

# Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers

Maartje Luijten<sup>1,2</sup>, David A. O'Connor<sup>1</sup>, Sarah Rossiter<sup>1</sup>, Ingmar H. A. Franken<sup>2,3</sup> & Robert Hester<sup>1</sup>

School of Psychological Sciences, University of Melbourne, Melbourne, Vic., Australia,<sup>1</sup> Institute of Psychology, Erasmus University Rotterdam, Rotterdam, the Netherlands<sup>2</sup> and Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands<sup>3</sup>

## ABSTRACT

**Background and aims** Susceptibility to use of addictive substances may result, in part, from a greater preference for an immediate small reward relative to a larger delayed reward or relative insensitivity to punishment. This functional magnetic resonance imaging (fMRI) study examined the neural basis of inhibiting an immediately rewarding stimulus to obtain a larger delayed reward in smokers. We also investigated whether punishment could modulate inhibitory control. **Design** The Monetary Incentive Go/NoGo (MI-Go/NoGo) task was administered that provided three types of reward outcomes contingent upon inhibitory control performance over rewarding stimuli: inhibition failure was either followed by no monetary reward (neutral condition), a small monetary reward with immediate feedback (reward condition) or immediate monetary punishment (punishment condition). In the reward and punishment conditions, successful inhibitory control resulted in larger delayed rewards. **Setting** Community sample of smokers in the Melbourne (Australia) area. **Participants** Nineteen smokers were compared with 17 demographically matched non-smoking controls. **Measurements** Accuracy, reaction times and brain activation associated with the MI-Go/NoGo task. **Findings** Smokers showed hyperactivation in the right insula ( $P < 0.01$ ), inferior and middle frontal gyrus ( $P < 0.01$ ), dorsolateral prefrontal cortex ( $P = 0.001$ ) and inferior parietal lobe ( $P < 0.01$ ) both during inhibition of an immediately rewarding stimulus to obtain a larger delayed reward, and during inhibition of neutral stimuli. Group differences in brain activity were not significant in the punishment condition in the right insula and dorsolateral prefrontal cortex, most probably as a result of increased activation in non-smoking controls. **Conclusions** Compared with non-smokers, smokers showed increased neural activation when resisting immediately rewarding stimuli and may be less sensitive to punishment as a strategy to increase control over rewarding stimuli.

**Keywords** fMRI, inhibitory control, punishment, reward, smokers, substance dependence.

Correspondence to: Maartje Luijten, Institute of Psychology, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, the Netherlands. E-mail: luijten@fsw.eur.nl

Submitted 10 November 2012; initial review completed 22 February 2013; final version accepted 12 June 2013

## INTRODUCTION

Reduced inhibitory control is one of the key mechanisms underlying addictive behaviours [1–4]. There is also evidence that poor inhibitory control, which refers to a decreased ability to suppress automatic and habitual behaviours, is prevalent in smokers [5,6]. Research examining the neural mechanisms underlying decreased inhibitory control in smokers has shown dysfunctional cortical activity in regions involved critically in inhibitory control, such as the inferior frontal gyrus (IFG), the dorsolateral prefrontal cortex (DLPFC), the anterior

cingulate cortex/pre-supplementary motor area (ACC/pre-SMA) and the anterior insula [6,7]. Reduced inhibitory control as a consequence of impaired prefrontal brain function may be especially problematic when habitual and rigid behavioural patterns require alteration, such as during an attempt to give up smoking. Among other explanations, difficulties inhibiting substance-related behaviours may be the result of the preference for an immediate small reward relative to a larger delayed reward [8], or may be the result of insensitivity to negative outcomes (punishment) [9]. While previous studies have linked the concepts of reward and

inhibitory control in substance dependence [10,11], the neural mechanisms that contribute to reduced inhibitory control over reward in substance-dependent humans have not yet been investigated fully. Therefore, the current study examined whether enhanced reward sensitivity and/or reduced punishment sensitivity may be associated with reduced inhibitory control in smokers.

The preference for smaller immediate rewards over larger delayed rewards has been found consistently in addicted individuals and is referred to as increased delayed discounting [8,12–15]. Decreased delay discounting in smokers has been associated with higher smoking rates [16] and unsuccessful quit attempts [15]. In line with addiction theories, it is likely that people with heightened reward sensitivity for the substance of abuse will experience stronger pre-potent approach tendencies, and these would require greater levels of cognitive inhibition [1,17,18]. Thus far, research examining inhibitory control in substance use typically employed Go/NoGo and Stop Signal tasks involving neutral, rather than rewarding, stimuli. A few studies in smokers, however, have investigated control over craving evoked by smoking-related pictures or videos. Kober and colleagues [19] showed that inhibition of craving is associated with increased activation in regions implicated in inhibitory control, such as the right inferior frontal gyrus, while reductions in activity were reported in reward-related areas such as the striatum. Similarly, increased dorsal ACC and decreased activation bilaterally in the cuneus and occipital gyrus was found in another study in which smokers resisted craving during exposure to smoking cues [20]. These studies suggest that applying control over reward-related stimuli may be associated with changes in the balance between prefrontal control regions and subcortical regions, as well as brain regions involved in visual processing. The current study examined whether inhibition of an immediate and overt rewarding stimulus in favour of a larger delayed reward also requires additional recruitment of control regions, consistent with the patterns of activation reported for the suppression of craving evoked by drug-related stimuli.

