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Striatal hyposensitivity to delayed rewards among cigarette smokers

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ABSTRACT

Background: Brain regions that track value (including the ventral striatum) respond more during the anticipation of immediate than delayed rewards, even when the delayed rewards are larger and equally preferred to the immediate. The anticipatory response to immediate vs. delayed rewards has not previously been examined in association with cigarette smoking.
Methods: Smokers ($n = 35$) and nonsmokers ($n = 36$) performed a modified monetary incentive functional Magnetic Resonance Imaging (fMRI) task (Knutson et al., 2000) that included opportunities to win either immediate or delayed rewards. The delayed rewards were larger and equally preferred to the immediate rewards.
Results: Across groups, greater activation was observed in regions previously shown to track value including bilateral ventral/dorsal striatum during the anticipation of immediate relative to delayed rewards. This effect was significantly greater among smokers than nonsmokers within the right ventral striatum. This group difference was driven particularly by low striatal activation among smokers during delayed reward trials.
Conclusions: The general tendency for striatal reward anticipatory activity to be attenuated when rewards are delayed is exaggerated among smokers relative to comparison participants. Among possible explanations of this relationship are that (1) low anticipatory response to delayed rewards is a phenotypic risk factor for smoking and (2) smoking-related neuroadaptations result in reduced recruitment during the anticipation of delayed rewards.

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1. Introduction

Immediate expectancies recruit more motivation than delayed expectancies. This phenomenon has been studied in experiments in which subjects are asked to choose between "smaller-sooner" (SS) and "larger-later" (LL) rewards. Parametric manipulation of rewards allows the characterization of individual willingness to tradeoff reward amount for reward immediacy ("delay discounting"). Delay discounting is one distinct way that "impulsivity" has been operationalized (Ainslie, 1975; Evenden, 1999; Monterosso and Ainslie, 1999).

Cigarette smoking (arguably the second leading cause of preventable death worldwide (Lopez et al., 2006)) has immediate consequences desired by the smoker, but undesired temporally distant consequences. It has been hypothesized that individuals exhibiting greater delay discounting are at greater risk for smoking (Bickel and Marsch, 2001; Ainslie, 1975; Vuchinich and Tucker, 1988; Madden et al., 1997; Bickel and Johnson, 2003), or alternatively, that chronic smoking might cause greater discounting (Bickel et al., 1999; Reynolds, 2004). Consistent with either hypothesis, smokers (and especially smokers more severely dependent (Heyman and Gibb, 2006; Ohmura et al., 2005; Sweitzer et al., 2008) and those who have more difficulty quitting (Krishnan-Sarin et al., 2007; Yoon et al., 2007)) have been found to express greater delay discounting (Bickel and Johnson, 2003; Gottdiener et al., 2008; Reynolds, 2006).

We recently showed a dissociation between the effect that delay has on valuation as inferred (1) from preference and (2) from brain responses during reward anticipation. The nature of this dissociation is perhaps most clearly illustrated by example: suppose that an individual responds to intertemporal choice questions in a way that indicates she is indifferent between $40 today and $50 in four months. That is, if she is offered more than $40 today, she takes it over $50 in four months, and if she is offered less than $40 today, she chooses to wait for the $50 in four months. By this method

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of "revealed preference", $40 today and $50 in four months are said to be of equal value to the individual. One can reasonably ask whether the immediate and delayed rewards comprising this indifference pair are equally valued when encountered separately. Evidence suggests that they are not. When participants performed a version of the Monetary Incentive Delay (MID) task (Knutson et al., 2000) in which they were given opportunities to win each of these rewards on separate trials, brain structures previously shown to track value during the task (Knutson et al., 2001) were preferentially recruited by the immediate rewards (Luo et al., 2009). The reason for this is not clear, but one interpretation is that processes engaged during intertemporal decision-making generally enhance the individual's willingness to wait, and since these processes are not engaged when rewards are anticipated outside of a decision context, the attenuating effect of delay on value is more dramatic. If that interpretation is correct, the dissociation may mark an underlying tendency to neglect delayed consequences. Such a tendency might manifest when trade-offs are less explicit than they are during delay discounting choice tasks (as is the case with cigarette smoking) or when decision-making resources are compromised. In the present study, we used functional Magnetic Resonance Imaging (fMRI) to compare the tendency of smokers and nonsmokers to exhibit differential activation in brain regions that track value during the anticipation of immediate and equally preferred delayed rewards.

