The influence of acutely administered nicotine on cue-induced craving for gambling in at-risk video lottery terminal gamblers who smoke

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Evidence indicates that tobacco use and gambling often co-occur. Despite this association, little is known about how tobacco use affects the propensity to gamble. Nicotine, the putative addictive component of tobacco, has been reported to potentiate the hedonic value of other nonsmoking stimuli. Environmental cues have been identified as an important contributor to relapse in addictive behavior; however, the extent to which nicotine can affect the strength of gambling cues remains unknown. This study examined whether nicotine influences subjective ratings for gambling following gambling cues. In a mixed within/between-subjects design, 30 (20 men) video lottery terminal (VLT) gamblers ('moderate-risk' or 'problem' gamblers) who smoke daily were assigned to nicotine (4 mg deliverable) or placebo lozenge conditions. Subjective and behavioral responses were assessed at baseline, following lozenge, following neutral cues, and following presentation of gambling cues. Nicotine lozenge was found to significantly reduce tobacco-related cravings ($P<0.05$) but did not affect gambling-related cravings, the choice to play a VLT, or other subjective responses. These results suggest that a low dose of acutely administered nicotine does not increase cue-induced craving for gambling in at-risk VLT gamblers who smoke. *Behavioural Pharmacology* 24:124–132 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Tobacco use and gambling frequently co-occur (McGrath and Barrett, 2009). Rates of smoking among pathological gamblers range from 41% (Smart and Ferris, 1996) to 60% (Cunningham-Williams *et al.*, 1998); and numerous studies have also found that both regular gamblers (McGrath *et al.*, 2012a) and pathological gamblers who use tobacco experience poorer psychosocial and gambling-related outcomes compared with pathological gamblers who do not smoke (Petry and Oncken, 2002; Potenza *et al.*, 2004; Grant and Potenza, 2005).

Contemporary studies on smoking and gambling suggest that these addictive behaviors may also share some common underlying mechanisms. For instance, research on the neurochemical underpinnings of tobacco use (Pontieri *et al.*, 1996) and gambling (Breiter *et al.*, 2001; Linnet *et al.*, 2010) has found that both are associated with increased dopaminergic neurotransmission. In addition, there is evidence to suggest that nicotine may influence primary processes related to gambling. In animal models, nicotine has been found to enhance the reinforcement value of other reinforcing behavior such as lever pressing to visual stimuli through nonassociative mechanisms (Donny *et al.*, 2003; Palmatier *et al.*, 2006; Chaudhri *et al.*, 2007). In humans, the acute administration of nicotine has been found to result in greater responsiveness to a card-sorting task among heavy smokers (Dawkins *et al.*, 2006) as well as increased response toward a rewarding stimulus (i.e. monetary reward) among nonsmokers (Barr *et al.*, 2008). Although these findings suggest that nicotine may influence other reinforcing behaviors, only a select few laboratory studies have investigated its impact on actual gambling. In a recent study conducted in our laboratory, we examined the effects of acute nicotine administration among regular video lottery terminal (VLT) gamblers who smoke (McGrath *et al.*, 2012b). It was found that nicotine replacement therapy (NRT) delivered through inhaler acutely reduced subjective craving for cigarettes; however, nicotine did not alter gambling-related cravings or VLT betting behavior (e.g. dollars spent gambling). The available evidence to date is mixed, with some studies supporting the reinforcement-enhancing properties of nicotine for other reinforced behavior (Dawkins *et al.*, 2006; Barr *et al.*, 2008); whereas, our findings suggest that nicotine has little effect on actual gambling behavior (McGrath *et al.*, 2012b). Although these results do not directly implicate nicotine in the modification of gambling outcomes, they do raise the possibility that nicotine may influence psychological processes associated with gambling.

The cue-reactivity paradigm has become an important framework for investigating the role of cue-induced craving in addiction (Tiffany and Wray, 2009). Cue-reactivity paradigms involve exposing individuals to drug-related stimuli commonly associated with the use of a particular substance. In most cases, behavior, subjective

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responses, and/or physiological changes following exposure to stimuli are recorded and examined (Carter and Tiffany, 1999). Recent research also indicates that laboratory-based cue-reactivity paradigms are also useful for understanding craving for gambling (Kushner *et al.*, 2008). For instance, an exciting gambling video was found to elicit greater urges to gamble among pathological gamblers than among social gamblers (Sodano and Wulfert, 2010); viewing images of preferred gambling activities elicited greater craving among pathological gamblers than images of nonpreferred activities (Wulfert *et al.*, 2009); and gambling imagery scripts have been found to elicit higher ratings of excitement than gambling images among student gamblers (Ashrafioun *et al.*, 2011). Other studies suggest that gambling-related audio (Blanchard *et al.*, 2000) as well as imagining gambling (Sharpe, 2004) can increase physiological arousal [e.g. heart rate (HR)] in problem gamblers compared with social gamblers. Finally, recent neuroimaging investigations of problem gamblers reveal dorsolateral prefrontal activity while watching gambling-related videos (Crockford *et al.*, 2005) and frontoparietal activation following exposure to a blackjack scenario (Miedl *et al.*, 2010), indicating that memory networks associated with gambling are triggered by cues. In a sample of treatment-seeking gamblers exposed to gambling cues, Goudriaan *et al.* (2010) found increased activity in brain regions implicated in motivation and visual processing, areas also associated with cue reactivity in other substance dependence including tobacco. Although gambling-focused cue-reactivity research is still in its infancy, the aggregate of these findings suggests that this paradigm reliably induces craving for gambling in experimental settings.

