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The Effects of Smoking Abstinence on Incentivized Spatial Working Memory

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ABSTRACT

Background and Objective: Reward processing and working memory (WM) underlie value-based decision-making; consequently, joint examination of these systems may further our understanding of why smokers choose to smoke again following a quit attempt (relapse). While previous studies have demonstrated altered reward and WM function associated with nicotine exposure, little is known about the effects of abstinence on the joint function of these systems. The current study aims to address this gap. *Method:* Eighteen daily smokers were tested on a monetarily incentivized memory guided saccade (MGS) task on two separate, counterbalanced occasions, an abstinent and a non-abstinent session. The MGS task is a widely used metric of spatial working memory and enables precise quantification of the effects of rewards and nicotine exposure on behavior. *Results:* During the non-abstinent session, participants showed increased accuracy of the initial saccade towards the remembered target location on reward vs. neutral trials. Participants also showed increased accuracy of the final saccade towards the target, across incentive types, only during the non-abstinent condition. *Discussion and Conclusions:* Our observation that rewards improve the accuracy of the initial memory guided saccade during the non-abstinent but not abstinent condition extends a growing literature indicating reduced motivation towards monetary rewards during abstinence. Further, differences in the accuracy of the final corrective saccade during the non-abstinent but not the abstinent condition suggests smoking abstinence-related effects on WM precision beyond those related to incentive motivation (e.g., sustained attention). *Significance:* This work extends our fundamental understanding of smoking's effects on core affective and cognitive processes.

KEYWORDS
Smoking; rewards; working memory; addiction; eye movements

Introduction

Attempts to maintain abstinence from smoking often are unsuccessful in the long-term, even with behavioral and pharmacological assistance (CDC 2002; Giovino, 2007). Characterization of basic mechanisms underlying decisions to continue smoking after a quit attempt may be critical to improve individualized treatment and facilitate prevention efforts. Models of nicotine dependence posit that smoking-related alterations in reward processing as well as deficits in cognitive control are two key factors contributing to continued smoking after a quit attempt (Bechara, 2005; Lydon, Wilson, Child, & Geier, 2014). In terms of decision-making, dysregulated reward drives (heightened response to smoking cues and reduced responses to non-drug cues, discussed below) and deficits in regulatory, cognitive control may collectively contribute to biased choices, such that individuals choose smoking over alternative reinforcers or behaviors. Despite theoretical links between reward, cognitive control, and smoking, relatively little empirical work has explicitly examined their interaction. Below, we first briefly review previous work on the effects of smoking on aspects of cognitive control. We then highlight work on dysregulated reward processing associated with smoking. Finally, we discuss what has been done in terms of understanding the interaction between these systems and how the current study furthers this work.

Cognitive control

Generally, daily smokers demonstrate reduced performance relative to non-smokers on tasks indexing aspects of cognitive function, including (but not limited to) working memory and inhibitory control (Foulds et al., 1996, Spilich, June, & Renner, 1992; Spinella, 2002; Greenstein & Kassel, 2009; Ernst et al., 2001), with more pronounced impairments often emerging during smoking abstinence (Ernst et al., 2001; Mendrek, et al., 2006; McClernon, et al., 2016; Kozink, Lutz, Rose, Froeliger, & McClernon, 2010; Myers, Taylor, Moolchan, & Heishman, 2008). This diminished ability during abstinence to inhibit acute impulses to smoke and to retain

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long-term goals of abstinence in mind likely contributes to biased decision-making favoring drug-use over continued abstinence (Bechara, 2005; Jentsch & Taylor, 1999). Effects of nicotine on cognition are also demonstrated in studies that re-expose abstinent smokers to nicotine, resulting in a reversal of observed abstinent-related cognitive deficits (e.g., Davis et al., 2005; Myers et al., 2008).

