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# Addictive Behaviors



# Flexible emotion-based decision-making behavior varies in current and former smokers



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#### HIGHLIGHTS

- · We examined the influence of smoking status on flexible decision-making.
- · Both current- and former smokers displayed poorer decision-making than non-smokers.
- Current smokers had poorer flexible decision-making than former- and non-smokers.

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#### ABSTRACT

Introduction: Suboptimal decision-making is a feature in the initiation and maintenance of substance use, often manifested in choosing for short-term benefits rather than long-term gain, and the failure to display cognitive flexibility, respectively. Studies of nicotine users typically focus on characterizing those who are already addicted; less is known about decision-making in former smokers.

Methods: Non- (n = 21), former daily- (n = 23) and current daily smokers (n = 24), completed the contingency-shifting variant lowa Gambling Task (csIGT), in which the reward and punishment contingencies of the decks are systematically varied after 100 trials of the 'standard' IGT. Scores on the standard blocks of the csIGT provided an index of emotion-based decision-making, while the contingency-shifting blocks assessed flexible decision-making. Subjective ratings were also recorded at 20-trial intervals.

Results: Both current and former smokers showed significantly impaired performance relative to non-smokers when making decisions during the standard blocks of the csIGT. Both former and non-smokers' awareness of the reward/punishment contingencies was significantly higher than those of current smokers at the end of the standard IGT. Both former and non-smokers had significantly better performance on the contingency shifting blocks, relative to current smokers.

Conclusions: The findings indicate that both current and former smokers display a suboptimal pattern of decision-making than non-smokers during the standard IGT. However, with respect to the ability to change behavior following reversed contingencies, former smokers are more similar to non-smokers than to current smokers. Former smokers were also more aware of the contingencies than current smokers.

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## 1. Introduction

Decision-making, the process of making a choice upon considering the consequences of that choice (Bechara, 2005), is intrinsic to addiction. Previous studies have described impaired decision-making among heroin (Heyman & Dunn, 2002), methamphetamine (Paulus et al., 2002), cocaine (Kirby & Petry, 2004), marijuana (Whitlow et al., 2004), and alcohol misusers (Le Berre et al., 2014). For example, numerous studies using delay discounting tasks show that, relative to non-smokers,

smokers tend to prefer smaller immediate rewards over larger delayed rewards (Bickel, Odum, & Madden, 1999; Reynolds, Richards, Horn, & Karraker, 2004; Sweitzer, Donny, Dierker, Flory, & Manuck, 2008). Similarly, heavy smokers exhibit lower rates of probability discounting than non-smokers, indicating a greater inclination toward risky decisions (Poltavski & Weatherly, 2013).

The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) approximates the complexities of real-life decision-making insofar as choices are based on uncertain approximations of future consequences rather than exact calculations (Dunn, Dalgleish, & Lawrence, 2006). On each trial of the IGT, the participant chooses a card from one of four available decks in an effort to maximize long-term monetary gain. Feedback is then given regarding the money

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gained or money lost, if applicable. Two of the decks produce higher immediate gains on most trials, but are ultimately disadvantageous, resulting in long-term losses. The other two decks produce lower immediate gains but are ultimately advantageous, resulting in long-term gains. Initially, participants typically choose from the high immediate gain decks. However, as the task progresses and affective consequences of the decks are experienced, healthy individuals gradually favor the advantageous decks (Dymond, Cella, Cooper, & Turnbull, 2010; Steingroever, Wetzels, Horstmann, Neumann, & Wagenmakers, 2013). Conversely, individuals with particular impairments, such as damage to the ventro-medial prefrontal cortex or in addiction, continue to select from the disadvantageous decks (Bechara et al., 1994; Bechara et al., 2001; Damasio, 1994).

Inferior IGT performance has been found in heroin (Petry, Bickel, & Arnett, 1998), cocaine and cannabis (Verdejo-Garcia et al., 2007), alcohol (Mazas, Finn, & Steinmetz, 2000), and polysubstance abusers (Grant, Contoreggi, & London, 2000), relative to healthy controls. However, mixed results exist when comparing smokers to nonsmokers. Both adolescent smokers (Xiao et al., 2008) and methadoneusing smokers (Rotheram-Fuller, Shoptaw, Berman, & London, 2004) had significantly lower mean net IGT scores (i.e. frequency of advantageous minus frequency of disadvantageous choices) than nonsmokers. Ert, Yechiam, and Arshavsky (2013), using a modified version of the IGT, found smokers progressively increased their selections from a disadvantageous deck with high immediate gains and infrequent large losses, while non-smokers learned to avoid these decks. However, the groups did not significantly differ in overall proportion of disadvantageous choices. Further comparisons between smokers and nonsmokers have failed to reveal statistically significant differences in IGT performance (Buelow & Suhr, 2014; Businelle, Apperson, Kendzor, Terlecki, & Copeland, 2008; Lejuez et al., 2003), despite sample sizes of 136, 119 and 60, respectively. We address potential reasons for these inconsistent findings in the Discussion.