2. Methods

2.1. Participants

Thirty-five cigarette smokers (all nicotine dependent according to DSM-IV criteria, as assessed using the M.I.N.I. (Sheehan et al., 1998)) and 36 individuals that had smoked no more than 5 cigarettes in their life participated in the study. Both groups had no Axis I pathology or neurological disorders. Additionally, smoker inclusion required (1) self-reported smoking of at least 15 cigarettes per day for at least two years and (2) biochemical confirmation of smoking by either carbon monoxide in expired breath during a baseline visit of at least 15 ppm, or a positive cotinine urinalysis (cutoff level = 200 ng/ml). The two groups did not differ in age (smokers 34.1 ± 7.9, nonsmokers 31.3 ± 7.1, $t(69) = 1.6$, $p = .12$) or gender (42.9% females among smokers and 36.1% females among nonsmokers; $\chi^2(1) = .34$, $p = .55$), but smokers reported significantly fewer years of education than nonsmokers (smokers 14.2 years $\pm$ 1.75, nonsmokers 15.5 ± 1.1; $t(69) = 3.63$, $p < .01$). Among smokers, Fagerström scores (Heatherton et al., 1991) ranged from 1 to 9, with a mean of 4.97 ± 1.90, and the group smoked on average 19.4 ± 4.3 cigarettes per day.

2.2. Procedure overview

Prior to fMRI, participants completed a computerized version of the "Monetary Choice Questionnaire" (Kirby et al., 1999) which was used to estimate each participant's overall level of delay discounting, by fitting data to the function $V_d = A/(1 + kD)$, where 'V_d' represents the value of the delayed reward, 'A' represents the amount of the delayed reward, 'D' represents the delay (here, in days), and 'k' is a fit parameter used to model the participant's behavior, with $k = 0$ indicating no discounting, and higher numbers indicating greater discounting (Monterosso et al., 2007). Next, participants completed an adaptive intertemporal choice task specifically designed to derive two immediate-delayed reward indifference pairs. In the procedure, amounts were adjusted in order to determine the precise immediate amount of money that, for each participant, was equally preferred to (1) $53 delayed by four months and (2) $28 delayed by four months. The choice procedure continued until stability criteria were reached (Luo et al., 2009). Participants were instructed that one of their choices would be randomly selected and paid using a Visa gift card that would not be activated until any associated delay had transpired.

Participants were then trained to associate a particular colored square with each of the four rewards that comprised the two "indifference pairs" that had been established. Once learning criteria were reached, participants completed a variant of the MID task (Knutson et al., 2000). At the onset of each trial, one of the colored squares was presented, indicating the potential prize for that round. Participants waited between 4 and 4.5 s for a target to appear, at which point they responded as quickly as they could by pressing a button. Feedback directly following indicated whether their response was fast enough to win the prize indicated for the round. At the end of each of two task runs, one trial was selected to be "real", and if (and only if) the participant won on that trial, he or she received the specified prize (again, delivered via Visa gift card). In this way, participants were incented to try to win each round, but the magnitude of the incentive was a function of his or her valuation of the available prize for that round. The critical period for analysis was the 4–4.5 s anticipation window, when the participant knew what he or she stood to win, and was poised to try to respond to the target (for details of the procedure used, see Luo et al., 2009).

Smokers were not required to abstain prior to testing. All were invited to smoke immediately prior to entering the neuroimaging centre. Smokers were instructed that the next smoking opportunity would be after neuroimaging procedures, which would take approximately 50 min.

A subset of participants ($N = 35$; 20 nonsmokers and 15 smokers) completed a choice task after the MID task that allowed us to test for the possibility of systematic drift in individuals' degree of delay discounting. These participants were presented with 48 intertemporal choice trials (always an immediate amount vs. a four month delayed amount). Half of these trials were generated to be of equivalent value based on the individual's original level of discounting, and half were generated to be moderately "mismatched" in value. These mismatched trials were generated by creating indifference pairs based on a k fit parameter estimate that was one log unit larger (50% of trials) or one log unit smaller (50% of trials) than the participant's actual fit parameter estimate. Significant drift would thereby be detectable as a high number of choices that are systematically divergent from original behavior.