Given that cognitive control is an extremely broad construct, we narrow our focus in this paper on working memory, a crucial component of cognitive control and centrally involved in decision-making (Bechara & Martin, 2004; Hinson, Jameson, & Whitney, 2003). Previous studies have been mixed in terms of finding altered performance on WM tasks when smokers are abstinent vs. not; when observed, it is often evidenced by reduced accuracy and slower response times (Ernst et al., 2001; Mendrek, et al., 2006; McClernon et al., 2016; Cohen and Ross, 1978; Blake & Smith, 1997; Jacobsen, Mencl, Constable, Westerveld, & Pugh, 2007; Heishman, 1999; Greenstein and Kassel, 2009; Park, Knopick, McGurk, & Meltzer, 2000; Xu, Mendrek, & Cohen, 2005). Individual differences in working memory ability or nicotine dependence severity across subjects likely play roles in the mixed findings, but it might also reflect the fact that WM is not a unitary process. That is, WM is comprised of various sub-processes (e.g. cognitive processes like encoding, maintenance, and motor processes like saccade response) (Scherf, Sweeney, & Luna, 2006; Baddeley, Della Sala, Robbins, & Baddeley, 1996; Baddeley, 1996), each of which is subserved by different neural circuitry and could be differentially affected by nicotine exposure. In the current study, we use an experimental paradigm that begins to give us some leverage on this issue.

Reward processing

The effect of smoking on reward system function has been extensively studied. Prolonged smoking impacts the mesolimbic dopamine system such that drug-associated rewards (smoking) gain increased incentive salience while the incentive salience of non-drug rewards (e.g. food, money) is reduced (Koob & Le Moal, 1997; Robinson & Berridge, 2008). As nicotine maintains the ability to increase dopamine transmission in areas of the brain associated with reward during dependence, the alterations in reward functioning are more pronounced during periods of smoking deprivation, when the acute effects of nicotine on the dopaminergic mesolimbic system are absent (Dawkins, Powell, West, Powell, & Pickering, 2006; Powell, Tait, & Lessiter, 2002; Sweitzer et al., 2014). In the context of these reward system alterations, attention processes are biased towards drug-associated stimuli and incentive motivation to consume drugs is triggered when drug-associated stimuli are encountered (Robinson & Berridge, 2008). Further, the experience of reduced sensitivity to non-drug rewards, like impaired cognitive functioning, is associated with smoking cessation failure (Leventhal et al., 2009; Leventhal et al., 2008).

The interaction between cognitive control and reward processing in smokers

Cognitive control and reward processing interact to guide behavior in at least two ways (Botvinick & Braver, 2015; Geier & Luna, 2009). First, in the context of nicotine dependence, it is the combination of reduced sensitivity to non-drug reward, increased sensitivity to drug-associated reward, and abstinence-related cognitive deficits that drive relapse behavior, as incentive motivation towards drug-rewards is difficult to regulate due to both strong approach motivation and weak cognitive control abilities (Bechara, 2005). Second, motivation to avoid drug use may bolster cognitive control in line with research demonstrating a facilitating effect of incentives on cognition (Veling & Aarts, 2010; Locke & Braver, 2008; Gilbert & Fiez, 2004; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). This second, understudied perspective underlies the approach of contingency management smoking interventions that include components aimed at enhancing the value of continued abstinence through the provision of an incentive in order to encourage the allocation of cognitive resources to achieve successful abstinence outcomes (Marteau et al., 2010).

Our previous work has shown the smoking context-specific ability of monetary incentives to improve cognitive control, indicating that monetary incentives improve inhibitory control during non-abstinence but not during abstinence (Lydon et al., 2014). This finding suggests that the nicotine-associated alterations in reward processing and cognitive control (Koob & LeMoal, 1997; Robinson & Berridge, 2008; Volkow, Fowler and Wang, 2004) limit the generalizability of the motivation-related improvements in cognition observed in non-drug dependent samples and suggests that the use of monetary incentives in attempts to recruit cognitive resources to promote continued abstinence in interventions may be suboptimal for many smokers.

The present study

To examine the effects of smoking on incentivized WM performance, a within-subjects repeated measures design was used in which daily smokers performed a monetary incentivized spatial working memory task (the memory guided saccade, MGS, task) during abstinent (12-hours) and non-abstinent states. In line with findings demonstrating abstinence-related reward alterations (Sweitzer et al., 2014; Geier, Sweitzer, Denlinger, Sparacino, &

Donny, 2014) and reduced ability for incentives to impact inhibitory control during smoking abstinence (Lydon et al., 2014), we hypothesized that WM performance would be more accurate on rewarded vs. non-rewarded trials during the non-abstinent condition but not during abstinence. Further, we hypothesized that smokers would demonstrate overall deficits on the MGS task (regardless of incentive) following abstinence.