Decision-making impulsivity and traits such as sensation-seeking (Verdejo-García & Pérez-García, 2007) and extraversion (Whelan et al., 2014) are associated with addiction. However, a feature of the addicted state is that substance use is maintained by compulsive behaviors (i.e., by negative reinforcement), which can be observed in both humans (Lucantonio, Stalnaker, Shaham, Niv, & Schoenbaum, 2012) and animals (Calu et al., 2007) as cognitive inflexibility (i.e., perseverative behavior) during reversal-learning tasks. This inability to change behavior despite negative contingencies has been previously reported in smokers versus non-smokers (Kalmijn, Van Boxtel, Verschuren, Jolles, & Launer, 2002; Nooyens, van Gelder, & Verschuren, 2008). Less is known about the influence of smoking status on flexibility in decision-making. An extension to the IGT - the contingency-shifting variant IGT (csIGT) - provides a measure of the ability to adjust decision-making to changing reward and punishment schedules (Dymond et al., 2010; Turnbull, Evans, Kemish, Park, & Bowman, 2006). Impaired learning on this task has been observed in individuals with depression (Cella, Dymond, & Cooper, 2010), schizophrenia (Turnbull et al., 2006) and psychosis-prone individuals (Cella, Dymond, & Cooper, 2009) relative to healthy controls. In the csIGT, the contingencies learned on the first 100-trials (i.e., the 'standard' IGT) are subsequently systematically changed during three successive (usually) unsignaled shift periods, each of which consist of two blocks of 20 trials (Dymond et al., 2010). In the modified task then, the deck contingencies shift value across blocks after initial (and presumably) stable, exposure to the original reward and punishment schedules. Thus, the csIGT provides an extended measure of the flexible use of decision-making in a way that resembles studies of reversal learning (Fellows & Farah, 2005) or set-shifting ability (Dias, Robbins, & Roberts, 1996) and which may prove useful in further understanding cognitive (in)flexibility in addictive behaviors such as smoking.

Addiction studies typically focus on understanding the etiology of dependence and characterizing the addicted brain (Garavan, Brennan,

Hester, & Whelan, 2013). However, research is sparse regarding the neurobiological processes involved in successful abstinence. Garavan et al. (2013) postulate that recovery from addiction consists of two distinct processes: The restoration of brain structure and function, and the active process of maintaining abstinence through prefrontally mediated cognitive control. The finding that former smokers displayed greater prefrontal activity than both never- and current smokers on an attentional bias paradigm lends support to this concept (Nestor, McCabe, Jones, Clancy, & Garavan, 2011). Former smokers have exhibited equivalent levels of impulsive decisionmaking in a delayed discounting task to non-smokers — both significantly less than current smokers (Bickel et al., 1999; Sweitzer et al., 2008). In contrast, one of the few studies which investigated the decision-making of former smokers in the IGT found that re-categorizing former smokers as smokers strengthened the difference between this group and the non-smoking group (Ert et al., 2013). This indicates that former smokers' IGT performance is closer to that of current smokers than non-smokers. However, this inference should be treated cautiously as the former smoker cohort consisted of only seven participants. On the IGT, acutely abstinent (12-h) smokers selected significantly more from a disadvantageous deck than did satiated smokers, while neither group differed significantly from non-smokers (Buelow & Suhr, 2014). However, on a set-shifting task Nesic, Rusted, Duka, and Jackson (2011) revealed that acutely abstinent high-dependent smokers significantly outperformed their smoking-satiated counterparts. The relationship between non-acute abstinence, emotion-based decision-making (as measured by the 'standard' blocks of the csIGT) and flexible decision-making (as measured by the 'contingency-shifting' blocks of the csIGT) is as yet underdetermined.