A few studies have also investigated the potential for cue-reactivity paradigms to elicit craving in drug challenge experiments in which nicotine was administered. For instance, Reid *et al.* (1998) reported that transdermal nicotine potentiated cue-induced cocaine craving in abstinent smokers with a history of crack-cocaine use. Attwood *et al.* (2009) recently found that administration of nicotine-containing cigarettes enhanced attractiveness ratings of pictorial facial cues in nondaily smokers than denicotinized cigarettes. These findings indicate that nicotine may potentiate the hedonic value of other visual stimuli that are unrelated to smoking itself. As such, it is possible that a nicotine challenge may also influence craving ratings for visual cues associated with other behaviors commonly associated with smoking such as gambling.

The present study sought to further clarify the relationship between nicotine and gambling using a laboratory-based drug challenge experiment. The study protocol was designed to accomplish a set of specific goals. First, some evidence suggests that nicotine may influence other reinforcing behaviors in humans (Dawkins *et al.*, 2006; Barr *et al.*, 2008); whereas, our recent study indicates that this may not be the case for actual gambling behavior (McGrath *et al.*, 2012b). The primary goal of current study was to provide further evidence of whether acutely administered nicotine can influence gambling craving in gamblers who smoke. Second, the current study was also designed to improve upon potential methodological limitations of the protocol previously used in our laboratory (McGrath *et al.*, 2012b). Specifically, we previously recruited smokers who were regular gamblers; however, participants were not required to meet diagnostic criteria for problem or pathological gambling. It is highly possible that regular gamblers do not experience intense cravings for gambling in a manner similar to that of problem gamblers. Indeed, results from Sodano and Wulfert (2010) suggest that pathological gamblers report greater urge to gamble following cue exposure than social gamblers. In the current study, the sample was comprised solely of 'moderate-risk' or 'problem' VLT/slots gamblers as defined by a score of 3 or more on the Canadian Problem Gambling Index (CPGI). This selection procedure was designed to exclude individuals who may only gamble occasionally or socially. The final goal of the current study was to investigate the potential for using a gambling-cue-reactivity paradigm in a nicotine drug challenge experiment. Cue-reactivity paradigms from other domains (e.g. cocaine use, facial attractiveness) have successfully induced craving across pharmacological conditions; however, no known studies have directly examined the utility of a gambling-cue procedure with similar nicotine protocols. On the basis of previous literature illustrating the secondary-reinforcement properties of nicotine, it was predicted that relative to placebo, nicotine administration would be associated with elevated subjective gambling craving and heightened response on physiological indices (i.e. average HR) following exposure to gambling cues. It was also hypothesized that participants in the nicotine condition would be significantly more likely to accept an offer to gamble on a VLT following gambling-cue exposure compared with those in the placebo condition.

Methods

Participants

All individuals were recruited from the Halifax Regional Municipality via Internet bulletin boards. Participants were screened through telephone calls for the following inclusion criteria: (a) being 19 years of age or older, (b) regular daily smoking for the past 12 months, (c) a score of more than 3 on the Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.*, 1991), (d) have played VLTs at least once a month for the past 6 months, and (e) a score of 3 or more on the CPGI indicating 'moderate-risk' (between 3–7.5) or 'problem' gambling (between 8–27). Individuals were excluded if they had ever sought treatment for gambling, were currently trying to quit smoking or gambling, or for women, were currently pregnant or were planning to conceive. The experimental protocol received ethics approval from the Capital District Health Authority

Research Ethics Board and was conducted in accordance with the Declaration of Helsinki.

Participants were 30 (20 men) regular VLT gamblers who smoked daily, with a mean age of 32.2 years (SD = 11.8). The sample reported smoking an average of 15.5 cigarettes/day (SD = 8.9) and a mean FTND score of 5.7 (SD = 1.6). The mean CPGI score was 8.6 (SD = 4.5), with 12 participants being 'moderate-risk' gamblers and 18 participants meeting the criteria for 'problem gambling'.