As an exploratory aim, we also examined whether different components of WM (encoding/maintenance vs. motor execution) may be differentially affected by nicotine exposure in order to examine how generalizable nicotine-induced deficits are on cognition. If nicotine status (abstinent vs. non-abstinent) affects encoding/maintenance functions, then this should be reflected by reduced accuracy of the initial and/or final saccade towards the remembered target across abstinent and non-abstinent conditions (Luna et al., 2004). If motor (saccade) execution is affected by nicotine status, this should be reflected by differences in the latency and velocity of the saccade(s) across abstinent and non-abstinence.

Methods

Participants

Upon approval by the Institution Review Board, 23 daily smokers (16 males) aged 18–62 ($M = 30.87$, $SD = 13.17$) were recruited as part of a larger study on the effects of abstinence on reward and cognitive functions, including inhibitory control (not reported here). Inclusion criteria included: ≥18 years old, daily smoking for at least the past year, inhaling while smoking, and no intention to quit in the next month. Exclusion criteria included: self-reported current illicit drug use, dependence on alcohol, current depression, women who were, or planned to be, pregnant or breastfeeding during the study, and reports of other tobacco use within the past year.

Procedure

Participants attended a baseline session during which they completed a breath carbon monoxide (CO) analysis to establish baseline CO levels utilizing a coVita|Bedfont Micro Smokerlyzer®. The Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) and the Center for Epidemiologic Studies Depression Scale –Revised (Eaton, Smith, Ybarra, Muntaner, & Tien, 2004) were used to screen for depression. A self-report screening for dependence on illicit drugs was administered. Nicotine dependence was assessed using the FTND (Ebbert, Patten, & Schroeder, 2006), and craving was assessed using the Questionnaire of Smoking Urges – Brief (Cox, Tiffany, & Christen, 2001).

Participants attended two counterbalanced (abstinent and non-abstinent) sessions. For abstinent sessions, participants were instructed not to smoke for at least 12 hr (overnight) before the session. For non-abstinent sessions, participants were instructed to continue their regular smoking habits. Participants' CO levels and recent substance use were assessed at the start of both experimental sessions. In the abstinent session, participants CO level must have decreased by 50% from their baseline level to continue with the session. Each session lasted approximately two hours.

Memory guided saccade task

Participants completed an incentivized MGS task (see Figure 1) presented in (Psychology Software Tools, Inc., Pittsburgh, PA) E-Prime. Participants were told they could earn up to $10 ($5 per session) based on their performance on the working memory task. This payment was in addition to a $10 per session participation payment. The amount earned per trial was left intentionally ambiguous to promote consistent performance across all trials. Similar to work described elsewhere (Geier et al., 2014), at the beginning of each trial participants were visually cued as to whether the forthcoming trial was a 'reward' trial ($$$) or a 'neutral' trial (###). An equal number of rewarded and neutral trials were presented. Subjects were to fixate on a centrally located yellow cross subtending ~0.5 degrees of visual angle for 2,425 ms. A target stimulus was then presented (75 ms) in the

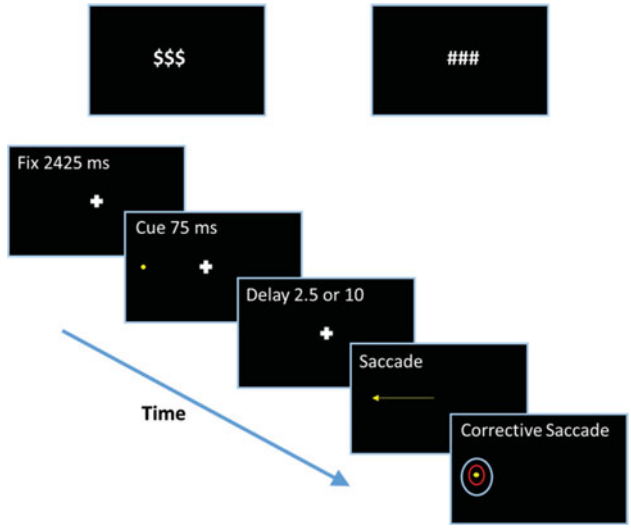

Figure 1. The incentivized memory guided saccade task. Three dollar signs ($$$) or three hash tags (###) first appeared on each trial to indicate whether the forthcoming trial would be rewarded or non-rewarded, respectively. See text for task details. The yellow arrow appearing in the 'Saccade' slide in this figure is presented to indicate the correct direction of required eye movement but was not presented to participants.