The present study investigated the influence of smoking status on flexible decision-making in three cohorts of adults: Non-smokers, former daily smokers, and current daily smokers (for brevity hereafter referred to as former- and current smokers). Specifically, the groups were compared on their task performance on the standard and contingency-shifting blocks of the csIGT, as well as their subjective awareness of the reward/punishment contingencies of the decks. We expected that non-smokers would display a greater preference for advantageous decks during the standard csIGT blocks than both current- and former smokers. Given that former smokers may be capable of demonstrating greater cognitive flexibility, thereby counteracting learned compulsive behavior, we speculated that former smokers would perform similarly to non-smokers, and better than current smokers, during the contingency-shifting blocks.

#### 2. Materials and methods

#### 2.1. Participants

Sixty-eight university students, aged 18–21 years, were recruited in University College Dublin, Ireland. This sample size was selected on the basis of earlier relevant research (e.g., Cella et al., 2010 (N=39, n=20/19); Cella, Dymond, Cooper, & Turnbull, 2012 (N=49, n=24/25); Lejuez et al., 2003 (N=60, n=26/34). Participants' demographic, cigarette smoking, alcohol usage, and other substance use data were obtained with a modified version of the European School Survey Project

**Table 1** ESPAD bands.

	ESPAD scores							
	1	2	3	4	5	6	7	
No. of cigarettes (30 days) All other questions	Not at all 0	<1 per week 1–2	<1 per day 3-5	1–5 per day 6–9	11-20 per day 10-19	20+ per day 20-39	40+	

**Table 2**Means and standard deviations of ESPAD data.

	Non-smokers	Former smokers	Current smokers	Test statistic	Post-hoc tests***
Gender (M/F)	9/12	12/11	12/12	$X^2(2) = .41$	-
No. of cigarettes (lifetime)	3.05 (1.86)	7.00 (.00)	7.00 (.00)	$F(2,65) = 106.87^{**}$	FS & CS > NS
No. of cigarettes (30 days)	1.00 (.00)	1.26 (.45)	4.75 (.53)	$F(2,65) = 604.94^{**}$	CS > NS & FS
Age smoked first cigarette	12 years	14 years	14 years	=	_
Age smoked on daily basis	Never	15 years	15 years	=	_
No. of alcoholic drinks (30 days)	3.43 (1.47)	3.65 (1.30)	3.83 (1.34)	F(2,65) = .49,	_
Use of cannabis (30 days)	1.05 (.22)	1.00 (.00)	1.04 (.20)	F(2,65) = .52	_
Use of cannabis (lifetime)	3.19 (2.16)	5.00 (2.05)	4.79 (2.41)	$F(2,65) = 4.34^*$	FS > NS
Use of other drugs (30 days)	1.00 (.00)	1.00 (.00)	1.00 (.00)		_
Use of other drugs (lifetime)	1.14 (.48)	2.17 (1.83)	2.08 (1.72)	$F(2,65) = 3.16^*$	p > .017

Note. All scores are mean (standard deviation) unless otherwise stated. Other drugs include amphetamines, tranquilizers/sedatives, ecstasy, LSD, crack, cocaine, heroin, magic mushrooms, GHB, and anabolic steroids. NS = non-smoker; FS = former smoker; CS = current smoker.

on Alcohol and Other Drugs (ESPAD) Questionnaire on Substance Use (Hibell et al., 2012; see Table 1 for band range), as shown in Table 2. Purposive sampling was employed to recruit approximately equivalent numbers of current-, former-, and non-smokers. Non-smokers (n=21) had not smoked any cigarettes in the previous 30 days and never smoked on a daily basis. Former smokers (n=23) previously smoked on a daily basis, but had not smoked in the previous 30 days (74%) or smoked fewer than one cigarette per week (26%). Current smokers (n=24) reported daily cigarette smoking. Participants did not engage in the regular use ( $\geq 3$  times in the previous 30 days) of illicit substances (i.e., cannabis, cocaine, ecstasy, anabolic steroids, amphetamines, tranquilizers/sedatives, LSD, crack, heroin, magic mushrooms, & GHB).

#### 2.2. Procedure

The University College Dublin Human Research Ethics Committee approved study procedures and all participants provided informed consent. Participants completed an assessment of demographics and substance use before completing the csIGT in a sound-attenuated booth. Participants could not smoke approximately 30 min prior to the task (the time needed to complete the consent protocol, questionnaires and to receive task instructions). Participation was not compensated.