Punishment insensitivity in addicted individuals may be another factor contributing to deficient inhibitory control [9]. Although this is a relatively unexplored area, reduced sensitivity to punishment in behavioural performance has been suggested in addicted individuals [21–24]. Neuroimaging studies of drug-dependent patients have also shown a diminished neural response to monetary loss [25–27] in both subcortical ‘limbic’ regions such as the striatum and cortical regions such as the anterior cingulate cortex. A functional magnetic resonance imaging (fMRI) study in smokers showed reduced activity in the ventrolateral prefrontal cortex compared to healthy controls during punishment trials of a reversal

learning task [28]. These studies have typically not examined the consequences of a reduced loss-response to the ability to control behaviour [29]. Pre-clinical research in rats, however, showed that with extended cocaine self-administration rats develop resistance to the inhibitory effect of punishment on drug self-administration, while punishment stimulated the inhibition of drug self-administration in rats without an extended history of self-administration of cocaine [9,30,31].

To examine the effect of reward and punishment on brain activation associated with inhibitory control, a modified version of the Go/NoGo paradigm (i.e. the Monetary Incentive Go/NoGo task [32,33]) was administered to smokers and non-smoking controls. This task aims to examine neural activity during attempts to inhibit a pre-potent response to a rewarding NoGo stimulus. To mimic a rewarding scenario during smoking abstinence, the following contingencies were introduced. First, NoGo stimuli were assigned via learning trials to be associated with monetary reward. Secondly, failed inhibition over these NoGo trials resulted in small immediate monetary rewards in the reward condition, while in the punishment condition failure to inhibit resulted in immediate monetary loss. Successful inhibitory control over NoGo trials in both conditions resulted in a larger delayed reward. Finally, the task also involved neutral NoGo trials without any rewarding or punishing contingencies as a comparison condition. In line with the above-mentioned theories of addiction, we hypothesized that smokers would have significantly greater difficulty inhibiting their response to an immediate rewarding stimulus when compared to matched control participants, neutral conditions or both. With regard to punishment, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behaviour to the same extent in smokers.

## MATERIALS AND METHODS

### Participants

Nineteen smokers participated in this study. Groups were matched for age, estimated IQ [34] and gender. Exclusion criteria for both groups were (i) current substance abuse or dependence (other than nicotine for the smoking group), (ii) the presence of any physical or psychological illness, (iii) use of psychotropic medication or medication that may affect blood circulation and/or respiration, (iv) fMRI contraindications and (v) left-handedness [35]. Smokers smoked at least 15 cigarettes per day for the duration of at least 2 years. The average score on the Fagerström Test for Nicotine Dependence (FTND) [36] for

**Table 1** Participant characteristics.

	Smokers ( <i>n</i> = 19)			Controls ( <i>n</i> = 17)			<i>P</i> -value
	Mean	SD	Range	Mean	SD	Range	
Age	26.89	8.11	19–52	24.47	7.79	20–44	0.83
Gender (male/female)	6/13	–	–	7/10	–	–	0.54
Estimated IQ	114.72	5.00	102–122	114.80	7.67	102–122	0.97
Cigarettes a day	18.95	4.40	15–30	–	–	–	–
Years of smoking	9.19	4.16	2.5–25	–	–	–	–
FTND scores	3.79	2.10	1–8	–	–	–	–

FTND = Fagerström Test for Nicotine Dependence; SD = standard deviation.

smokers was 3.79. Non-smokers had smoked 10 cigarettes or fewer during their life-time; see Table 1 for details on participant characteristics. Smokers were instructed to abstain from smoking for 1 hour before the experiment. This short period of smoking deprivation was introduced in order to reduce the acute effects of nicotine on cognitive performance without introducing significant withdrawal effects on cognitive performance. The study was conducted in accordance with the Declaration of Helsinki and all participants provided written informed consent before study onset. The human research ethics committee of the University of Melbourne approved the study.