Procedure

Blinding

To control for demand characteristics, participants were not informed of the specific ingredients they would ingest before their participation. Rather, they were told the lozenges 'may contain some of the ingredients commonly found in cigarettes (e.g. tar, ammonia, carbon monoxide, menthol, nicotine, sucrose, etc.)'. In addition, the experimenter remained blind to both the lozenges administered and the content of the second slideshow viewed by participants. Lozenges and slideshows were blinded by a research assistant who was not directly involved in participant testing. Before testing, the lozenge was placed in an envelope by the research assistant and then given to the experimenter. Participants were asked to take the lozenge out of the envelope and place it in their mouth without showing it to the experimenter. They were also asked not to divulge information regarding the content of lozenges or slideshows to the experimenter.

Testing protocol

For this mixed within/between-subjects design, each experimental session was conducted in a neutral testing room (i.e. undecorated walls and no other visual cues) and took place during mornings only (between 09:00 h and noon). Fifteen participants were randomly assigned to a nicotine lozenge (NL) condition and 15 were assigned to a placebo lozenge (PL) condition. Following informed consent, 12-h overnight tobacco abstinence was verified with a carbon monoxide expired air reading (< 15 parts/million) and an alcohol analyzer breath sample (0.00 blood-alcohol concentration). Participants were also asked not to consume caffeine on the morning on the day of the session. The first task assigned to participants in both conditions was to complete baseline subjective craving and HR measurements [time 1 (T1)]. Participants were then provided with a lozenge (nicotine or placebo) and were asked to complete a second set of identical craving measures [time 2 (T2)] 30 min after the start of lozenge administration. Next, all participants viewed the neutral-cue slideshow (always presented first) and completed the third set of measures [time 3 (T3)]. Finally, both groups viewed the gambling-cue slideshow (always presented second) and completed the final set of craving measures [time 4 (T4)]. The time elapsed between the end of the neutral-cue slideshow and the beginning of the gambling-cue slideshow was ~5 min. HR was recorded during both cue slideshow presentations. Neutral-cue presentations were always shown before the gambling-cue presentation to reduce the chance of carryover effects on craving ratings and to minimize the need for counterbalancing presentations (Sayette *et al.*, 2010). Following completion of the last set of measures, participants were provided with $10 CAD and the option of keeping the money or using it to play a VLT. At the end of the session, all participants were compensated with an additional $30 CAD/session plus any amount won while gambling.

Cue presentations

The gambling-cue presentation consisted of 40 high resolution electronic gaming-related images (e.g. rows of slot machines, individuals of varying ages/ethnicities/sexes playing slots) paired with an audio soundtrack of background casino noise. The slideshow presentation was 2 min long with each photograph displayed for 3 s. Previous studies indicate that pairing images with sounds can effectively induce craving for gambling (Sodano and Wulfert, 2010). Images were carefully selected to avoid inclusion of other addictive substances (e.g. tobacco, alcohol, illicit drugs). The neutral-cue presentation was designed to be congruent with the gambling slideshow. The presentation consisted of 40 high resolution dishwasher and washing machine images (e.g. rows of washing machines, individuals of varying ages/ethnicities/sexes operating the appliances) paired with an audio soundtrack of washing machine sounds.

Lozenges

Nicotine was administered through NRT mint-flavored quick release lozenges (4 mg of nicotine, NiQuitin; GlaxoSmithKline, Brentford, UK). The lozenges are not commercially available in Canada, thus limiting prior participant experience with this NRT. The placebos comprised pharmacologically-inert breath mints similar in size and appearance. The dissolution characteristics of lozenges were not identical; however, participants in both conditions were given identical instructions to place the lozenge in their mouth, occasionally move it from one side of their mouth to the other (not chew or suck the lozenge), and allow it to dissolve over 30 min. Recent evidence indicates that quick release NLs are effective in acutely reducing cigarette craving in a time course similar to the present study (Barrett and Wagner, 2011). Reviews of the pharmacokinetic properties of NRT indicate that NLs (4 mg) result in mean blood nicotine levels of ~6.0 ng/ml at 25–30 min postadministration (Shiffman *et al.*, 2005; McEwen *et al.*, 2008).

Measures

Visual analog scale

The visual analog scale (VAS) consisted of 16 items, which measure subjective mood states: 'relaxed', 'pleasant', 'head rush', 'stimulated', 'jittery', 'dizzy', 'irritable', 'trouble concentrating', 'anxious', 'satisfied', 'high', 'alert', 'frustrated', 'sedated' 'crave cigarette', and 'crave VLTs/slots'. Each item

was rated from 1 = 'not at all' to 10 = 'extremely', with participants asked to rate their present feelings. Similar VAS items have been found to reliably measure subjective drug effects in humans (Bond and Lader, 1974).

The gambling craving scale

The gambling craving scale (GACS) is a nine-item self-report scale of current subjective craving for gambling comprising three factors: 'anticipation of gambling', 'desire for gambling', and 'relief of negative affect'. The GACS contains good psychometric properties with α's ranging from 0.81 to 0.85 among its three factors (Young and Wohl, 2009).