#### 2.3. Measures

#### 2.3.1. Contingency-shifting variant Iowa Gambling Task (csIGT)

A computerized version of the csIGT (Dymond et al., 2010; Turnbull et al., 2006) measured decision-making in an emotion-based learning context. Instructions were presented on-screen before beginning the task, which consisted of 11 blocks of 20 trials each. The first five blocks of the task represented the standard IGT (Bechara et al., 1994). The contingency-shifting phase of the csIGT occurred during the final six blocks. Participants also provided subjective experience ratings of the "goodness" of each deck following each of the 11 blocks, on a 1–10 Likert scale. Details regarding the csIGT have been published elsewhere (Dymond et al., 2010).

#### 2.3.2. Questionnaire on substance use

A modified version of the ESPAD questionnaire on substance use (Hibell et al., 2012) was employed. This 22-item instrument assessed four domains: demographics, cigarette smoking, alcohol use, and other substance usage (cannabis, amphetamines, tranquilizers/sedatives, ecstasy, LSD, crack, cocaine, heroin, magic mushrooms, GHB, and anabolic steroids). The full ESPAD has good test–retest reliability (Molinaro, Siciliano, Curzio, Denoth, & Mariani, 2012) and has been reported as a valid measure of substance use (Hibell et al., 2012).

#### 2.4. Data analysis

Mean net scores were calculated for each block of the cslGT by subtracting the frequency of disadvantageous choices in the respective block from the advantageous choices. Mean net subjective ratings were calculated for each block by subtracting the ratings of the disadvantageous decks from those of the advantageous decks. Statistical analyses were conducted separately for the standard and contingency-shifting phases of the cslGT. Mixed between-within subjects ANOVAs tested for the main effects of the between-subjects (smoking status) and within-subjects (block) independent variables and their interaction effect on the dependent variables (mean net scores and ratings). Statistically significant differences (p < .05) were investigated with Bonferroni corrected post-hoc tests. Spearman's rho correlations were conducted to assess the relationship between ratings and task performance separately for the three groups on the standard and contingency-shifting phases of the cslGT.

#### 3. Results

#### 3.1. Mean net scores

In order to investigate the impact of smoking status on participants' performance across the five standard blocks of the cslGT, a 3 (group)  $\times$  5 (block) mixed ANOVA was conducted. There was a significant interaction between smoking status and block (Wilks' Lambda = .75,  $F(8,124)=2.36,\ p=.022,\ \eta^2=.13)$ , indicating that scores differed among the groups at different stages of the task. Post-hoc tests with the Bonferroni correction (p < .017) revealed no statistically significant differences between the groups in the first three blocks. However, in Blocks 4 and 5, non-smokers displayed significantly higher mean net scores than current- and former smokers (Fig. 1).

A 3 (group)  $\times$  3 (block) mixed ANOVA was also carried out to assess the influence of smoking status on participants' performance in the contingency-shifting Blocks 7, 9 and 11 of the cslGT. There was a significant main effect for block (Wilks' Lambda = .76, F(2, 64) = 10.19, p < .001,  $\eta^2 = .24$ ), and smoking status (F(2, 65) = 35.96, p < .001,  $\eta^2 = .53$ ). Bonferroni corrected post-hoc tests showed that both nonand former smokers had significantly higher mean net scores than current smokers on the contingency-shifting blocks. There was no statistically significant interaction between smoking status and block (Wilks' Lambda = .96, F(4, 128) = .72, p = .58,  $\eta^2 = .02$ ).

### 3.2. Mean net ratings

A 3 (group)  $\times$  5 (block) mixed ANOVA was conducted to examine the impact of smoking status on mean net ratings of the decks across

<sup>\*\*\*</sup> p < .017 (i.e. .05 Bonferroni corrected).

<sup>\*\*</sup> p < .001.

<sup>\*</sup> p < .05.

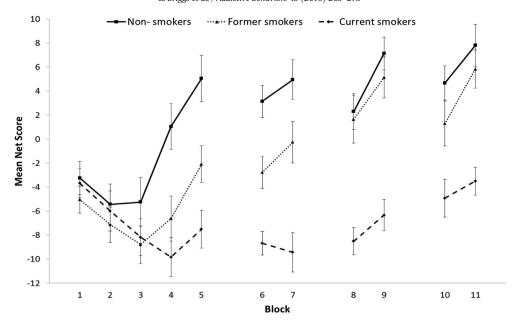


Fig. 1. Mean net scores for non-smokers, former smokers, and current smokers. Error bars represent the standard error of the mean.

the five standard csIGT blocks. There was a significant main effect for block (Wilks' Lambda = .73, F(4,62) = 5.75, p = .001,  $\eta^2 = .27$ ), and smoking status (F(2,65) = 4.87, p = .011,  $\eta^2 = .13$ ). Post-hoc tests with the Bonferroni correction (<.017) showed that non-smokers had significantly higher mean net ratings than current smokers on Block 3, while both non- and former smokers had significantly higher ratings on Block 5 (Fig. 2). There was no statistically significant interaction between smoking status and block (Wilks' Lambda = .88, F(8, 124) = 1.01, p = .43,  $\eta^2 = .06$ ).

