artifact leaving 22 smokers and 22 non-smokers in the MFN analysis; and additional smoker and five controls were eliminated from the Flanker design for EEG artifact or performance on the task resulting in too few trials in one or more conditions leaving 21 smokers and 17 controls in the ERN analysis. The

smoking group had more female participants and more Caucasians than the control group. The groups did not differ significantly on age or years of education (all p 's > .1).

Non-smokers reported smoking fewer than 10 cigarettes during their lifetime. Smokers reported smoking at least 10 cigarettes per day for the past year and were not currently attempting to quit or significantly reduce their smoking. To minimize effects of nicotine withdrawal, smokers were required to smoke one cigarette of their own brand just prior to beginning each EEG session. Both smokers and non-smokers provided an expired air sample for carbon monoxide (CO) analysis at session start (Vitalograph, Inc.; Lenexa, KS) for verification of non-smoking/smoking status. All controls had CO of less than 5 ppm (mean 2.6 ppm); all smokers had CO of at least 8 ppm (mean 29.5 ppm).

Participants were assessed on impulsivity, an aspect of personality associated with increased immediate reward preference, by self-report using the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) and the Eysenck I7 Impulsiveness Questionnaire (Eysenck et al., 1985). The groups did not differ on either the BIS-11 or the I7 (both p 's > .1). Smokers were also administered the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68; Piper et al., 2004), and the Questionnaire of Smoking Urges (QSU; Tiffany and Drobes, 1991). See Table 1 for participant information.

2.2 EEG Acquisition and ERP Analysis

EEG data was acquired with a 128 channel Electrical Geodesics System 250 (Electrical Geodesics, Inc., Eugene, OR). EEG data were acquired continuously sampled at 250 Hz with .1 – 100 Hz analog filtering, referenced to the vertex, then digitally filtered offline at 20 Hz lowpass to reduce residual noise outside the frequency range of the MFN and ERN. For the MFN, stimulus-locked EEG data were segmented off-line into 1000 ms epochs spanning 200 ms pre- to 800 ms post-stimulus around the critical S2 event (see Sections 3.1 and 4.2 for descriptions of the stimuli and design). For the ERN, the EEG was segmented into 600 ms epochs from 100 ms before to 500 ms after the keypress response. EEG segments were digitally screened for artifact (e.g., eye blinks, horizontal eye movement, head movement) using EGI's Netstation Artifact Detection software (v.4; default settings) and contaminated trials removed. For the ERN the minimum number of trials per condition to include a participant was set at 10, greater than the six established by Olvet and Hajcak (2009), and at 20 trials for the MFN following Marco-Pallares et al. (2010). For the ERN the average number of artifact free correct trials was 230 and 42 error trials; for the MFN there were an average 171 predicted trials and 43 unpredicted trials (trials in which the participant responded with the correct keypress but outside the allowed response window, i.e., too slow responses, are not reported here). There were no significant differences between the groups on the number of retained trials per cell except that on the ERN task the controls had slightly more retained trials than the smokers (276 versus 262). The retained data were sorted by condition and averaged to create the ERPs. The 1000 ms MFN waveform was baseline corrected over a 200 ms baseline period relative to segment start, the 600 ms ERN waveform for 100 ms pre-response, and rereferenced to an average reference frame to remove topographic bias (Dien, 1998). The subject-averaged ERPs were averaged together

to produce the mean waveform across subjects, the grandaverage waveform, to illustrate the central tendencies in the data.

2.3 Reward Prediction Violation Experiment

2.3.1 Experimental Design—The design was drawn from the reward prediction violation design presented in Potts et al. (2006). Stimuli were drawings of lemons (no reward value) and gold bars (reward value of \$.05 each). Each trial consisted of a fixation, a predictor stimulus (S1), a reward determining stimulus (S2), and feedback. Participants initiated each trial by keypress which caused a fixation cross to appear at the center of the computer screen for 300 ms followed by the predictor stimulus (S1) replacing the fixation for 500 ms, followed by a second fixation cross replacing S1 with a duration of 300 ms followed by the reward-determining stimulus (S2) for 500 ms then by another 300 ms fixation then by feedback that stated the value of the reward and the participant's current bankroll. The feedback remained onscreen until the participant initiated the next trial by keypress.