periphery at ± 4 or ± 8 degrees of visual angle. As is standard in MGS studies, the location of the stimulus on each trial was randomized and counterbalanced across visual hemifields such that participants were unable to reliably predict the location of the forthcoming stimulus (Geier et al., 2014). Participants were instructed to attend to and remember the location of the stimulus (using peripheral vision) but maintain fixation to the central fixation throughout the stimulus presentation and for the duration of the following delay period. An equal number of two delay periods were randomly presened, 2.5 s ("short") or 10 s ("long"). Following the delay period, the central fixation disappeared, cueing participants to look toward the remembered location of the peripheral stimulus. The stimulus then reappeared with a red circle around it indicating where participants should have looked. Participants were instructed to make visual corrections if necessary so that they were fixating on the target stimulus. An inter-trial fixation period (1200 ms) separated trials. A total of 4 runs (comprised of 48 trials each) were completed across two visits totaling 192 trials. Eye movement data were obtained using a table-mounted (Applied Science Laboratories, Bedford, MA) ASL Model 506 eye-tracking system (Psychology Software Tools) that recorded eye position by pupil and corneal reflection. Participants were instructed to complete the task as quickly and accurately as possible.

Analysis

Studies using MGS tasks typically emphasize analysis of the initial and final saccade towards remembered target locations. Variables of interest for the initial saccade, the first eye movement exceeding a velocity criterion of 30 degrees/sec following the removal of the central fixation (Luna, Velanova, & Geier, 2008), included latency, accuracy (distance in degrees/visual angle from the target), and peak velocity. The accuracy of the final 'corrective' saccade (the last saccade made prior to the re-appearance of the stimulus (Luna et al., 2008) was also of interest. Saccade latencies under 80 ms and longer than 900 ms were removed as outliers (Hardin, Schroth, Pine, & Ernst, 2007). Peak velocity and accuracy values exceeding ±2 SDs from the mean were also removed to avoid spurious outliers. Latencies and peak velocities were log transformed due to skewness.

Data from the two runs within each session were combined given no significant differences. Further, no significant differences across delay lengths (2.5 vs. 10 sec) were found in our sample, so data from short and long delay trials were also combined. Repeated measures ANOVAs were conducted in SPSS to examine the effect of session type (abstinent vs. non-abstinent) and incentive (reward vs. neutral), and their interaction on the accuracy, peak velocity, and latency of the initial saccade and the accuracy of the final saccade. Significant effects were followed up with paired-samples *t*-tests. Statistical significance was evaluated at $\alpha = .05$. A power analysis was completed (from Park et al., 2000), and it was determined that a sample size of 14 was needed to detect significant session differences in WM with .80 power and $\alpha = .05$.

Results

Participants with data available for the entire procedure ($n = 18$) are reported on here (Table 1). Two participants

Table 1. Shows average smoking statistics demonstrating that participants were, on average, light smokers. The CO Level and QSU Scores demonstrate compliance between the non-abstinent and abstinent session. Table 1 also lists the means and SD's for the distance from the target (accuracy), saccade latency (reaction time) and peak velocity of the initial saccade, and the distance from the target (accuracy) of the final saccade for reward and neutral trials, across sessions (abstinent vs. smoke as usual). Peak Velocity is listed in degrees per second, Reaction Time is listed in milliseconds, and accuracy is listed in degrees of visual angle. *Note.* FTND = Fagerström Test of Nicotine Dependence; CO = Breath Carbon Monoxide; QSU = Questionnaire of Smoking Urges – Brief; *M* = Mean; *SD* = Standard Deviation.