2.3. MRI acquisition

Using 3T Siemens MAGNETOM Tim/Trio scanner, Blood oxygen level-dependent (BOLD) response was obtained by echo planar imaging (EPI) sequence with TR = 2 s, TE = 30 ms, flip angle = 90°, FOV = 192, and in-plane resolution = 64×64. A total of thirty-two axial slices were used to cover the whole brain with no gap.

2.4. Data analysis

Overall level of delay discounting as captured by the fit parameter 'k' was transformed by natural log prior to parametric analyses. Discounting behavior of smokers and nonsmokers was compared by t-test, and the relationship between discounting and smoking severity (Fagerström score) was assessed by robust regression using the "rlm" function in the statistical package "R"(Venables and Ripley, 2002). Median reaction time (RT) for each subject on the MID task was subjected to repeated measures ANOVA with magnitude (high/low) and delay (today/4 months) included as within-subject factors. FMRI analysis (focusing on the 4–4.5 s anticipation period) was performed using FEAT (fMRI Expert Analysis Tool) version 5.98, part of the Oxford University Centre for Functional MRI of the Brain (FMRIB) Software Library (www.fmrib. ox.ac.uk/fsl). The preprocessing included motion correction, temporal filtering, spatial smoothing (Gaussian kernel of full-width at half-maximum of 5 mm), and spatial transformation to standard space (Montreal Neurological Institute). We performed a categorical analysis contrasting anticipation of immediate rewards vs. preference-matched delayed rewards. Because smokers reported fewer years education than nonsmokers, follow-up analyses of group differences included this variable in a regression model. Correction for multiple comparisons (the search space of the brain) was made using cluster-level corrected statistics, with voxel-level threshold of $Z = 2.3$ and cluster-level probability threshold of $p = .05$ (Worsley, 2001). This approach protects from Type 1 error by comparing observed spatial clustering of voxels crossing the designated threshold (here, $Z = 2.3$) to clusters that would be expected given the null hypothesis and the magnitude of the search space (Worsley, 2001).

We previously reported on data from the same study in a subset of 37 participants included in the present study (12 of whom were smokers). However, because the sample size was judged to be insufficient for group comparisons, no analyses were made in that report comparing smokers and nonsmokers. There were no significant temporal gaps between data collection of those participants (predominantly nonsmokers) and the subsequent participants (which were predominantly smokers).

3. Results

3.1. Behavioral results

The median k-value parameter fit for smokers was .025, and among nonsmokers was .018 ($t(69) = .67$, $p = .51$). Among smokers, there was marginal evidence of an association between more severe dependence (quantified by Fagerström score) and steeper discounting based on robust regression ($\beta = .2351$, $p = .06$).

RT was faster during trials in which the reward was from the higher indifference pair (either $53 delayed by four months, or the immediate amount equally preferred to it) than during trials in which the reward was from the lower pair ($F(1,69) = 10.1$, $p = .002$) and faster for trials with immediate than delayed rewards ($F(1,69) = 10.0$, $p = .002$). No interactions or effects of group were observed on RT.

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In the post MID task reassessment that tested for the presence of systematic drift (administered to a subset of participants $N = 37$), among trials generated to be equally valued based on models of individual discounting derived prior to scanning, the SS alternative was chosen on 46.9% of all trials, suggesting no overall drift (one sample t-test comparison to 50%, $t(36) = .55$, $p = .58$). Among the half of trials predicted to elicit either SS or LL responses given the level of discounting observed prior to scanning, the predicted response was observed in 90.2% of trials. The number of model-inconsistent LL choices did not significantly differ from the number of model-inconsistent SS choices ($6.2 \pm 13\%$ vs. $3.6 \pm 7.9\%$; $Z = .73$, $p = .47$), nor was there any suggestion of a difference between smokers and nonsmokers in the direction of model-inconsistent choices ($Z = .06$, $p = .96$).