On 80% of the trials S1 and S2 were the same, thus S1 was predictive of S2. On the remaining 20% of the trials, S1 and S2 were different (violated predictions). If S2 was a gold bar then the participant received a reward of \$.25; if S2 was a lemon the participant received nothing. Thus if S1 and S2 were both gold bars (40% of the total trials) then a Predicted Reward was delivered. Trials on which S1 predicted a reward (bar) but S2 did not match S1 (lemon) created the Unpredicted No Reward (predicted reward withheld) condition, which occurred on 10% of the trials. When S1 was a lemon, predicting no reward, S2 was usually a lemon and no reward was delivered (40% of the trials), creating the Predicted No Reward condition. On the 10% of the total trials S1 was a lemon, predicting no reward, but S2 was a gold bar, delivering a reward: the unpredicted reward condition. Stimuli were presented in a random order for a total of 480 trials separated into 8 blocks of 60 trials each with a brief break between blocks. Participants began each block with \$1. At the end of the experiment, participants were paid their total from one of the eight blocks, chosen by random draw, averaging \$8.50.

The MFN was extracted by taking the mean ERP amplitude across a spatial region-of-interest comprised of 9 medial frontal electrodes and across a temporal window from 240 ms – 320 ms post-S2 for each condition and each participant based on prior studies that find the MFN as the most negative point between 200 – 400 ms, peaking around 285 ms (van der Helden et al., 2010), and using similar windows, e.g., 220 – 320 ms (Boksem et al., 2011), and by a visual inspection of the MFN deflection in the current data (see Figure 1). The apriori hypothesis that the smokers' MFN to unpredicted rewards would be more positive than non-smokers was tested with one-tailed t-tests for two groups with equal variance. Exploratory analyses were performed by entering the MFN into a repeated-measures ANOVA with Prediction (Predicted, Unpredicted) and Reward (Delivered, Withheld) as within subjects factors and Group (Smoker, Control) as the between factor.

2.3.2 Results—Waveform plots of the MFN in the medial frontal ROI and the distribution of the mean MFN voltage across groups and conditions are presented in Figure 1. A repeated-measures ANOVA showed a main effect for Group, with the smokers ERP overall

more positive in the MFN window than the controls, $F(1, 42) = 6.59$, $p < .05$. This Group effect was modified by an interaction with Prediction that approached significance, $F(1, 42) = 3.43$, $p = .07$, suggesting that the more positive MFN in the smoking group occurred only when outcomes were unpredicted. Simple effect analysis of this trend, which is the same as the apriori hypothesis test, showed that the MFN to the unpredicted rewards was more positive in the smokers than in the control group, smokers mean = $1.36 \mu V$ ($SD = 2.11$), control mean = $-0.24 \mu V$ (2.14), $t(40, 2\text{-sided}) = 2.49$, $p < .01$. The ANOVA also showed that rewarding outcomes elicited a significantly more positive ERP in the MFN window than non-rewarding outcomes, $F(1, 42) = 14.28$, $p < .001$, and this effect was also modified by interaction with Prediction, $F(1, 42) = 10.20$, $p < .005$, indicating that the difference between the rewarding and non-rewarding outcomes occurred only when those outcomes were unpredicted. Test of individual contrasts indicated that, in addition to the a-priori hypothesized group difference in the unpredicted reward condition, the MFN was different between the smokers and controls when a predicted reward was not delivered (unpredicted no reward) with the MFN significantly more negative in the control group, smokers mean = $0.00 \mu V$ (1.57), controls -1.06 (1.57), $t(40, 2\text{-sided}) = 2.25$, $p < .05$.