	Initial Saccade						Final Saccade	
	Distance From Target		Saccade Latency		Peak Velocity		Distance From Target	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Abstinent *Neutral*	.66	.12	370.57	71.40	127.71	37.05	.0148	.0052
Non Abstinent *Neutral*	.65	.19	354.14	63.10	126.00	33.12	.0129	.0047
Abstinent *Reward*	.71	.17	361.67	68.99	123.23	28.55	.0120	.0043
Non Abstinent *Reward*	.60	.17	355.34	63.99	123.20	36.06	.0148	.0049
Average Cigarettes per day	9.67	6.12						
Avg. Age Smoking Initiation	19.17	6.58						
FTND Score	2.17	3.78						
	Non Abstinent M	*Non Abstinent SD*		*Abstinent M*	*Abstinent SD*			
CO Level	12.61	7.84		5.67	4.31			
QSU Score	22.65	10.78		31.29	16.87			

did not complete all sessions, one failing to show up for the abstinent session and one for the smoke as usual session. Technical problems with the eye tracker led to missing working memory data from 3 participants, with one participant providing no data for both smoke as usual and abstinent sessions, one missing data for the smoke as usual session, and one missing data for the abstinent session. Means and standard deviations of accuracy, saccade latency, and peak velocity of the initial saccade and accuracy of the final saccade are shown in Table 1.

Abstinence verification

One participant's abstinent session was rescheduled as they reported drinking alcohol in the previous 24 hours. Two participants failed to reduce their CO level from their baseline session and their abstinent session was rescheduled. All participants verbally reported no use of nicotine products for ≥12 hours preceding their abstinent (or rescheduled abstinent) sessions. Indeed, participants' expired CO levels during the non-abstinent session were significantly greater than levels during the abstinent session $t(17) = 5.62$, $p < .01$ and scores on the QSU during the non-abstinent session were significantly less relative to the abstinent session, $t(17) = -3.22$, $p < .01$.

Initial saccade

In line with our hypothesis that *accuracy* would be improved on incentivized trials when participants were non-abstinent vs. abstinent, there was a significant incentive by session interaction, $F(1, 17) = 4.76$, $p = .04$, $\eta_p^2 = .22$. During the non-abstinent session, participants were more accurate on reward relative to neutral trials, $t(17) = -2.39$, $p = .03$, $\eta^2 = .25$. There were no significant differences in accuracy between the reward and neutral trials during the abstinent session, $t(17) = 1.35$, $p = .19$. There was no significant main effect of incentive, $F(1, 17) = 0.001$, $p = .97$, $\eta_p^2 < .001$, or session, $F(1, 17) = 2.92$, $p = .11$, $\eta_p^2 = .15$.

For saccade *latency*, there was no significant main effect of incentive, $F(1, 17) = .20$, $p = .66$, $\eta_p^2 = .01$, session, $F(1,17) = .58$, $p = .46$, $\eta_p^2 = .03$, or interaction between reward by session interaction, $F(1,17) = 1.89$, $p = 1.9$, $\eta_p^2 = .10$.

For peak *velocity*, there was a significant main effect of incentive, $F(1, 17) = 5.04$, $p = .04$, $\eta_p^2 = .23$. Peak velocity was greater on neutral relative to reward trials, $t(17) = .04$, $p = .04$. However, there was no significant main effect of session, $F(1,17) = .001$, $p = .98$, $\eta_p^2 < .01$, and the incentive by session interaction was not significant, $F(1,17) = .24$, $p = .63$, $\eta_p^2 = .01$.

Final (corrective) saccade

For accuracy, there was a main effect of session, $F(1,16) = 5.95$, $p = .03$, $\eta_p^2 = .27$. Participants demonstrated increased accuracy during the non-abstinent relative to the abstinent session, $t(16) = -.11$, $p = .03$. There was no main effect of incentive, $F(1,16) = .60$, $p = .45$, $\eta_p^2 = .04$, or incentive by session effect, $F(1,16) = .97$, $p = .34$, $\eta_p^2 = .06$.

Discussion

This study employed a novel application of an incentivized MGS task to examine smokers' use of spatial working memory in rewarded vs. neutral contexts during smoking abstinent and non-abstinent states. Additionally, our application of this eye movement paradigm allowed us to explore the effects of nicotine on component processes of working memory.