A 3 (group)  $\times$  3 (block) mixed ANOVA was conducted to investigate the influence of smoking status on mean net ratings in the contingency-shifting Blocks 7, 9 and 11 of the csIGT. The analysis revealed no

significant main effect for block (Wilks' Lambda = 1.00, F(2, 64) = .10, p = .90,  $\eta^2 = .00$ ), smoking status (F(2, 65) = 2.59, p = .08,  $\eta^2 = .07$ ) or interaction between smoking status and block (Wilks' Lambda = .87, F(4, 128) = 2.25, p = .07,  $\eta^2 = .07$ ).

### 3.3. Association between ratings and task performance

Six Spearman's rho correlations were conducted to explore the relationship between task performance (scores) and awareness of the deck contingencies (ratings) for non-smokers, former-, and current smokers. A statistically significant correlation between scores and ratings on the standard blocks of the cslGT was found for current smokers (r = .456,

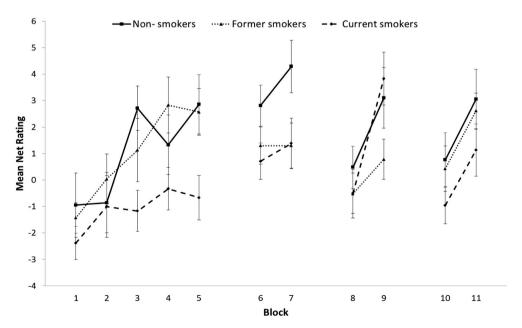


Fig. 2. Mean net ratings for non-smokers, former smokers, and current smokers. Error bars represent the standard error of the mean.

p = .025), but not for non-smokers (r = .321, p = .16) or former smokers (r = .144, p = .51). On the contingency-shifting blocks of the csIGT, statistically significant correlations between scores and ratings were observed for both non-smokers (r = .709, p < .001) and former smokers (r = .544, p < .01), but not for current smokers (r = .023, p = .92).

#### 4. Discussion

This study investigated the relationship between smoking status and decision-making. Initially, non-, former-, and current smokers' mean net scores did not differ significantly on the csIGT. However, non-smokers learned to select the decks with smaller rewards that yielded long-term gains, whereas both former- and current smokers continued to make long-term disadvantageous choices. Consistent with our hypothesis, both non- and former smokers demonstrated greater flexible decision-making (significantly higher mean net scores) than current smokers upon introducing the contingency-shifting blocks. However, across the contingency-shifting blocks, no significant differences between the three groups in mean net ratings were observed.

The present study's results are consistent with previous research in which smokers displayed significantly impaired IGT performance relative to non-smokers (Rotheram-Fuller et al., 2004; Xiao et al., 2008). However, conflicting findings are also reported (Buelow & Suhr, 2014; Businelle et al., 2008; Lejuez et al., 2003). Variations in study population, operational definition of smokers and outcome variable may have contributed to these differing results. For example, the summary score based on percentage of disadvantageous selections across the first 100 trials utilized by Lejuez et al. (2003) as an outcome variable may have concealed the differences that typically emerge between groups in the earlier blocks of the task (Buelow & Suhr, 2009). Furthermore, age (Cauffman et al., 2010) and education (Evans, Kemish, & Turnbull, 2004) have been found to influence IGT performance, thus the tertiary education and younger age of participants in the present study, relative to those of Businelle et al. (2008) may have contributed to the discordant findings.

This study represents the first investigation into the relationship between subjective awareness and decision-making in non-smokers, former and current smokers. Awareness of deck contingencies (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Damasio, & Damasio, 2000) is associated with success in the standard IGT (Guillaume et al., 2009), as well as the contingency-shifting blocks of the csIGT (Dymond et al., 2010). Current smokers displayed lower mean ratings than both non- and former smokers during the standard phase of the csIGT, suggesting that this group had a lower awareness of the reward/punishment contingencies of the decks. Current smokers were also the only group that demonstrated a significant relationship between task performance and subjective awareness ratings during this part of the task (i.e., higher awareness ratings during this part of the task was associated with better task performance). However, the former smokers had awareness ratings comparable to the nonsmokers, yet had inferior performance on the standard IGT, suggesting that they were making risky decisions rather than failing to learn the contingencies.