### Task paradigm

Participants completed the Monetary Incentive Go/NoGo (MI-Go/NoGo) task that has been described previously [32,33]. For a complete task description and details on timing of stimuli presentation see the Supporting information. In short, the MI-Go/NoGo task consisted of two types of Go trials and three types of NoGo trials. The first type of Go trial was a regular Go-trial that required a button response. The second type of Go trial was a Go-Money trial that also required a button response and additionally paid monetary rewards in proportion to response speed. Participants were asked to withhold their response upon presentation of NoGo stimuli. Three types of NoGo trials were differentiated, i.e. NoGo neutral, NoGo reward and NoGo punishment. For NoGo neutral trials, no monetary reinforcement was applied to inhibition success or failure. The goal of NoGo reward trials was to measure inhibition of immediate rewarding stimuli. To cultivate an association with immediate reward, stimuli presented as NoGo reward trials were selected from a preceding task block in which this stimulus was presented as a Go-Money trial. Consequently, the stimuli used as NoGo reward trials were learned to be associated with immediate monetary reward. Additionally, failure to exert control over NoGo reward trials resulted in small immediate monetary rewards, whereas successful inhibi-

tory control resulted in a larger but delayed reward comprising the sum of the longest run of consecutive successful inhibitions. The objective of NoGo punishment trials was to measure whether or not punishment of failed inhibition over previously rewarding stimuli can be used to overcome difficulties with inhibition of these stimuli. Therefore, NoGo punishment trials were also selected from a previous block in which they acted as a Go-Money trial, and successful inhibitory control resulted a large delayed reward comprising the sum of the longest run of consecutive successful inhibitions. However, failed inhibition of NoGo punishment trials resulted in an immediate monetary loss.

### Image acquisition

fMR images were acquired using a 3T scanner (Siemens Magnetom TrioTim, Erlangen, Germany). A total of 183 echo-planar imaging (EPI) sequences providing T2\*-weighted blood oxygenation level-dependent (BOLD) were acquired for each functional run with the following parameters: repetition time (TR), 2000 ms; echo time, 35 ms; flip angle, 90°; 32 contiguous slices of 4 mm thickness, in-plane resolution; 3.6 mm × 3.6 mm × 4 mm. Eight functional runs were collected for each participant. A rapid-acquisition gradient echo T1-weighted image was acquired in 208 contiguous axial slices with TR of 1900 ms, TE of 2.3 ms, field of view (FOV) of 250 mm and isotropic voxel size of 0.8 mm<sup>3</sup> for anatomical reference.

### Data analyses

Imaging data were analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Pre-processing of the functional data included realignment of all functional images. Movement of all participants was less than 3 mm in any direction and movement parameters did not differ between groups. The anatomical scan was coregistered to the mean T2\*-weighted image. Segmentation and normalization were performed using

the unified segment and normalize framework implemented in SPM8 [37] using the SPM T1-weighted MNI template. Voxel size was re-sampled to  $2 \times 2 \times 2$  mm during normalization. Functional scans were spatially smoothed using a three-dimensional full-width at half-maximum Gaussian kernel of 8 mm. Correct trials for the NoGo conditions (NoGo neutral, NoGo reward and NoGo punishment), as well as Go-Money trials, were modelled in the context of the general linear model using delta functions convolved with a canonical haemodynamic response function. Additional regressors for events were included for errors and feedback epochs. The baseline estimate was the mean activation recorded during the ongoing trial period (Go trials), such that the activation observed during successful NoGo trial responses represents activation over and above that required for the ongoing Go trials. Activation clusters revealed by a whole-brain one-sample *t*-test across groups including NoGo neutral, reward and punishment trials (AND map) were used to create functionally derived regions of interest (ROIs;  $P < 0.005$ , familywise error rate (FWE)-corrected, cluster size  $\geq 50$  voxels). Activation estimates (beta-values) for all participants in the three NoGo conditions were extracted in the ROIs using Marsbar [38]. Due to a priori interest in the activity of the ventral striatum, an anatomically defined ROI [39] was created in the right and left nucleus accumbens (NAcc). Activation estimates in the ROIs were analysed using group (smokers versus controls)  $\times$  condition (NoGo neutral versus NoGo reward for the first research question and NoGo neutral versus NoGo punishment for the second research question) repeated-measures analyses of variance (RM-ANOVA) in SPSS. Accuracy rates and reaction times for Go, NoGo and Go-Money trials were analysed using the same group  $\times$  condition RM-ANOVAs. In order to investigate NAcc activation associated with immediate reward without the need for inhibition, activation estimates for Go-Money trials in the NAcc were analysed using a group  $\times$  condition RM-ANOVA. Condition was included as a three-level within-subject factor in this analysis, as no specific hypotheses were specified for Go-Money activation during the reward or punishment condition versus the neutral condition.

## RESULTS

### Behavioural results reward

Group (smokers versus controls)  $\times$  condition (neutral versus reward) RM-ANOVAs did not show significant main or interaction effects of group and condition for either NoGo, Go and Go-Money accuracy rates. NoGo error reaction times did not show a main effect of group or condition. However, a group  $\times$  condition interaction

was found. *Post-hoc t*-tests revealed that NoGo error reaction times in smokers were faster in the reward condition relative to the neutral condition, whereas there was no effect of condition on NoGo reaction times for non-smoking controls. Go reaction times showed a main effect of condition, indicating that Go reaction times were faster for both groups in the reward versus neutral condition. No main or interaction effects of group were found for Go reaction times. Go-Money reaction times showed a similar pattern. A main effect of condition showed that Go-Money reaction times were faster in both groups in the reward versus neutral condition. No main or interaction effects of group were found for Go-Money reaction times. See Table 2 for means, standard deviations (SDs) and *F*- and *P*-values of behavioural data.