The questionnaire of smoking urges – brief

The questionnaire of smoking urges – brief (QSU-B) is a 10-item self-report measure used to assess current smoking urges. It contains two factors: 'intention to smoke', and 'withdrawal/negative affect'. The QSU-B is psychometrically sound with both factors displaying strong internal consistency ($\alpha = 0.96$ and 0.93, respectively) (Cox *et al.*, 2001).

Behavioral task

At the end of the experimental session, participants were presented with a choice of either (a) receiving $10 to keep; or (b) receiving $10 to gamble on a VLT for up to 15 min. Participants were free to spend as much of the $10 as they wished and were paid for any amount they won gambling.

Apparatus

An expired air carbon monoxide reader (piCO Smokerlyzer; Bedfont Scientific Ltd, Maidstone, UK) was used to confirm smoking abstinence. Alcohol abstinence was also confirmed using a breathalyzer (Alcomate Premium; AK Solutions, Palisades Park, New Jersey, USA). A HR monitor (Polar Electro Canada Inc., Lachine, Quebec, Canada) was used to measure average HR. The average number of beats was recorded over a 2-min interval for each individual measurement period.

As a part of the experimental protocol, participants were offered an opportunity to play an authentic VLT provided by the Atlantic Lotto Corporation and the Nova Scotia Gaming Corporation. Gambling took place in a 'bar-lab' decorated to resemble a real-world VLT gambling environment. The lab was decorated with a bar, stools, brightly colored walls, beer posters, and contained two VLT machines identical to those in the local marketplace (see Stewart *et al.*, 2000 for a complete description). VLT play was restricted to a spinning reels game (i.e. Royal Spins) to guarantee a similar gambling session for all participants (Ellery *et al.*, 2005).

Statistical analyses

All analyses were carried out using SPSS version 17 (SPSS Inc., Chicago, Illinois, USA). The dependent variables included VAS ratings, GACS subscale scores (Young and Wohl, 2009), QSU-B factor scores (Cox *et al.*, 2001), average HR, and 'choice to play/not to play the VLT'. Each dependent variable was analyzed using mixed modeling with drug (NL, PL) and time [baseline (T1), following lozenge administration (T2), following neutral-cue presentation (T3), and following gambling-cue presentation (T4)] entered as fixed and repeated factors, respectively; sex was entered as a fixed factor and a separate variable containing prelozenge baseline scores (T1) was entered as a time-varying covariate for each dependent variable. Covariance structures were chosen on the basis of model simplicity and the likelihood ratio test (West, 2009). For each dependent variable involving time (i.e. VAS, GACS, QSU-B, average HR), the interaction of drug with time was of primary interest. A χ^2-test was carried out for 'choice to play/not to play the VLT' across NL and PL conditions.

Results

Craving

Of the 16 VAS items, four were found to have significant drug × time interactions (Table 1). Significant interactions were found for 'head rush', 'alert', and 'satisfied'. For 'head rush', NL ratings were higher at T2 ($M = 3.90$, SE = 0.44) and T4 ($M = 3.05$, SE = 0.44) than PL at T2 ($M = 1.86$, SE = 0.44) and T4 ($M = 1.66$, SE = 0.44); for 'alert', PL ($M = 6.15$, SE = 0.49) ratings were greater than NL ($M = 4.82$, SE = 0.49) at T2; and although there was significant interaction for 'satisfied', no individual time point differences were found. No significant interactions were found for the remaining mood-related VAS items.

A significant drug × time interaction was found for ratings of 'crave cigarette' (Table 1). Lower cigarette craving ratings were found for NL relative to PL at T2 (following lozenge) ($P < 0.01$) and T3 ($P < 0.05$) (following neutral cues) and a marginal effect ($P = 0.07$) at T4 (following gambling cues) (Fig. 1a). Notably, there was no significant drug × time interaction for the gambling-related VAS item 'crave VLTs/slots' (Fig. 1b). However, there was a significant main effect of time [$F(2, 58) = 22.60$, $P < 0.01$], with mean ratings at T4 ($M = 5.48$, SE = 0.40) being significantly higher than those at T2 ($M = 3.05$, SE = 0.40) and T3 ($M = 3.35$, SE = 0.40) suggesting higher overall cravings following presentation of gambling cues (Fig. 2). No significant differences were found between T2 and T3 ($P = 0.37$). There were no significant interactions involving sex. Finally, post-hoc analyses revealed that the three-way drug × time × CPGI category interaction for 'crave VLTs/slots' was not significant [$F(3, 44) = 1.03$, NS], suggesting no differences in ratings between 'moderate-risk' and 'problem' gamblers.