2.3.3 Discussion—The MFN showed effects of reward prediction violation, but the effect was different between the smoking and non-smoking groups. The general MFN window effect in this design is enhanced positivity to unpredicted rewards (outcome better than expected) and enhanced negativity when a predicted reward is not delivered (worse than expected; Potts et al., 2006). The non-smokers showed the worse than expected effect, enhanced negativity when a predicted reward was not delivered; in contrast, the smokers had essentially the same MFN amplitude for all conditions except in better than expected unpredicted reward condition, where their ERP was most positive. Thus the smokers were most responsive when the outcome was more positive than predicted, while the non-smokers were most responsive when the outcome was more negative than predicted. The larger positivity to unexpected rewards in smokers is consistent with the hypothesized heightened reward sensitivity, while the smaller negativity when an expected reward was not delivered in smokers is consistent with reduced punishment sensitivity. This is partially consistent with prior results we obtained in participants assessed for impulsivity, a personality characteristic associated with heightened reward sensitivity, rather than for smoking behavior. In a design similar to the one used here, but with multiple, smaller reward and punishment values, high impulsive individuals had a greater difference in MFN amplitude between unpredicted rewards and lack of rewards than low impulsive individuals, and the waveforms suggested that this was due to both enhanced positivity to unpredicted rewards and enhanced negativity when a predicted reward was withheld, indicating both enhanced reward and punishment sensitivity (Martin and Potts, 2004). Similarly, Smillie et al. (2010), using the same design as the current study, found a larger difference between unpredicted rewards and lack of rewards in extroverted, compared to introverted, participants. Our result here of greater positivity when an unpredicted reward is delivered in smokers (enhanced reward sensitivity in the smokers) is not consistent with the finding of Franken et al. (2010) who showed a correlation between drinking frequency and MFN amplitude using the same reward prediction design used here in which greater drinking frequency was associated with

greater MFN negativity when a predicted reward was withheld (greater punishment sensitivity in the more frequent drinkers).

One potential explanation for the only partially consistent results is that the reward prediction design is passive, not requiring any active decision or response by the participant. Previous studies have shown that active responding increases the MFN effect (Martin and Potts, 2011; Yeung et al., 2005), which may lead to more robust individual differences. In addition, in the current design, the negative outcome was the unexpected withholding of a reward rather than the delivery of a punishment. A more aversive outcome, like the actual loss of money, rather than failure to win, might provide a better assessment of neural punishment sensitivity. We tested this hypothesis in a second experiment with the same participants, requiring active responding and including a condition in which participants lost money.

2.4 Motivated Flanker Task Experiment

2.4.1 Participants—The participants were the same as in Experiment 1 except that three controls were eliminated due to perfect performance in at least one condition, leaving no error trials for analysis, and two additional controls and two smokers were eliminated for excessive artifact or poor task performance, thereby leaving 21 smokers and 17 controls in the analyzed sample.

2.4.2 Experimental design—We used a flanker task derived from the design by Eriksen and Eriksen (1979), modified so that some trials were potentially rewarding and others potentially punishing as described in (Potts, 2011). Stimuli were the letters S and H presented in five-letter strings. The five letters were either all the same (congruent trials) or the center letter did not match the flanking letters (incongruent trials). Participants were to press one key with the index finger of one hand if the center letter was an H, another key with the index finger of the other if the center letter was an S. One of the letters was designated the rewarding stimulus such that a correct response resulted in a \$.05 reward while an incorrect response resulted in nothing; the other stimulus was the punishing stimulus and incorrect responses to those stimuli resulted in a \$.05 loss while correct responses resulted in nothing (response key to letter mapping and rewarding and punishing stimuli were counterbalanced across subjects). Participants were instructed which letter was rewarding and which was punishing and given several practice trials.

A trial started with a fixation cross, replaced by a warning asterisk, followed the by stimulus string, followed by another fixation cross. The trial ended with a feedback screen showing the monetary outcome of the current trial (“+\$.05”, “0.00” or “–\$.05”) and the running total for the block. There were 640 trials divided into 8 blocks, and trial type was chosen randomly without replacement from a pool of equiprobable trial types, congruence (incongruent, congruent) x motivation (reward, punish).