3.2. Imaging results

Signal during anticipation of immediate vs. delayed rewards (which were equally preferred) was compared in whole-brain analysis. Consistent with the previously reported data which was based on a subset of these participants that were predominantly nonsmokers (Luo et al., 2009; Knutson et al., 2000, 2001), signal was significantly greater during the anticipation of immediate reward in regions including bilateral caudate/putamen/ventral striatum, bilateral insula, bilateral prefrontal cortex/frontal pole, bilateral superior frontal gyrus, bilateral thalamus, brain stem, and anterior cingulate cortex/supplementary motor cortex ($Z > 2.3$, $p < .05$ cluster-level correction, Fig. 1 and top of Table 1).

We compared this "immediate > delayed" effect between smokers and nonsmokers. The effect is conceptually orthogonal to delay discounting during decision-making, since the procedure starts with equally preferred immediate and delayed rewards. We observed a larger "immediate > delayed" effect among smokers than nonsmokers in several regions, including the right ventral striatum, bilateral caudate, right putamen, left thalamus, left hippocampus/parahippocampal gyrus and lateral occipital cortex (Fig. 2). Because smokers reported fewer years education than did nonsmokers, we assessed whether this factor contributed to the finding by including years education as a covariate in a re-analysis of the effect of group on signal change. The association remained significant, and years of education were not related to signal change differences between immediate and delayed rewards.

In order to assess whether the group difference in the immediate–delay contrast was driven by hypersensitivity among smokers to the immediate rewards, or hyposensitivity among smokers to delayed rewards, or perhaps both, we extracted MRI signal separately for immediate and delayed rewards (relative to implicit baseline) from all voxels that were both (1) more active for immediate rewards and (2) in which a significant group difference between smokers and nonsmokers was observed. All voxels meeting both these criteria were in the striatum, and in particular, in the right caudate, left caudate extending into the left ventral portion of the striatum, and the right putamen. Signal was extracted as the mean for each condition of all voxels meeting these criteria. We then compared signal in smokers and nonsmokers separately during anticipation of the immediate and during anticipation of the delayed rewards. The pattern did not suggest hypersensitivity to immediate rewards among smokers. Indeed means were in the direction of *less* activity among smokers than nonsmokers during anticipation of immediate rewards ($t(69) = 1.57$, $p = .12$). The bases of the group difference depicted in Fig. 2 were instead less signal among smokers relative to nonsmokers in the identified regions during the anticipation of the delayed rewards ($t(69) = 3.02$, $p = .004$) rather than by high striatal activation among smokers during immediate reward trials.

Table 1
Top of table summarizes results for the overall contrast (immediate–delay), and bottom summarizes regions in which smokers > nonsmokers with respect to this contrast. Cluster peak coordinates are reported in MNI space, along with corresponding voxel Z-scores.

	Whole brain	x, y, z	Max Z
Immediate–delayed	L ventral striatum	−14, 14, −6	3.82
	L putamen	−18, 14, −6	4.25
	l caudate	−10, 14, 0	3.95
	L insula/frontal operculum cortex/central opercular cortex	−38, 14, −4	4.64
	L thalamus	−10, −2, 8	4.64
	L frontal pole/prefrontal cortex	−30, 44, 18	4.89
	L pallidum	−16, 4, −6	3.99
	L postcentral gyrus/supramarginal gyrus	−56, −22, 22	4.18
	L precentral gyrus/inferior frontal gyrus	−48, 4, 20	3.15
	L superior frontal gyrus	−20, 6, 60	4.4
	R ventral striatum	12, 18, −4	2.53
	R putamen	18, 6, −4	3.65
	R caudate	10, 6, 6	3.66
	R insula/frontal operculum cortex/central opercular cortex	34, 18, 6	3.44
	R thalamus	8, −18, 6	4.03
	R frontal pole/prefrontal cortex	40, 48, 24	4.11
	R pallidum	18, 4, −2	3.41
	R postcentral gyrus/supramarginal gyrus	64, −32, 32	4.48
	R precentral gyrus/inferior frontal gyrus	56, 16, −2	3.53
	R superior frontal gyrus	4, 14, 58	3.49
	Anterior cingulate cortex	2, 16, 40	4.17
	Supplementary motor cortex	2, 2, 54	4.68
Group difference: immediate–delayed	R ventral striatum	0, −94, 10	4.07
	R putamen	0, −56, 24	3.26
	R caudate	10, 20, 2	2.8
	R lateral occipital cortex	30, −70, 28	3.36
	L caudate	−6, 10, 2	2.9
	L thalamus		
	L hippocampus/parahippocampal gyrus	−26, −34, −4	3.35
	L lateral occipital cortex	−40, −84, 22	3.61
	Cuneal cortex/precuneous cortex	2, −76, 22	3.79