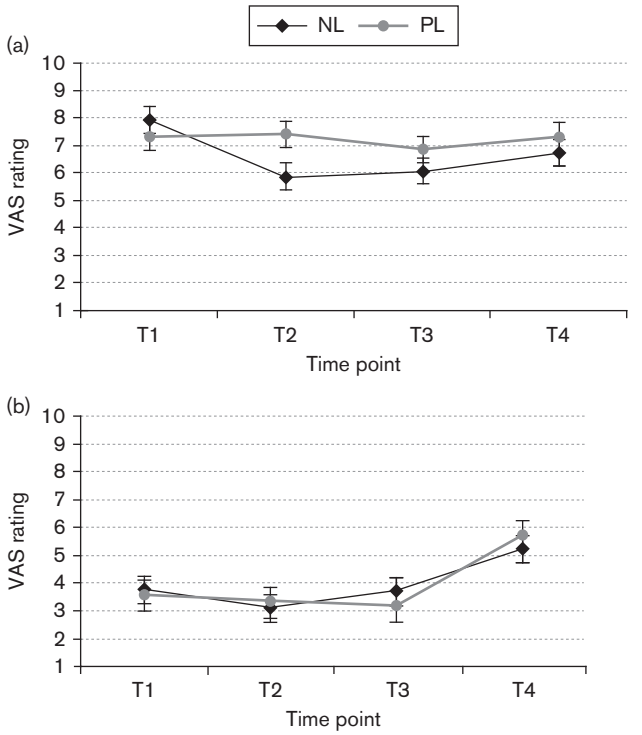
NL and PL conditions were compared across the three GACS factors. No significant differences were found between NL and PL on the 'anticipation of gambling' scale [$F(3, 44) = 0.58$, NS], the 'desire for gambling' scale

Table 1 Summary of mixed models examining time and the time × drug interaction for visual analog scale

Sources	*d.f.*	*F*	*P*
'Relaxed'			
Time	(2, 57)	1.44	0.25
Time × drug	(3, 44)	1.12	0.35
'Pleasant'			
Time	(2, 58)	0.23	0.80
Time × drug	(3, 44)	0.71	0.55
'Head rush'			
Time	(2, 60)	1.67	0.20
Time × drug	(3, 44)	4.43	0.01*
'Stimulated'			
Time	(2, 58)	5.60	0.01*
Time × drug	(3, 44)	0.71	0.55
'Jittery'			
Time	(2, 57)	5.76	0.01*
Time × drug	(3, 43)	1.56	0.21
'Dizzy'			
Time	(2, 59)	5.86	0.01*
Time × drug	(3, 45)	2.63	0.06
'Irritable'			
Time	(2, 58)	3.47	0.04*
Time × drug	(3, 44)	1.29	0.29
'Trouble concentrating'			
Time	(2, 60)	0.80	0.46
Time × drug	(3, 44)	0.47	0.70
'Anxious'			
Time	(2, 56)	1.88	0.16
Time × drug	(3, 42)	0.30	0.83
'Satisfied'			
Time	(2, 60)	1.02	0.37
Time × drug	(3, 44)	3.26	0.03*
'High'			
Time	(2, 42)	0.08	0.92
Time × drug	(3, 34)	0.58	0.63
'Alert'			
Time	(2, 58)	3.60	0.03*
Time × drug	(3, 44)	2.75	0.05*
'Frustrated'			
Time	(2, 55)	0.03	0.97
Time × drug	(3, 41)	0.72	0.55
'Sedated'			
Time	(2, 60)	0.82	0.45
Time × drug	(3, 44)	2.01	0.13
'Crave cigarette'			
Time	(2, 59)	3.10	0.05*
Time × drug	(3, 45)	4.33	0.01*
'Crave VLT/slots'			
Time	(2, 58)	22.60	0.01*
Time × drug	(3, 44)	0.85	0.47

Prelozenge baseline scores for each item were entered as covariates.
VLT, video lottery terminal.
*$P < 0.05$.

Fig. 1



Unadjusted mean ratings (±SE) for visual analog scale (VAS) item 'crave cigarette' (a) and VAS item 'crave video lottery terminals (VLTs)/slots' (b) for nicotine lozenge (NL) and placebo lozenge (PL) conditions at: baseline (T1); following lozenge administration (T2); following neutral-cue presentation (T3); and following gambling-cue presentation (T4). Baseline values were fixed as time-varying covariates in the analyses. NL significantly reduced ratings for 'crave cigarette' at T2, T3, and marginally at T4 relative to PL. No differences were observed between NL and PL for any time point on ratings for 'crave VLTs/slots'. There was also a significant main effect of time for 'crave cigarette' with mean ratings at T4 being significantly higher than those at T2 and T3.

[$F(3, 44) = 0.63$, NS], or the 'relief of negative affect' scale [$F(3, 45) = 0.56$, NS] (Fig. 3a–c). However, as seen with 'crave VLTs/slots', significant main effects for time were found for 'anticipation of gambling' [$F(2, 58) = 14.17$, $P < 0.01$], 'desire for gambling' [$F(2, 60) = 17.29$, $P < 0.01$], and 'relief of negative affect' [$F(2, 59) = 8.84$, $P < 0.01$]. In each case, total T4 ratings were higher than those for T2 and T3 (Fig. 3a–c). No significant interactions involving sex were observed for any of the indices. The three-way drug × time × CPGI category interactions for 'anticipation of gambling' [$F(3, 44) = 0.28$, NS], 'desire for gambling' [$F(3, 44) = 0.14$, NS], and 'relief of negative affect' [$F(3, 45) = 0.11$, NS] were not significant.