The experiment started with the imperative stimulus duration set at 100 ms and the allowable response window set at 600 ms. Responses slower than 600 ms were counted as errors to provide time pressure and induce behavioral errors. To keep performance accuracy between 75 – 85%, accuracy was computed every 10 trials and if performance was below

75% the stimulus duration was increased by 15 ms and the response window increased by 25 ms; if accuracy was above 85% the stimulus duration was decreased by 15 ms (to a lower limit of 30 ms) and the allowable response window was decreased by 25 ms. Participants started the experiment with \$5 in their 'bank' and the rewards and punishments were added to and subtracted from that bank. Participants were given several practice trials prior to the first block during which they received "correct", "incorrect", and "too slow" feedback; during the experiment they only received the trial's monetary outcome feedback. Trials with anticipatory ($RT < 100$ ms), slow (outside the response window), or missing responses were not included in the ERP analyses; the slow responses were included in the behavioral analyses. At the experiment's end participants were paid their winnings in cash. EEG acquisition was as described in experiment 1 except that the EEG was segmented into 600 ms epochs around the keypress response, from 100 ms before to 500 ms after, and baseline correction performed over the 100 ms pre-response period.

The ERN was quantified as the mean ERP amplitude across a spatial region-of-interest comprised of 8 medial frontal electrodes largely overlapping the MFN window but slightly more posterior, and across a temporal window from 40 ms – 140 ms post-response. The a-priori hypothesis that only the controls and not the smokers would have a larger ERN on punishment motivated trials was tested with one-tailed t-tests. Exploratory analyses were performed by entering the ERN into a repeated-measures ANOVA with Response (Correct, Error) and Motivation (Reward, Punish) as within subjects factors and Group (Smoker, Control) as the between factor.

2.4.3 Results—For all statistics: degrees of freedom: 1, 36 for accuracy, 1, 33 for reaction time (RT); three participants were 100% accurate in at least one condition and thus had missing data in that condition for error responses.

2.4.3.1 Behavioral: Participants were more accurate on congruent trials, $F = 96.70$, $p < .001$, congruent accuracy 95.3% (8.7% SD), incongruent 80.8% (8.7%), with a larger accuracy difference between the congruent and incongruent stimuli when performance was reward motivated, Congruence $\times$ Motivation, $F = 20.89$, $p < .001$, (congruent 96.4% (3.1), incongruent 77.9% (9.4)) than punishment motivated (congruent 94.2% (11.8), incongruent 83.7% (6.9)).

Participants were significantly slower on reward than punishment motivated trials, $F = 22.99$, $p < .001$, and there was a trend suggesting that this difference was greater in the smokers, carried mostly by slower responses by the smokers on reward motivated trials, $F = 3.10$, $p = .088$. Participants were faster on congruent than incongruent trials, $F = 7.14$, $p < .05$, but only the controls showed this RT advantage of congruence (Group $\times$ Congruence $F = 6.94$, $p < .05$). Participants were also slower when responding correctly than incorrectly, $F = 20.16$, $p < .001$, and this also was true only in the controls, Response $\times$ Group $F = 8.44$, $p < .01$. There was a trend for a Motivation $\times$ Response interaction, $F = 3.78$, $p = .060$, suggesting that the slower responses on correct trials were greater when performance was reward-motivated. The Congruence $\times$ Response interaction was significant, $F = 27.69$, $p < .001$, showing that the RT difference between error and correct trials was only present when the stimuli were incongruent. The 3-way Motivation $\times$ Congruence $\times$ Response interaction,

$F = 7.90$, $p < .01$, showed that the slower RTs when responding correctly on incongruent trials occurred only under reward motivation.