4. Discussion

We observed that smokers exhibited greater striatal recruitment than nonsmokers during the anticipation of immediate relative to equally preferred delayed rewards. Post hoc analysis of signal change within these regions indicated that the effect was driven by low activation among smokers (relative to nonsmokers) during the anticipation of delayed rewards, with no indication of high activation (again relative to nonsmokers) during the anticipation of immediate rewards.

We did not observe greater delay discounting among smokers relative to nonsmokers. Although there are several reports in the

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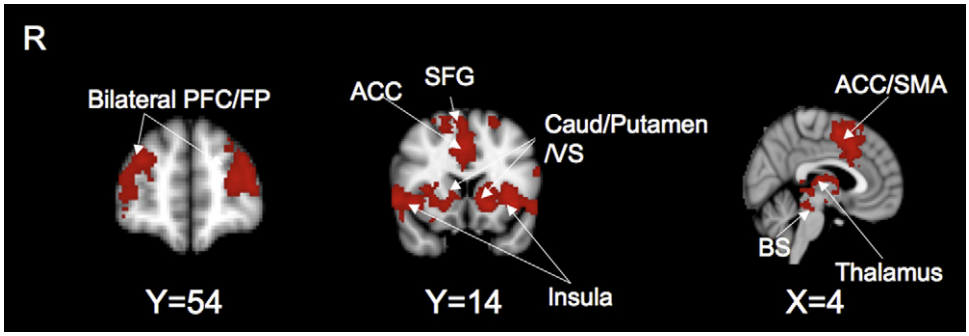

Fig. 1. Immediate vs. delay contrast. Immediate rewards recruited greater signal change than delayed rewards in bilateral caudate/putamen/ventral striatum (VS), bilateral insula, bilateral prefrontal cortex (PFC)/frontal pole (FP), bilateral superior frontal gyrus (SFG), bilateral thalamus, brain stem (BS), and anterior cingulate cortex (ACC)/supplementary motor cortex (SMA).

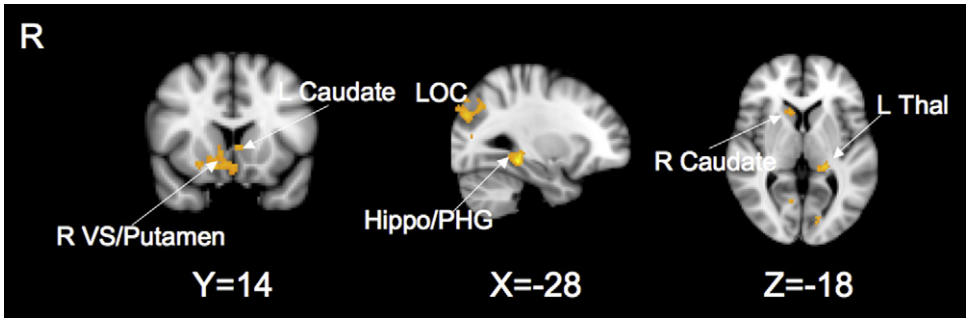

Fig. 2. Smokers showed a significantly larger "immediate > delayed" effect in the right ventral striatum (VS), bilateral caudate, right putamen, left thalamus (Thal), left hippocampus (Hippo)/parahippocampal gyrus (PHG) and lateral occipital cortex (LOC).