NL and PL conditions were compared across the two QSU-B factors. There was a significant drug × time interaction for ratings on 'intention to smoke' [$F(3, 46) = 4.44$, $P < 0.01$]. NL ratings were significantly lower at T2 ($M = 21.01$, SE = 1.73) and T3 ($M = 22.91$, SE = 1.73) than PL at T2 ($M = 29.81$, SE = 1.76) and T3 ($M = 29.06$, SE = 1.76). No significant differences were found between NL and PL on the 'withdrawal/negative affect' scale [$F(3, 46) = 1.02$, NS]. There were no significant interactions involving sex.

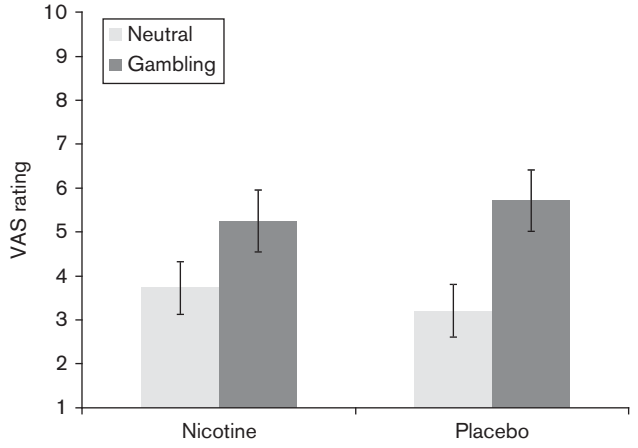
Behavioral task

For the decision to play or not to play the VLT, no significant difference was found between the number of participants in NL ($N = 9$) and PL ($N = 13$) conditions, who chose to play the VLT [$\chi^2(1, 30) = 2.73$, $P = 0.10$].

Heart rate

There was a significant drug × time interaction for average HR [$F(3, 43) = 5.64$, $P < 0.01$]. Average HR was found to be higher in the NL than in the PL condition at T2 (following lozenge) [$M = 76.34$ (SE = 1.32) vs.

Fig. 2



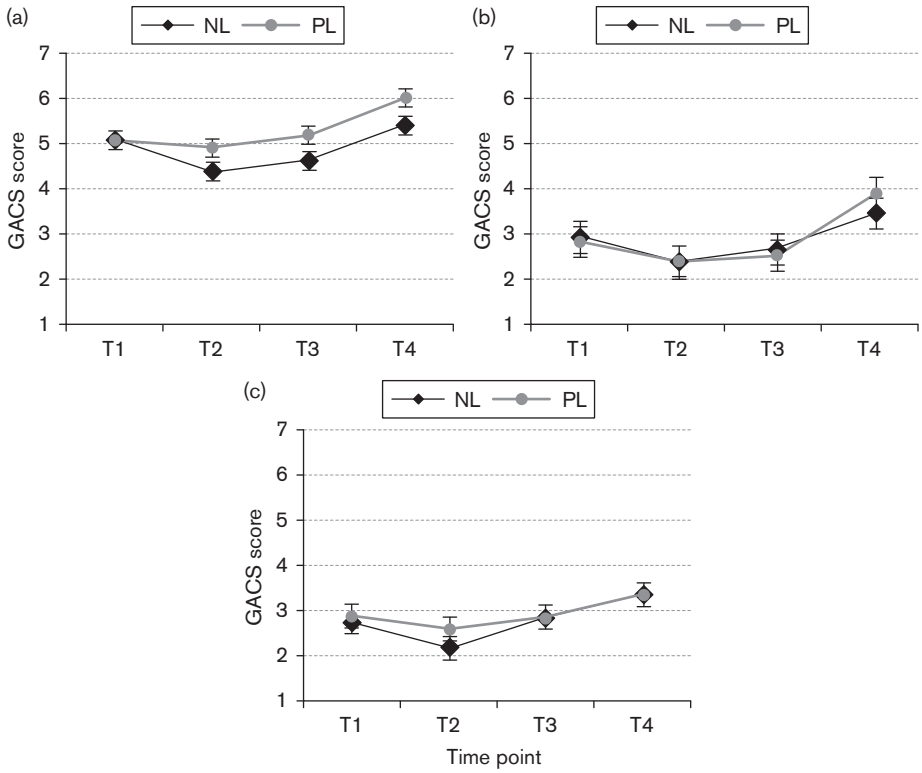
Unadjusted mean ratings (±SE) for visual analog scale (VAS) item 'crave video lottery terminals (VLTs)/slots' for nicotine lozenge (NL) and placebo lozenge (PL) conditions following neutral-cue presentation (T3) and following gambling-cue presentation (T4). There was a significant main effect of time for 'crave VLTs/slots', with ratings being significantly greater at T4 compared with T3 in both conditions.