2.4.3.2 ERP results: The waveforms from the flanker task are shown in Figure 2. There was a main effect for Response with a more negative ERN on error trials, $F = 9.66$, $p < .01$. The Motivation $\times$ Group interaction approached significance, $F = 3.72$, $p = .062$. The a-priori hypothesis that only controls, but not smokers, would have a more negative ERN on punishment trials was supported: control $t(20) = 2.28$, $p < .05$; smokers $t(17) = .71$, $p = ns$.

2.4.4 Discussion—The design elicited a larger ERN on error trials in both groups, reflecting the standard error effect. There was no impact of group on the ERN unmodified by motivation, indicating that smokers are as effective as non-smokers at detecting and/or processing behavioral errors. The Group $\times$ Motivation interaction was nearly significant, indicating that the controls had a larger ERN on punishment motivated trials. The exact cognitive operation indexed by the ERN is still debated. Some theories hold that the ERN indexes either the detection that the response was an error or some post-error corrective action (Gehring et al., 1993). However, other studies suggest that the ERN reflects more motivational or affective processes, reflecting negative affect associated with making a mistake. For example, Hajcak et al. (2005) found that the ERN was larger when accurate performance was rewarded with larger amounts of money, compared to smaller amounts, and when performance was externally evaluated compared to when motivation was simply the instruction to participants to try their best. Luu et al. (2000) found that, in anxious individuals, the ERN was larger on early trials and smaller on late trials, compared to non-anxious individuals. This was interpreted as indicating that the anxious participants cared more about their performance early in the task, but later stopped caring as much once they discovered that they could not achieve perfect performance and thus not avoid the negative affect associated with making mistakes.

Using a design almost identical to the one used here, we have shown that participants unscreened for smoking behavior, like the non-smokers here, had a larger ERN on punishment motivated trials (Potts, 2011). We have also previously shown that in a sample assessed for impulsivity, low impulsive individuals showed this enhanced ERN on punishment trials but high impulsive individuals did not (Potts et al., 2006), indicating that impulsive individuals are less sensitive to punishment signals. We would make that same interpretation here, that the non-smokers were more motivated to avoid loss than to seek gain, but that the smokers did not have this punishment avoidance bias, despite the lack of significant difference in self-reported impulsivity between the groups. This interpretation is supported by the behavioral data suggesting that the smokers were slower on reward-motivated trials, indicating that they were more careful when attempting to acquire a gain than when trying to avoid a loss.

3. DISCUSSION

Nicotine has several actual or perceived short-term benefits, including improved mood, i.e., increased positive affect (Cook et al., 2007) and reduced negative affect (Kassel et al., 2003), more focused attention (Ernst et al., 2001), better general cognitive performance

(Foulds et al., 1996), and improved social standing (Halpern-Felsher et al., 2004). Smoking also has numerous, well documented and well publicized long-term negative consequences, primarily health risks (Freund et al., 1993). Risky (impulsive) decision-making consists of choosing short-term rewards at the cost of the potential long-term negative outcomes, an immediate reward bias. Thus, at least the initial decision to try smoking is a classic example of risky choice, choosing the immediate satisfaction provided by the substance of abuse despite the long-term health costs. The neural responses measured here from experiments designed to engage the reward system without using smoking-related stimuli or tasks indicate that smokers are more responsive to reward and less responsive to punishment, consistent with risky decision-making. The ERP components assessed, the MFN and ERN, have been both theoretically (Holroyd and Coles, 2002) and experimentally (Potts et al., 2006) linked to the brain's reward system.