### Behavioural results punishment

Group (smokers versus controls)  $\times$  condition (neutral versus punishment) RM-ANOVAs did not show significant main or interaction effects of group and condition for either NoGo, Go and Go-Money accuracy rates. NoGo reaction times did not show a main effect of group or condition. However, a group  $\times$  condition interaction was found. *Post-hoc t*-tests revealed that NoGo error reaction times in controls were slower in the punishment condition relative to the neutral condition, whereas there was no effect of condition on NoGo reaction times for smokers. No significant main or interaction effects of group and condition were found for either Go or Go-Money reaction times. See Table 2 for means, SDs and *F*- and *P*-values of behavioural data.

### Imaging results

Activation associated with correct inhibitory control was observed in the right inferior/middle frontal gyrus (IFG/MFG), the right DLPFC, the right pre-SMA, the bilateral anterior insula, the bilateral inferior parietal lobe (IPL), the bilateral superior temporal gyrus (STG), the posterior cingulate cortex (PCC), the right thalamus and bilateral occipital regions (see Table 3 and Fig. 1). These regions were used for functionally defined ROI analyses.

#### *Imaging results reward*

Activation for inhibitory control during neutral and reward conditions showed increased activation in smokers relative to non-smoking controls in the right IFG/MFG, the right DLPFC, the right anterior insula and the right IPL. No main effect of condition or group  $\times$  condition interaction effects were found. The remaining ROIs did not show main effects of group, condition or group  $\times$  condition interactions. See Fig. 1 and Table 3 for details of results in all regions of interest, including *F*- and *P*-values.

**Table 2** Accuracy rates and reaction times for the MI-Go/NoGo task.

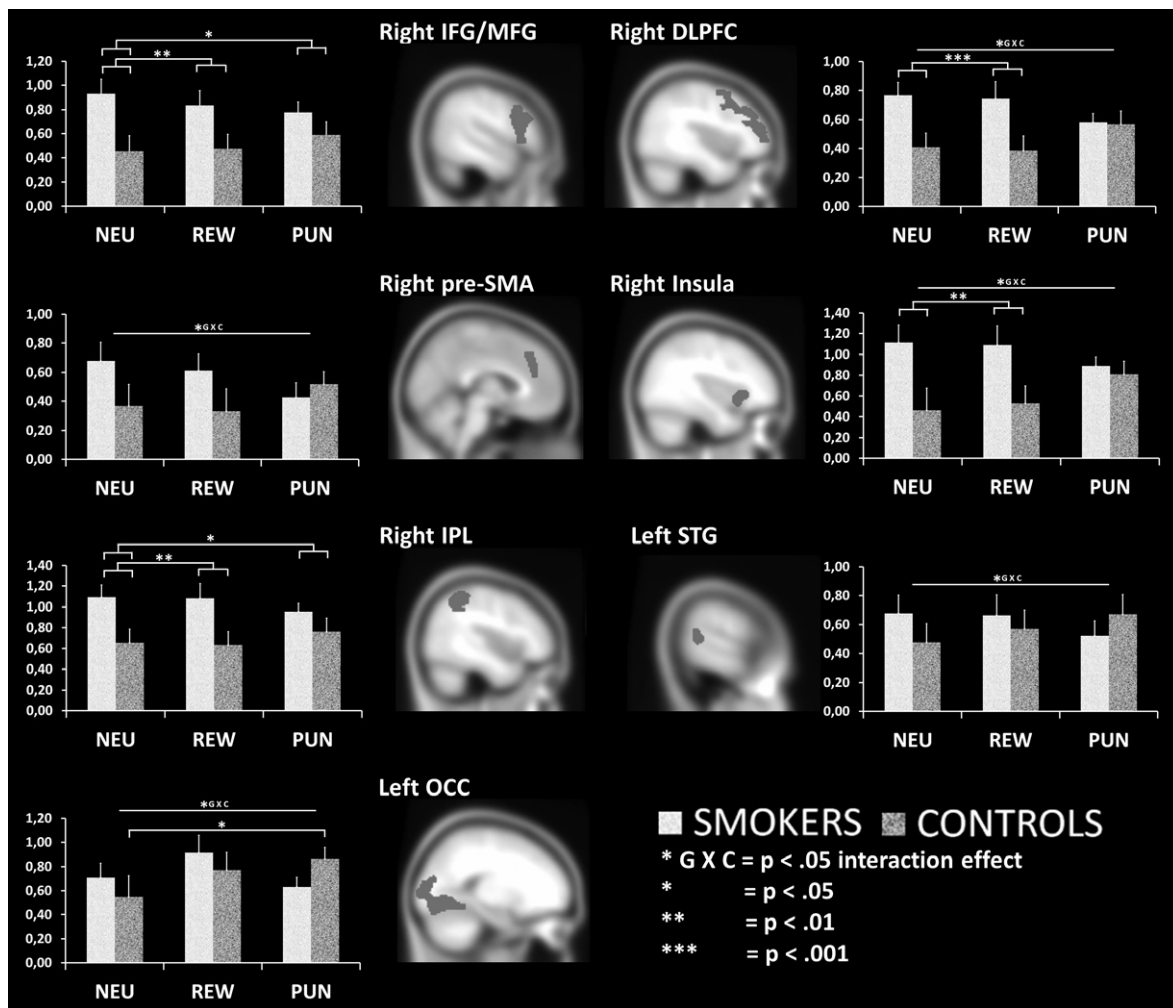
Category	Accuracy				Reaction times				Statistics reaction times	Condition
	Smokers		Controls		Smokers		Controls			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
NoGo										
Neutral	79.16	14.83	81.12	13.15	376.70	65.56	359.72	51.15		
Reward	82.65	10.29	82.29	10.29	349.30	47.59	370.80	49.26	$F_{(1,23)} = 4.19, P = 0.05$	Smokers and not controls Reward < neutral, $P < 0.05$
Punishment	78.00	11.67	82.65	7.47	362.13	38.11	389.46	46.77	$F_{(1,23)} = 4.19, P = 0.05$	Controls and not smokers Punishment > neutral, $P < 0.05$
Go										
Neutral	99.11	2.28	96.59	12.38	407.13	52.54	406.26	47.97		
Reward	99.42	0.96	97.41	8.13	392.25	44.92	391.16	43.80		$F_{(1,34)} = 18.17, P < 0.001$ Reward < neutral, $P < 0.001$
Punishment	95.53	1.02	99.29	1.96	408.90	40.47	414.83	53.07		
Go-Money										
Neutral	96.63	4.03	93.76	12.16	398.92	38.42	404.07	42.07		
Reward	98.05	3.36	96.76	8.34	379.49	38.20	381.11	44.49		$F_{(1,34)} = 30.06, P < 0.001$ Reward < neutral, $P < 0.001$
Punishment	97.47	2.59	97.41	4.64	407.23	32.67	406.47	51.30		