$M = 69.03$ (SE = 1.30), $P = 0.01$], T3 (following neutral cues) [$M = 71.66$ (SE = 1.32) vs. $M = 67.39$ (SE = 1.36), $P < 0.05$], and T4 (following gambling cues) [$M = 73.33$ (SE = 1.32) vs. $M = 67.28$ (SE = 1.30), $P < 0.01$]. There were no significant interactions involving sex.

Assessment of carryover effects

Although steps were taken to minimize the potential for carryover effects associated with the order of cue presentations (i.e. neutral cues followed by gambling cues) an additional group of participants was recruited for the purpose of directly assessing such effects. These participants were tested in the same manner as the main sample except that they received neutral cues twice (i.e. neutral–neutral) instead of gambling cues (i.e. neutral–gambling). The second sample consisted of eight (seven men) VLT gamblers who smoked daily with a mean age of 28.1 years (SD = 8.9). The average age [$t(36) = 0.90$, NS], mean FTND score of 6.1 (SD = 2.0) [$t(36) = 0.65$, NS], and mean CPGI score ($M = 9.3$, SD = 4.4) [$t(36) = 0.38$, NS] of this sample did not significantly differ from those of the main sample.

Fig. 3



Unadjusted mean ratings (±SE) for the gambling craving scale (GACS) (Young and Wohl, 2009) factors 'anticipation of gambling' (a), 'desire for gambling' (b), and 'relief of negative affect' (c) for nicotine lozenge (NL) and placebo lozenge (PL) conditions at baseline (T1), following lozenge administration (T2), following neutral-cue presentation (T3), and following gambling-cue presentation (T4). Baseline values were fixed as time-varying covariates in the analyses. No significant differences were observed between NL and PL at any time point on ratings for any of the GACS factors. There was also a significant main effect of time for 'anticipation of gambling', 'desire for gambling', and 'relief of negative affect', with mean ratings at T4 being significantly higher than those at T2 and T3 for all three factors.

The potential influence of time on gambling craving ratings within this subset of participants was then examined in a second set of analyses. Gambling-related subjective measures (i.e. 'crave VLTs/slots', GACS factors) were examined, with the main effect of 'time' being of primary interest. No significant main effects of time were found for 'crave VLTs/slots' [$F(2, 16) = 0.57$, NS], the GACS 'anticipation of gambling' scale [$F(2, 15) = 2.23$, NS], the GACS 'desire for gambling' scale [$F(2, 15) = 1.67$, NS], or the GACS 'relief of negative affect' scale [$F(2, 15) = 0.50$, NS]. These findings suggest that gambling-related craving was not influenced by prior exposure to neutral cues.

Discussion

The present study investigated the potential for acutely administered nicotine to augment cue-induced gambling cravings in VLT gamblers who smoke. No significant drug × time interactions were found on gambling-related subjective measures, including 'crave VLTs/slots' or GACS (Young and Wohl, 2009) subscales 'anticipation of gambling', 'desire for gambling', and 'relief of negative affect'. There were, however, significant main effects of time, indicating that overall gambling craving ratings were higher following gambling cues than at any other point. This suggests that gambling cues elicited greater overall gambling-related craving than neutral cues. Furthermore, no differences between NL and PL conditions were detected for the behavioral measure 'decision to play VLT'. In contrast to previous studies (Reid *et al.*, 1998; Attwood *et al.*, 2009), which found that nicotine enhanced ratings of other positive/hedonic cues, nicotine did not influence gambling craving following exposure to gambling-related cues in the present study. These findings are consistent with those of our previous work (i.e. McGrath *et al.*, 2012b) and suggest that acute administration of nicotine does not appear to influence VLT gambling-related craving.

Another goal of the current study was to examine the potential utility of gambling-cue-reactivity paradigms for drug challenge experiments. Previous work has established that the presentation of gambling-related visual and auditory cues can successfully induce craving in gamblers (Wulfert *et al.*, 2009). However, no known studies have directly compared cue-induced craving for gambling between pharmacological conditions in a drug challenge protocol. Despite the lack of predicted interaction effects of nicotine on subjective craving for gambling, the results of this study do suggest that meaningful differences in craving can be detected between neutral and gambling cues in both drug and placebo conditions. Validation of this type of laboratory-based gambling-cue paradigm may have benefits for future drug challenge experiments involving other substances frequently co-used with electronic gambling (e.g. alcohol, illicit drugs, etc.).