A now extensive animal literature and growing human hemodynamic neuroimaging literature has also linked the mesotelencephalic DA network to addiction (Vinar, 2001; Volkow et al., 1996; Wise, 1999). For example, one model of the role of DA at the nucleus accumbens (NA) in substance-abuse disorder is that the NA was under-responsive to DA in substance abuse patients, due to abnormalities in DA receptors (particularly the D2 receptor subtype; Blum et al., 2000). Since DA at the NA is related to subjective pleasure, the reduced DA sensitivity would lead to anhedonia, a lack of subjective pleasure. In this model, drug use is seen as a reaction to this under-responsive system in an attempt to chemically introduce more DA into the NA, increasing subjective pleasure. However, this model fails to account for some characteristics of addictive behavior, e.g., substance abusers report a reduction or loss of pleasure from using the substance across time, but a sustained or increase in craving for and use of the drug (Robinson and Berridge, 1993). Other models of reward system involvement in substance abuse are more complex, involving multiple neuromodulators (e.g., glutamate at the NMDA receptor, 5-HT) and neural structures (e.g., amygdala, thalamus) that lead ultimately to dysregulation of the DA reward system, causing it to be hypoactive in some situations (e.g., during nicotine withdrawal; Epping-Jordan et al., 1998) but hyperactive in others (Bardo et al., 1996; Vallone et al., 2000). For example, one recent study demonstrated that nicotine exposure induced both acute and chronic hypersensitivity of the DA reward system (Kenny and Markou, 2006). DA reward system abnormalities associated with reward sensitivity have also been linked to the personality traits of impulsivity and novelty seeking and to a variety of compulsive disorders other than substance abuse (Comings, 1994; Comings et al., 2002).

Different structures along the mesotelencephalic DA reward pathway participate in decision-making by estimating the potential reward value of a choice, comparing the received reward with the expected reward, and updating the reward expected from an action (Balleine et al., 2007; Bush et al., 2002; Lee, 2005; Sanfey et al., 2006). Humans (and animals) always prefer an immediate to a delayed reward, and the degree to which an individual will delay gratification is captured in the delay discounting function, a curve that plots the value of a reward against the time the individual has to wait for that reward (Madden et al., 2003). Structures in the DA reward system compute delay discounted reward values contributing to the decision whether to take the immediate reward or decline in favor of longer-term outcomes (Roesch et al., 2007). Alterations in DA transmission efficiency can predispose an

individual towards making riskier choices (van Gaalen et al., 2006), perhaps by impacting the immediate versus delayed reward value estimates. Smokers show a steeper delay discounting function in laboratory tasks, indicating greater value placed on immediate reward (Baker et al., 2003; Bickel et al., 1999), indicating a greater valuation placed on immediate reward, a greater immediate reward bias. However, these behavioral studies cannot assess the neural substrates of this reward bias.

In previous studies, we have demonstrated that individuals who score higher on self-reported impulsivity are more responsive to reward signals indexed by MFN in a passive reward prediction design similar to the one used here and less sensitive to punishment signals indexed by the ERN in the reward and punishment motivated flanker task employed here (Martin and Potts, 2004; Potts et al., 2006). In the current study we show that smokers have the same neural reward bias as impulsive individuals, with an enhanced MFN to unexpected rewards and a reduced ERN on punishment motivated trials, indicating a reward motivation bias. This immediate reward bias may provide the neural substrate of the steeper delay discounting function shown behaviorally in smokers (Baker et al., 2003; Bickel et al., 1999), and that steeper delay discounting function may contribute to the risky choice to smoke.

We cannot tell from the current data whether this reward bias in smokers reflects a preexisting trait or an adaptive change in neural function due to nicotine exposure. However, a reward bias is consistent with the risky choice to use nicotine, selecting the short-term benefits derived from nicotine and discounting the potential long-term negative consequences. If smokers do have a neural reward bias, being more sensitive to reward than punishment signals, this would have implications for behavior change intervention strategies. Most campaigns targeting smokers to motivate them to quit smoking focus on the long-term negative health consequences of smoking. If smokers are relatively insensitive to punishment motivation, then messages more focused on immediate benefits of quitting might be more engaging.