SD = standard deviation.

**Table 3** Regions of event-related activation during successful NoGo trials.

Region	MNI coordinates			Reward		Punishment		Interaction
	X	Y	Z	Group		Group		
	mm <sup>3</sup>							
Pre-SMA	6	26	32	1448	-	-	-	$F_{(1,34)} = 4.08, P = 0.05$
Right insula <sup>a</sup>	38	20	-6	3088	Main effect S > C $F_{(1,34)} = 8.56 P < 0.01$	Neutral S > C $F_{(1,34)} = 5.89, P < 0.05$	-	$F_{(1,34)} = 5.44, P < 0.05$
Right IFG/MFG <sup>a</sup>	47	20	22	10 584	Main effect S > C $F_{(1,34)} = 9.65 P < 0.01$	Punishment -- Main effect S > C $F_{(1,34)} = 7.12, P < 0.05$	-	-
Right DLPFC <sup>a</sup>	38	27	34	14 544	Main effect S > C $F_{(1,34)} = 12.92 P = 0.001$	Neutral S > C $F_{(1,34)} = 7.23, P < 0.05$	-	$F_{(1,34)} = 5.19, P < 0.05$
Right IPL <sup>b</sup>	39	-51	49	10 840	Main effect S > C $F_{(1,34)} = 11.14 P < 0.01$	Punishment -- Main effect S > C $F_{(1,34)} = 5.09 P < 0.05$	-	-
Left insula	-36	16	-6	1488	-	-	-	-
Left IPL	-40	-52	48	2380	-	-	-	-
PCC	0	-26	30	3808	-	-	-	-
Right STG <sup>b</sup>	56	-39	6	8400	-	-	-	-
Left STG	-64	-46	6	1624	-	-	-	$F_{(1,34)} = 4.93, P < 0.05$
Right thalamus	22	-28	-4	440	-	-	-	-
Left OCC	-20	-80	-10	20 960	-	-	Controls: Punishment > neutral $F_{(1,34)} = 4.94, P < 0.05$	$F_{(1,34)} = 4.07, P = 0.05$
Right OCC <sup>b</sup>	31	-78	19	12 952	-	-	Smokers: --	-
Left NAcc	-10	12	-2	4120	-	-	-	-
Right NAcc	10	12	-2	4120	-	-	-	-

Pre-SMA = pre-supplementary motor area; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; DLPFC = dorsolateral prefrontal gyrus; IPL = inferior parietal lobe; STG = superior temporal gyrus; PCC = posterior cingulate cortex; OCC = occipital; NAcc = nucleus accumbens; S = smokers, C = controls. <sup>a</sup>These regions appeared originally as one big cluster (28 216 mm<sup>3</sup>) in the AND map, in order to retain anatomical specificity this cluster was separated into these three regions using the AAL atlas. <sup>b</sup>These regions appeared originally as one big cluster (232 192 mm<sup>3</sup>) in the AND map, in order to retain anatomical specificity this cluster was separated into these three regions using the AAL atlas.