Cognitive inflexibility displayed by smokers, relative to both nonand former smokers, has been found previously, for example in the Stroop Color Word Test (Nooyens et al., 2008). Similarly, highdependent smokers assigned to a period of acute nicotine abstinence displayed greater cognitive flexibility than smoking satiated controls on a set-shifting paradigm (Nesic et al., 2011). These findings are consistent with the present results. During the contingency-shifting blocks former smokers had significantly higher mean net scores than current smokers, demonstrating that those abstaining from smoking may possess greater cognitive flexibility. Current smokers, despite inferior behavioral performance, did not significantly differ from the nonsmoking groups in terms of their subjective evaluations of the decks, although their mean scores were lower. As with the standard blocks, current smokers had difficultly learning the contingencies; however, this was also the case, as expected during the reversal phase, for the other groups also. During the contingency-shifting phase of the csIGT, non-smokers and former smokers, but not current smokers, showed a significant relationship between task performance and awareness of deck contingencies, which may be a reflection of the greater variability in ratings and performance of non-smokers and former smokers in this phase.

It has been proposed that affective responses, or 'gut feelings' associated with each deck may assist decision-making more than conscious knowledge of deck contingencies, or are at least necessary for successful decision-making (Bechara et al., 1997; Damasio, 1994). A possible explanation for our finding could be that the integration of emotional and rational processing is disrupted in current smokers. This is in line with the Verdejo-García and Bechara's (2009) argument that substance abuse is associated with a defect in the neural circuits that underlie the integration of affective processing into the decision-making process. They implicate the ventromedial prefrontal cortex (vmPFC), and the orbitofrontal cortex (OFC) as key structures in the reflexive system, which bridges affective processing involving the amygdala, and executive control mechanisms involving the dorsolateral prefrontal cortex. The vmPFC and OFC are associated with IGT task performance (Bechara, Tranel, & Damasio, 2000; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009). Substance dependent individuals show a reduction in gray-matter concentration in the vmPFC (Franklin et al., 2002; Matochik, London, Eldreth, Cadet, & Bolla, 2003) and of functional activity, associated with increased drug use (Porrino, Smith, Nader, & Beveridge, 2007). Research has also found that a subgroup of substance-dependent individuals performed similarly to individuals with ventromedial lesions on the IGT – both behaviorally and physiologically (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002). These findings suggest that current substance users show a deficit in integrating affective cues into decision-making. Verdejo-García and Bechara (2009) suggest that in healthy individuals these affective cues are explicit as mental representations, before behavioral action is taken. As the discrepancy between task performance and subjective ratings only appeared during the contingency-shifting blocks of the csIGT, our findings suggest that current smokers have particular difficulties integrating affective cues, thus hindering their ability to be flexible given changed contingencies.

One limitation of this study is that the cross-sectional comparison of current- and former smokers does not indicate whether the differences observed preceded abstinence or arose consequently. Furthermore, the duration of time since a smokers' last cigarette was not recorded. Thus, it is possible that some individuals may have experienced nicotine deprivation during the study, which has been found to influence decision-making (Mitchell, 2004) and cognitive flexibility (Nesic et al., 2011).

In conclusion, our results suggest that current- and former smokers display poorer decision-making than non-smokers. However, former smokers and non-smokers demonstrate greater cognitive flexibility following changed reward and punishment contingencies, compared to current smokers. Former smokers also display greater subjective awareness in decision-making than current smokers. These findings shed light on real-world decisions made by current smokers, former- and non-smokers, and add to the literature (e.g., Secades-Villa, Weidberg, García-Rodríguez, Fernández-Hermida, & Yoon, 2014) showing differences between current and former smokers.

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#### **Contributors**

Z Briggs: data collection and manuscript preparation.
M O'Connor: statistical analysis and manuscript preparation.
EK Jollans: statistical analysis and manuscript preparation.
L O'Halloran: manuscript preparation.

S Dymond: manuscript preparation.

R Whelan: study design and manuscript preparation.

All authors contributed to and have approved the final manuscript.

#### Conflict of interest

All authors declare that they have no conflicts of interest.

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