In line with our hypothesis that participants would be more accurate on rewarded vs. non-rewarded trials during the non-abstinent condition, our results show a significant incentive by session interaction in the accuracy of the initial saccade towards the target, with saccades closer to the target location on reward vs. neutral trials during the non-abstinent but not during the abstinent condition. Moreover, the accuracy of the final saccade was higher during the non-abstinent vs. abstinent condition, regardless of incentive trial type.

Accuracy of memory guided saccades is widely thought to serve as a proxy for the fidelity of the internal representation of the stimulus, which reflects how well the spatial information was initially encoded and/or maintained across a delay period, and participants' effort to correct for any disparity between eye position and the remembered target location (Eaton et al., 2004; Weber & Daraoff, 1972). Our results indicate that deprived smokers may not be encoding the spatial position of the stimulus as well, or have reduced maintenance fidelity, when they are nicotine deprived. These results also suggest that initial vs. subsequent corrective saccades may be differentially affected by altered motivation-related processes during abstinence, as we found an incentive by condition interaction for the initial but not corrective saccades. It may be the case that corrective saccade accuracy reflects a different aspect of task performance, such as sustained attention, that may not be affected by altered incentive motivation but is affected by nicotine abstinence (e.g., Kozink et al., 2010).

Interestingly, participants demonstrated higher peak velocities on neutral compared to rewarded trials. This could be due to the participants being more 'cautious'

when a reward was at stake - a speed-accuracy trade off. Harris and Wopert (2006) reason that saccade trajectories have evolved to optimize a trade-off between the accuracy and duration of the movement. Somewhat surprisingly, the faster peak velocities in neutral trials were observed regardless of smoking session. This suggests that the motoric mechanism underlying the velocity at which the saccades were executed is unaffected by the presence or absence of nicotine, in apparent contrast to systems supporting representations of visual space (i.e., facilitating target localization as reflected by accuracy measures). However, additional research with larger sample sizes is needed to more fully characterize oculomotor and cognitive systems' apparent dissociated responses to nicotine deprivation. What is particularly notable about the velocity finding is that it stands in contrast to other saccade metrics observed across abstinence condition, especially accuracy. That is, we do not see evidence of reduced motivation to rewards for the abstinent vs. non-abstinent conditions in terms of velocity. It may well be the case that reduced motivation for money is manifested in more nuanced ways in the brain and behavior than typically appreciated in the literature. Future studies should examine this intriguing possibility in more detail.

These results should be considered in the context of the following limitations. Our behavioral effects are relative only to other smokers as there was no (non-smoking) control group. Second, time since the participant's last cigarette was unavailable, therefore there could have been variability (however, CO levels were measured). Third, the sample size for this preliminary study, although sufficiently powered, is modest and predominantly men. To mitigate this effect, however, we utilized a large number of trials (n = 192) and a within-subjects design. Despite these limitations, the present study is highly novel in the sense that it is one of the few existing studies to consider the *joint* operation of reward and cognitive control processing in line with theories of the interaction between these two systems in guiding decision-making, including decisions to smoke or to remain abstinent (Botvinick & Braver, 2015; Geier & Luna, 2009). While next steps will be to examine the functioning of these systems in real-world settings, isolating these mechanisms in an experimental design is a crucial first effort to directly measure the effects of nicotine on these processes as in real-world settings these mechanisms are compounded and therefore it is difficult to determine what specific processes nicotine affects.

In conclusion, our findings demonstrate specific deficits in smokers' performance on a rewarded memory guided saccade task during different smoking conditions. In addition, we demonstrate differences in the ability of rewards to improve cognitive performance when smokers are non-abstinent relative to abstinent. The inability of rewards to increase task performance during smoking abstinence may undermine efforts to use non-drug rewards to promote continued abstinence through the enhancement of cognitive processes (e.g., contingency management) (Geier et al., 2014). Accordingly, the MGS task used here, as well as other oculomotor paradigms, could be an effective means to further examine the nuanced effects of nicotine on affective and cognitive function.

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Competing interests

All authors have no competing interests.

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