**Figure 1** Activation patterns during successful NoGo trials in neutral, reward and punishment conditions in regions showing significant group or condition effects. NEU=neutral; REW=reward; PUN=punishment; MFG/IFG=middle frontal gyrus/inferior frontal gyrus; DLPFC=dorsolateral prefrontal cortex; IPL=inferior parietal lobe; STG=superior temporal gyrus; OCC=occipital

*Imaging results punishment*

Activation for inhibitory control during neutral and punishment conditions showed group  $\times$  condition interactions in the right anterior insula, the right DLPFC and the left occipital region. *Post-hoc* tests in the right insula and right DLPFC revealed similar activation patterns. During the neutral condition, smokers showed increased activation relative to controls in these regions, whereas no group differences were found during the punishment condition. *Post-hoc* tests in the left occipital region revealed that inhibitory control-related brain activation in controls was increased in the punishment condition relative to the neutral condition, whereas there was no effect of condition for smokers. Inhibitory control-related activation in the right IFG and right IPL was increased in smokers relative to controls regardless of task condition. The right pre-SMA and the left STG showed a

group  $\times$  condition interaction while *post-hoc* tests did not reveal significant effects for group or condition. The remaining ROIs did not show main effects of group, condition or group  $\times$  condition interactions. See Fig. 1 and Table 3 for details of results in all regions of interest such as *F*- and *P*-values.

*Imaging results nucleus accumbens Go-Money*

A main effect of group in the left NAcc showed that brain activation in smokers was enhanced for Go-Money trials across neutral, reward and punishment conditions  $F_{(1,34)} = 4.41, P < 0.05$ . No main or interaction effect of condition was found. No main effect of group, condition or group  $\times$  condition interactions were found for activation in the right NAcc during Go-Money trials (all *P*s  $> 0.06$ ).

## DISCUSSION

The current study examined the neural basis of inhibiting an immediately rewarding response in order to obtain a larger delayed reward in smokers and non-smoking controls. We also investigated whether punishment sensitivity could modulate the ability to execute inhibitory control. Results showed enhanced activation in the left NAcc in smokers relative to controls when they could earn money without the need for inhibition (i.e. in Go-Money trials), which is consistent with past findings of increased sensitivity to immediate reward in addicted populations [40,41]. With regard to the inhibition of rewarding stimuli, the hypothesis that smokers would have difficulty inhibiting an immediate reward in order to obtain a larger delayed reward was not confirmed by behavioural measures such as accuracy rates. However, greater BOLD activity in the right IFG/MFG, insula, DLPFC and IPL was found in smokers compared to non-smoking controls during successful inhibition of rewarding NoGo trials, suggesting the application of greater effort to inhibit rewarding stimuli in smokers. Increased brain activation during affectively neutral conditions in regions that are crucial for inhibitory control has been found previously in cannabis users [42,43] and has been interpreted as a compensatory mechanism [44,45], where maintaining equivalent performance compared to non-addicted individuals requires recruitment of additional cortical activation. Heightened brain activation in smokers in these regions was also found during inhibition of neutral stimuli, implying that differences in brain activation associated with inhibitory control in smokers versus non-smoking controls may not be specific to the reward-related context. As an alternative explanation, additional recruitment of cortical activation for response inhibition might be consistent with proactive versus reactive changes in Go/NoGo task related activation [46]. Research on individual differences in response inhibition indicates that better performance on tasks such as the Go/NoGo task is associated with a more cautious response style, or proactive cognitive control [47]. It may be that smokers implement less proactive control during our task, reflected in their faster failed NoGo reaction times; hence, when a NoGo trial appears, an increased reactive control response and associated neural activation must be implemented. Finally, the relatively short time-frame of smoking abstinence in the current study (1 hour) may have contributed to the equivalent behavioural performance of smokers and non-smoking controls (when combined with increased brain activation in smokers), as previous studies have shown that smoking abstinence and withdrawal modulate cognitive performance and prefrontal brain function [48,49].

The current study also examined the role of punishment on inhibitory control. It was hypothesized that punishments, via an immediate monetary fine for failed inhibition, would not improve inhibitory control in smokers to the same extent as in non-smoking controls. The behavioural data show such a trend, with control participants showing improved accuracy during the punishment condition (relative to neutral) and smokers showing a decline, but with our samples the small effect size renders this difference non-significant. Despite this, brain activation in the right IFG/MFG and DLPFC was increased in smokers relative to non-smoking controls during neutral and reward conditions, but not during the punishment conditions. Activation patterns (see Fig. 1) suggest that the absence of group differences under conditions of punishment reflects additional activation in non-smoking controls during the punishment compared to the neutral condition, an effect that was significant in left visual areas and was not observed in smokers. Involvement of visual areas in controlling behaviour was observed previously by Brody and colleagues [20] when smokers decreased visual processing of smoking cues in order to inhibit feelings of craving. Increased visual processing of NoGo stimuli during the punishment condition by non-smoking controls would be consistent with the heightened salience of punishment for non-smoking controls and may be associated with avoiding future punishment. Therefore, these findings provide tentative evidence that smokers, in contrast to non-smoking controls, may be less sensitive to punishment as a strategy to improve inhibitory control. The same pattern of performance has been shown previously in a larger sample of harmful drinkers using the same MI-Go/NoGo task [33]. The present results should, however, be replicated in smokers with higher FTND scores, as nicotine dependence levels in the current study were rather low, despite all smokers smoking at least 15 cigarettes a day.