Acknowledgments

Role of Funding Source

Funding for this study was provided by NIDA grant R21DA023273. The NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Highlights

- The study used the medial frontal negativity (MFN) and error-related negativity (ERN) event-related potential (ERP) components, related to the mesotelencephalic reward prediction neural system, to assess motivation bias in cigarette smokers
- We hypothesized that smokers would be more sensitive to reward and less sensitive to punishment than controls
- We used two experimental designs: a passive reward prediction design based on designs used to study the reward system in animals by delivering unpredicted rewards and withholding predicted rewards; and a flanker task, to induce errors, with performance on some trials motivated by potential reward and others by avoiding potential punishment.
- The smokers had a larger ERP positivity to unpredicted rewards and the controls had a larger negativity when a predicted reward was not delivered in the MFN component, and the controls, but not the smokers, had a larger ERN on punishment motivated trials.
- The smokers had a larger ERP response to reward and a smaller ERP response to punishment than the controls, indicating that smokers are more motivated by appetitive than aversive signals.

Figure 1. Reward Prediction Results

a) Waveform plots to S2, the reward determining stimulus, from the medial frontal region of interest (ROI), in Experiment 1, the Reward Prediction design in the Unpredicted Reward (UR), Unpredicted No Reward (UNR; i.e. reward predicted (S1 = gold bar) but not delivered (S2 = lemon)), Predicted Reward (PR), and Predicted No Reward (PNR) conditions. The MFN analysis window is shown with vertical lines. b) Histograms showing the mean voltage within the analysis window in each of the four conditions for the two groups (bars represent standard error). Lines link the significant individual contrasts (*: $p < .05$). Note the positivity for the unpredicted rewards in the smokers and the negativity to the unpredicted no reward in the controls. c) Medial frontal ROI shown in open circles in the 128 channel sensor net with 10/20 system locations marked for reference.

Figure 2. Motivated Flanker Results

a) Waveform plots to the keypress response in the flanker task from the medial frontal region of interest (ROI), in Experiment 2, the Motivated Flanker design in the Punishment Error (PE; punishment delivered), Punishment Correct (PC; punishment avoided), Reward Error (RE: reward missed), and Reward Correct (RC: reward obtained) conditions. The ERN analysis window is shown with vertical lines. b) Histograms showing the mean voltage within the analysis window in each of the four conditions for the two groups (bars represent standard error). Lines link the individual contrasts in the a-priori hypothesis; *: $p < .05$; NS: not significant. Note that the controls have a larger negativity on the punishment, compared

to reward, trials while the smokers do not. c) Medial frontal ROI shown in open circles in the 128 channel sensor net with 10/20 system locations marked for reference.

Table 1

	Controls-RP	Smokers-RP	Controls-MF	Smokers-MF
N	22	22	17	21
Age	31.0 (10.6)	34.0 (11.5)	33.1 (11.2)	35.0 (11.0)
Gender (#:% male)	11: 50%	13: 59%	7: 41%	11: 52%
Race (#:% Caucasian)	14: 64%	19: 86%	11: 65%	18: 86%
Years Education	13.0 (1.8)	13.3 (1.7)	14.0 (1.9)	13.3 (1.8)
CO (ppm)	2.6 (1.2)	29.5 (22.5)	2.6 (1.4)	30.7 (22.5)
FTND	•	5.2 (2.1)	•	5.4 (1.9)
WISDM	•	5.1 (1.5)	•	5.4 (1.2)
QSU	•	143.8 (27.1)	•	142.9 (28.3)
BIS-11	55.9 (11.7)	56.9 (12.0)	57.8 (12.4)	58.4 (12.8)
I7	32.9 (4.7)	33.8 (3.1)	32.4 (5.1)	33.8 (3.1)

Note: RP: Reward Prediction task; MF: Motivated Flanker task; N: Number of participants; CO: Carbon Monoxide in parts per million; FTND: Fagerstrom Test for Nicotine Dependence; WISDM: Wisconsin Inventory of Smoking Dependence Motives; QSU: Questionnaire of Smoking Urges; BIS-11: Barratt Impulsiveness Scale, v.11; I7: Eysenck Impulsiveness Questionnaire. Numbers are means with standard deviations in parentheses except for N, and for Gender and Race which are raw count and percentage of group.