Although gambling craving was unaffected by nicotine, subjective measures of cigarette craving were significantly lower in the NL condition. Ratings for the VAS item 'crave cigarette' in the NL group were lower than those in the PL condition at each time point (i.e. directly following lozenge, following neutral cues, following gambling cues) after lozenge administration. Similarly, ratings for the QSU-B (Cox *et al.*, 2001) factor 'intention to smoke' were lower in the NL condition following lozenge administration and following the neutral cues. Finally, significantly higher average HR was recorded at each time point following lozenge administration in the NL condition, indicating that the nicotine dose received resulted in a predictable increase in cardiovascular activity (Najem *et al.*, 2006). The timing of the NL administration was selected to result in a pharmacologically active dose at the time of the cue presentation (Shiffman *et al.*, 2005; McEwen *et al.*, 2008). However, it is important to note that the expected concentrations achieved (~6 nl/ml) would likely fall at the lower end of steady-state plasma levels that are typically associated with therapeutic administration (5–15 ng/ml) (Benowitz *et al.*, 2009).

There are a number of potential explanations for the failure of nicotine to enhance gambling craving in the current study. It is possible that some of the gamblers recruited do not normally experience gambling-related craving. For instance, 'moderate-risk' gamblers may differ qualitatively from those with severe gambling problems in terms of their gambling urges. However, post-hoc analyses comparing 'moderate-risk' and 'problem' gamblers in the current sample failed to find any significant interactions involving gambling status for 'crave VLTs/slots' or GACS factors (Young and Wohl, 2009). Also, significant main effects were found for subjective measures of gambling craving, indicating an overall increase in gambling craving following gambling cues but not following neutral cues. Regardless, future studies might consider including only individuals with a history of severe gambling to rule out this possibility. It is also possible that the moderate levels of nicotine dependence reported by this sample contributed to the null findings. Although all participants were daily smokers, the sample reported smoking an average of only 15.5 cigarettes/day (SD = 8.9) with a mean FTND score (Heatherton *et al.*, 1991) of 5.7 (SD = 1.6). It is conceivable that nicotine may exacerbate gambling-related craving among heavily dependent smokers to a greater extent than light/moderate smokers. Finally, the method of nicotine administration may have contributed to the negative findings for gambling craving. In the current study, as well as our previous experiment (McGrath *et al.*, 2012b), nicotine was delivered acutely in a form of NRT. However, Attwood *et al.* (2009) administered nicotine-containing and denicotinized cigarettes. It is possible that differences in the pharmacokinetic properties of tobacco and NRT may have contributed to the discrepant

findings between these studies. Moreover, results of a previous study in our lab suggest that both nicotine-containing cigarettes and denicotinized cigarettes significantly reduced subjective craving for smoking to a greater extent than nicotine inhalers (Barrett, 2010). The results of the current study, as well as those of McGrath *et al.* (2012b), suggest that different forms of NRT can acutely reduce cigarette craving relative to an inert placebo without exacerbating craving for gambling. However, because different NRTs have differing pharmacokinetic properties (e.g. transdermal patch, gum, nasal spray), and such products may be chronically administered, further work is necessary before definitively concluding that NRTs will not exacerbate problem gambling behaviors in high-risk gamblers.

This study contains several limitations. First, women comprised only one-third of the sample. There are a number of established sex differences in smoking and NRT use. For instance, women have been found to have lower quit rates with nicotine patches than men (Perkins and Scott, 2008) and are more responsive to smoking-related cues (Perkins *et al.*, 1999). Although no interaction effects involving sex were found in the current study, it is conceivable that a sample that included more women might result in different conclusions. Second, despite overnight smoking abstinence, participants in the current study may still have been under the influence of the chronic effects of tobacco. Achieving complete nicotine elimination can take several days (Matta *et al.*, 2007), so it is difficult to determine the extent to which chronic nicotine tolerance might have influenced the participants. Another potential limitation could be expectancy effects associated with the expectation of an opportunity to gamble. Participants were told during the informed consent procedure that they would be given a choice to play a VLT, with the decision to gamble being entirely up to them. It is possible that gambling-related craving ratings were influenced by this information before the start of testing procedures. However, it should be noted that mean craving ratings for gambling in both NL and PL conditions remained consistent until presentation of gambling cues, upon which a significant increase was seen at T4. The increase in average ratings at time 4 indicates that the gambling cues elicited a stronger craving response than the neutral cues. Finally, NLs are designed for long-term use to achieve smoking cessation. In the present study, lozenges were administered acutely; more research is needed to completely understand their long-term use on gambling craving following exposure to environmental cues.

Conclusion

Contrary to initial predictions, acute nicotine administration did not enhance cue-induced craving for gambling following exposure to gambling-related cues. However, nicotine was found to significantly reduce subjective tobacco-related craving, suggesting that the use of NLs may have some therapeutic potential for the treatment of smokers in gamblers. Future investigations should be directed toward establishing the safety and efficacy of NRTs in gamblers using dosages and administration patterns that correspond with typical therapeutic use.

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Conflicts of interest

There are no conflicts of interest.

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