In the current study, accuracy rates were not influenced significantly by reward and punishment conditions. Consequently, brain activation data should be interpreted in terms of compensation/more efficient recruitment of cortical regions leading to similar performance levels across conditions [45]. Reaction times, however, showed expected effects according to task conditions. For example, Go and Go-Money reaction times were faster in the reward versus neutral condition, suggesting that the availability of immediate reward elicited a higher degree of impulsive responding.

In conclusion, it was demonstrated that smokers showed hyperactivation in the right insula, IFG/MFG, DLPFC and IPL compared to non-smoking controls during inhibition of an immediately rewarding stimulus in order to obtain a larger delayed reward. Additionally,



tentative evidence is provided that smokers are less sensitive to the inhibitory effect of punishment to guide control over rewarding stimuli. Future studies should examine the role of punishment sensitivity as a core component of compulsive substance use.

#### Declaration of interests

None.

#### Acknowledgements

This research was supported by the Australian Research Council grant (DP1092852) and National Health and Medical Research Council grant (628495) (both for R.H.). We would like to thank Maria Di Biase for her assistance with participant recruitment and data collection.

#### References

- Dawe S., Gullo M. J., Loxton N. J. Reward drive and rash impulsiveness as dimensions of impulsivity: implications for substance misuse. *Addict Behav* 2004; **29**: 1389–405.
- Goldstein R. Z., Volkow N. D. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 2011; **12**: 652–69.
- Verdejo-García A., Lawrence A. J., Clark L. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev* 2008; **32**: 777–810.
- Jentsch J. D., Taylor J. R. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* 1999; **146**: 373–90.
- Luijten M., Littel M., Franken I. H. A. Deficits in inhibitory control in smokers during a Go/NoGo task: an investigation using event-related brain potentials. *PLoS ONE* 2011; **6**: e18898.
- Nestor L., McCabe E., Jones J., Clancy L., Garavan H. Differences in 'bottom-up' and 'top-down' neural activity in current and former cigarette smokers: evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *Neuroimage* 2011; **56**: 2258–75.
- De Ruiter M. B., Oosterlaan J., Veltman D. J., Van den Brink W., Goudriaan A. E. Similar hypo-responsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend* 2012; **121**: 81–9.
- Reynolds B. A review of delay-discounting research with humans: relations to drug use and gambling. *Behav Pharmacol* 2006; **17**: 651–67.
- Vanderschuren L. J., Everitt B. J. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 2004; **305**: 1017–9.
- Goldstein R. Z., Alia-Klein N., Tomasi D., Zhang L., Cottone L. A., Maloney T. *et al.* Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry* 2007; **164**: 43–51.
- Garavan H., Stout J. C. Neurocognitive insights into substance abuse. *Trends Cogn Sci* 2005; **9**: 195–201.
- Hoffman W. E., Schwartz D. L., Huckans M. S., McFarland B. H., Meiri G., Stevens A. A. *et al.* Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology (Berl)* 2008; **201**: 183–93.
- Petry N. M. Discounting of delayed rewards in substance abusers: relationship to antisocial personality disorder. *Psychopharmacology (Berl)* 2002; **162**: 425–32.
- Bickel W. K., Marsch L. A. Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction* 2001; **96**: 73–86.
- Sheffer C., Mackillop J., McGeary J., Landes R., Carter L., Yi R. *et al.* Delay discounting, locus of control, and cognitive impulsiveness independently predict tobacco dependence treatment outcomes in a highly dependent, lower socioeconomic group of smokers. *Am J Addict* 2012; **21**: 221–32.
- Heyman G. M., Gibb S. P. Delay discounting in college cigarette chippers. *Behav Pharmacol* 2006; **17**: 669–79.
- Goldstein R. Z., Volkow N. D. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002; **159**: 1642–52.
- Volkow N. D., Fowler J. S., Wang G. J. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology* 2004; **47**: 3–13.
- Kober H., Mende-Siedlecki P., Kross E. F., Weber J., Mischel W., Hart C. L. *et al.* Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci USA* 2010; **107**: 14811–6.
- Brody A. L., Mandelkern M. A., Olmstead R. E., Jou J., Tjongson E., Allen V. *et al.* Neural substrates of resisting craving during cigarette cue exposure. *Biol Psychiatry* 2007; **62**: 642–51.
- Bechara A., Damasio H. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* 2002; **40**: 1675–89.
- Ersche K. D., Roiser J. P., Clark L., London M., Robbins T. W., Sahakian B. J. Punishment induces risky decision-making in methadone-maintained opiate users but not in heroin users or healthy volunteers. *Neuropsychopharmacology* 2005; **30**: 2115–24.
- Fridberg D. J., Queller S., Ahn W. Y., Kim W., Bishara A. J., Busemeyer J. R. *et al.* Cognitive mechanisms underlying risky decision-making in chronic cannabis users. *J Math Psychol* 2010; **54**: 28–38.
- Grant S., Contoreggi C., London E. D. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* 2000; **38**: 1180–7.
- Beck A., Schlagenhauf F., Wustenberg T., Hein J., Kienast T., Kahnt T. *et al.* Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry* 2009; **66**: 734–42.
- Bjork J. M., Knutson B., Hommer D. W. Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction* 2008; **103**: 1308–19.
- Wrase J., Schlagenhauf F., Kienast T., Wustenberg T., Birmphohl E., Kahnt T. *et al.* Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage* 2007; **35**: 787–94.