literature indicating an association between smoking and delay discounting (reviewed above), a null finding is only moderately surprising given effect sizes reported. If the true effect size in the population is $D = .65$ (the median of those reviewed in Gottdiener et al., 2008), then null findings would be expected approximately 25% of the time given our sample size (and indeed, given the "file drawer problem", it is likely that the true effect-size is less than .65). Indeed two of the three studies previously reporting an association between smoking severity and steeper discounting did not observe statistically significant group differences between smokers and nonsmokers (Heyman and Gibb, 2006; Ohmura et al., 2005). In the present study, we observed marginal evidence ($p = .06$) consistent with the same association between severity of dependence and steeper discounting. It is likely that variability in severity of smokers included across studies is an important source of variability in findings regarding discounting behavior in smokers vs. nonsmokers. It is noteworthy that some participants that we identified as nicotine dependent (based on the M.I.N.I.) scored low on the Fagerström Test for Nicotine Dependence. These measures emphasize different features, and lack of correspondence has been previously reported. Indeed, in a large sample, Moolchan et al. (2002) reported that 24 of 216 individuals that met DSM criteria for nicotine dependence (11.1%) scored 0 or 1 on the Fagerström. The general pattern observed in our data suggests an overall group difference in delay discounting would likely be observed in a similar sample restricted to more severely dependent smokers.

The fact that intertemporal choices tend to be more farsighted than would be expected based on brain response to anticipated immediate and delayed rewards suggests an underlying disposition favoring immediate rewards (or neglecting delayed rewards) that goes beyond what is expressed in delay discounting tasks. Among smokers, the data indicated that striatal response was, relative to comparison participants, abnormally low during the anticipation of delayed rewards. It is possible that this represents dispositional phenotypic variance relevant to initiation or escalation of cigarette smoking. It is also possible that chronic cigarette smoking and/or acute smoking causes the observed effect. Acute nicotine administration enhances phasic responses to rewarding stimuli (Rice and Cragg, 2004) and lowers intracranial self-stimulation thresholds (Bauco and Wise, 1994). The effects of chronic nicotine administration on striatal reward response are complex and appear to include both a lowering of striatal D1 and D2 receptor availability (Dagher et al., 2001; Fehr et al., 2008), but also evidence of sustained hypersensitivity of the reward system (Kenny and Markou, 2005; Mansvelder and McGehee, 2000). The observed pattern of generally lower signal change in relation to monetary reward among smokers is consistent with prior reports based on Positron Emission Tomography. Martin-Soelch et al. (2001, 2003) reported data suggestive of hyporesponsiveness in non-abstinent smokers to rewards, relative to nonsmokers, especially within the striatum. It should be noted though, that our own data do not include statistical evidence of a group difference in response to immediate rewards.

Interestingly, it was recently reported that acute administration of L-Dopa (which increases dopamine release) was associated with an increased preference for immediate over delayed reward, and with increased attenuation of reward response as a function of delay in brain regions associated with discounting, including the striatum (Pine et al., 2010). It therefore seems possible that neuroadaptations associated with chronic smoking reduce striatal anticipatory response to delayed rewards, as observed in the present study.

While the significance of revealed preference with regard to addictive behavior is conceptually straightforward, the significance of anticipatory response to delayed rewards is not. What difference, one might reasonably ask, does it make if a hypothetical smoker exhibits low striatal response during the anticipation of delayed

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rewards, if she is nevertheless willing to choose larger delayed over smaller immediate rewards? One possibility is that low striatal response to delayed rewards represents an underlying disposition that may be expressed when trade-offs are less explicit, or when decision-making is compromised. While real-world choices that entail some trade-off between more and less immediate utility are ubiquitous, the trade-offs are rarely so explicit as they are in intertemporal choice experiments (what exactly is the cost of one cigarette, for example, and when is that cost borne?). There is evidence that discounting tends to be steeper when the trade-off is less easy to quantify than it is in monetary choice experiments (Chapman, 1996; Chapman and Elstein, 1995). There is also evidence that discounting tends to increase when participants are distracted (Mischel et al., 1972), under working memory load (Hinson et al., 2003), sexually aroused (Wilson and Daly, 2004), or in nicotine withdrawal (Field et al., 2006). One possibility, therefore, is that anticipatory responses to delayed reward may reveal an underlying tendency that is manifested during the less "tangible" (Rick and Loewenstein, 2008) trade-offs between reward magnitude and immediacy entailed in everyday choice, and or that is revealed when decision-making resources are compromised. If this is the case, the observed finding may play an important role in understanding variability in response among smokers to rational incentives favoring smoking cessation.

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Contributors

Authors Luo, Ainslie and Monterosso designed the study and Giragosian co-wrote protocol with Monterosso. Authors Luo and Monterosso carried out data analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they do not have any conflict of interests.

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