28. De Ruiter M. B., Veltman D. J., Goudriaan A. E., Oosterlaan J., Sjoerds Z., Van den Brink W. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology* 2009; **34**: 1027–38.
29. Hommer D. W., Bjork J. M., Gilman J. M. Imaging brain response to reward in addictive disorders. *Ann NY Acad Sci* 2011; **1216**: 50–61.
30. Xue Y., Steketee J. D., Sun W. Inactivation of the central nucleus of the amygdala reduces the effect of punishment on cocaine self-administration in rats. *Eur J Neurosci* 2012; **35**: 775–83.
31. Pelloux Y., Everitt B. J., Dickinson A. Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology (Berl)* 2007; **194**: 127–37.
32. O'Connor D. A., Rossiter S., Yücel M., Lubman D. I., Hester R. Successful inhibitory control over an immediate reward is associated with attentional disengagement in visual processing areas. *Neuroimage* 2012; **62**: 1841–7.
33. Rossiter S., Thompson J., Hester R. Improving control over the impulse for reward: sensitivity of harmful alcohol drinkers to delayed reward but not immediate punishment. *Drug Alcohol Depend* 2012; **125**: 89–94.
34. Nelson H. E. *National Adult Reading Test (NART): Test Manual*. Windsor, UK: NFER; 1982.
35. Oldfield R. C. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; **9**: 97–113.
36. Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27.
37. Ashburner J., Friston K. J. Unified segmentation. *Neuroimage* 2005; **26**: 839–51.
38. Brett M., Anton J. C., Valabregue R., Poline J. B. Region of interest analysis using an SPM toolbox. 8th International Human Brain Mapping Conference, Sendai, Japan, 2002.
39. Knutson B., Wimmer G. E., Rick S., Hollon N. G., Prelec D., Loewenstein G. Neural antecedents of the endowment effect. *Neuron* 2008; **58**: 814–22.
40. Van Hell H. H., Vink M., Ossewaarde L., Jager G., Kahn R. S., Ramsey N. F. Chronic effects of cannabis use on the human reward system: an fMRI study. *Eur Neuropsychopharmacol* 2010; **20**: 153–63.
41. Bjork J. M., Smith A. R., Hommer D. W. Striatal sensitivity to reward deliveries and omissions in substance dependent patients. *Neuroimage* 2008; **42**: 1609–21.
42. Tapert S. F., Schweinsburg A. D., Drummond S. P., Paulus M. P., Brown S. A., Yang T. T. et al. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology (Berl)* 2007; **194**: 173–83.
43. Hester R., Nestor L., Garavan H. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology* 2009; **34**: 2450–8.
44. Goh J. O., Park D. C. Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. *Restor Neurol Neurosci* 2009; **27**: 391–403.
45. Wilkinson D., Halligan P. The relevance of behavioural measures for functional-imaging studies of cognition. *Nat Rev Neurosci* 2004; **5**: 67–73.
46. Simoes-Franklin C., Hester R., Shpaner M., Foxe J. J., Garavan H. Executive function and error detection: the effect of motivation on cingulate and ventral striatum activity. *Hum Brain Mapp* 2010; **31**: 458–69.
47. Braver T. S. The variable nature of cognitive control: a dual mechanisms framework. *Trends Cogn Sci* 2012; **16**: 106–13.
48. Azizian A., Nestor L. J., Payer D., Monterosso J. R., Brody A. L., London E. D. Smoking reduces conflict-related anterior cingulate activity in abstinent cigarette smokers performing a Stroop task. *Neuropsychopharmacology* 2010; **35**: 775–82.
49. Froeliger B., Modlin L. A., Kozink R. V., Wang L., McClernon F. J. Smoking abstinence and depressive symptoms modulate the executive control system during emotional information processing. *Addict Biol* 2012; **17**: 668–79.

### Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1** Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers