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Research report

Shared and divergent neural reactivity to non-drug operant response outcomes in current smokers and ex-smokers

Liam J. Nestor [a,b,*], Ella McCabe [a], Jennifer Jones [a], Luke Clancy [c], Hugh Garavan [a,d]

[a] School of Psychology and Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[b] Neuropsychopharmacology Unit, Centre for Psychiatry, Imperial College London, UK
[c] TobaccoFree Research Institute Ireland, DIT, Dublin, Ireland
[d] Department of Psychiatry, University of Vermont, Burlington, VT, USA

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ABSTRACT

Addiction to cigarettes presents with considerable health risks and induces high costs on healthcare resources. While the majority of cigarette smokers endorse the desire to quit, only a small percentage of quit attempts lead to full abstinence. Failure to achieve abstinence may arise from maladaptive reactivity in fronto-striatal regions that track positive and negative valence outcomes, thus biasing the choice to smoke in the presence of alternative, non-drug reinforcement. Alternatively, long-term nicotine abstinence may reveal neural substrates of adaptive valence outcome processing that promote and maintain smoking cessation. The present study set out to examine the neural correlates of operant response outcomes in current smokers, ex-smokers and matched controls using a monetary incentive delay task during functional MRI. Here we report that compared to controls, both current smokers *and* ex-smokers showed significantly less activation change in the left amygdala during positive response outcomes, and in the anterior cingulate cortex, during both positive and negative response outcomes. Ex-smokers, however, demonstrated significantly greater activation change compared to smokers *and* controls in the right amygdala during negative response outcomes. Activation change in the anterior cingulate cortex and middle frontal gyrus of smokers was significantly negatively correlated with nicotine dependence and cigarette pack-years. These results suggest a pattern of shared and divergent reactivity in current smokers and ex-smokers within corticolimbic regions that track both positive and negative operant response outcomes. Exaggerated adaptive processing in *ex-smokers* may promote long-term smoking cessation through amplified negative valence outcome monitoring.

1. Introduction

Addiction to cigarettes presents with considerable health risks (Bartal, 2001) and induces high costs on healthcare resources (Leistikow et al., 2000). While the majority of cigarette smokers endorse the desire to quit, reported abstinence rates after twelve months are in the modest region of 5–17% (Hughes et al., 2008), with the vast majority relapsing to smoking within a week of cessation (Zhu et al., 2012). This continued use in the face of adversity is a powerful testimony to the effects of nicotine dependence, demonstrating its reinforcing effects. The reinforcing effects of nicotine (Brody et al., 2006; Domino et al., 2012; Tuesta et al., 2011), particularly in brain regions involved in motivation and reward processing (prefrontal cortex and striatum) in humans (Brody et al., 2004), are likely to be complicit in this failure to achieve abstinence. Recidivism in nicotine addiction may arise from maladaptive reactivity in fronto-striatal regions, whereby there are neural deficits when processing non-drug outcomes. For example, deprived smokers who exhibit the weakest ventral striatal responses to monetary reward are more likely to subsequently choose smoking over monetary reinforcement (Wilson et al., 2014). Similarly, fronto-striatal regions in nicotine-deprived smokers show a more pronounced response during smoking compared to monetary reward anticipation (Sweitzer et al., 2014). These disturbances in reward processing may bias the choice to smoke in the presence of alternative, non-drug reinforcement.

We have previously reported that current smokers *and* ex-smokers, compared to controls, demonstrate heightened fronto-striatal activation during gain and loss anticipation (Nestor et al., 2016a), supporting previous research findings in nicotine addiction (Martin et al., 2014). We proposed that this may represent a

* Corresponding author at: Neuropsychopharmacology Unit, Centre for Psychiatry, Imperial College London, UK.
E-mail address: liam.nestor@imperial.ac.uk (L.J. Nestor).

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sensitization by nicotine within this circuitry of smokers, that triggers the excessive "wanting" of rewards in response to non-drug cues (Berridge and Robinson, 1998). This excessive "wanting" during anticipation may also arise from a dissociation from consummation or receipt of rewards, where there is a diminished response in regions that process incentive outcomes. Diminished responses during reward outcomes may trigger reactions that are characterized by a heightened motivation during the anticipation of rewards. Indeed this dissociation has been observed in several populations. Cigarette smokers, for example, show increased ventromedial prefrontal cortex activation during loss anticipation of monetary incentives, but decreased activation in the inferior frontal gyrus during the receipt of monetary gains (Martin et al., 2014). Similar patterns of anticipation and outcome divergence have also been reported in binge-eating disorder patients, with increased fronto-striatal activation during loss and gain anticipation, but decreased activation to loss and reward notifications (Balodis et al., 2013). Pathological gamblers have also demonstrated similar differences in response to anticipation and outcomes, showing a hyper responsiveness in the ventral striatum during loss anticipation, but a hypo responsiveness during successful loss avoidance (Romanczuk-Seiferth et al., 2015). These findings, therefore, appear to suggest that in some addiction populations there is a divergence in reactivity between the anticipation and delivery of non-drug reinforcement in fronto-striatal regions, possibly due to deficits in valence outcome processing. Hyperactivity in lateral and medial prefrontal regions that sub-serve inhibitory control functioning and error monitoring have been reported in ex-smokers (Kroenke et al., 2015; Nestor et al., 2011). This may suggest that the emergence of amplified prefrontal cognitive functioning is necessary for successful abstinence in addiction. Therefore, similar adaptations that are represented by an amplified valence outcome monitoring may also promote the control over addiction-related behaviours (Garavan and Stout, 2005), even in the presence of heightened and sustained "wanting" of rewards.

Therefore, the present study set out to examine the effects of both current and previous nicotine exposure on corticolimbic correlates of operant response outcomes. Here we compared current smokers, ex-smokers and demographically matched healthy controls using a monetary incentive delay task. Specifically, we aimed to elucidate whether 1) current smokers and ex-smokers demonstrate shared or divergent reactivity compared to controls in the neural substrates of tracking positive and negative operant response outcomes, and 2) whether divergent reactivity to positive and negative outcomes distinguishes ex-smokers from current smokers.

2. Results

2.1. Demographics

The groups did not significantly differ on age, years of education, verbal intelligence, gender distribution or alcohol use history. The ex-smoker group had been abstinent from nicotine, on average, 84.8 weeks (range: 52–180 weeks) at the time of testing (see Table 1 in supplementary materials for a more detailed description of group demographics).

2.2. Behaviour

Fig. 1a shows the mean MID accuracy (% "hits") for the three conditions in the three groups. A three (Group: Control vs. Ex-smoker vs. Smoker) by three (Condition: Neutral vs. Loss vs. Gain) analysis of variance showed that there was a significant effect of condition ($F = 5.6$; df = 111, 2; $p < .01$), with greater accuracy on loss compared to neutral ($p < .05$) and gain compared to neutral ($p < .01$) trials. There was no effect of group ($F = 0.5$; df = 111, 2; $p = .6$) and no condition x group interaction ($F = 0.09$; df = 111, 4; $p = .99$). Fig. 1b shows the mean MID reaction time (milliseconds) for the three conditions in the three groups. There was a significant effect of condition ($F = 2.6$; df = 111, 2; $p < .05$), with faster reaction time on the gain compared to neutral ($p < .05$) trials only. There was no effect of group ($F = 1.4$; df = 111, 2; $p = .3$) and no condition x group interaction ($F = 0.1$; df = 111, 4; $p = 1.0$).

2.3. Functional MRI

We collapsed across conditions (gain, loss, neutral) for each of the operant response outcome types ("Hit" and "Miss") separately, as we did not detect any significant group differences on the conditions independently.

2.3.1. Positive operant response outcomes

There were five clusters that showed a group effect in the ROI mask, comprising the anterior cingulate cortex (ACC: 733 voxels; x = 4; y = 14; z = 26; $Z_{stat} = 4.71$; $p < .0001$; smoker < control, $p < 0.0001_{Bonferroni}$; ex-smoker < control, $p < 0.001_{Bonferroni}$); right amygdala (353 voxels; x = 20; y = −6; z = −20; $Z_{stat} = 3.37$; $p < .001$; smoker < control, $p < 0.001_{Bonferroni}$; smoker < ex-smoker, $p < 0.0001_{Bonferroni}$ – Fig. 2A); frontal pole (347 voxels; x = 48; y = 40; z = 20; Z_{stat}=5.38; $p < .001$; smoker < ex-smoker, $p < 0.05_{Bonferroni}$); middle frontal gyrus (MFG: 325 voxels; x = 36; y = 20; z = 40; Z_{stat}=7.23; $p < .001$; smoker < control, $p < 0.05_{Bonferroni}$;

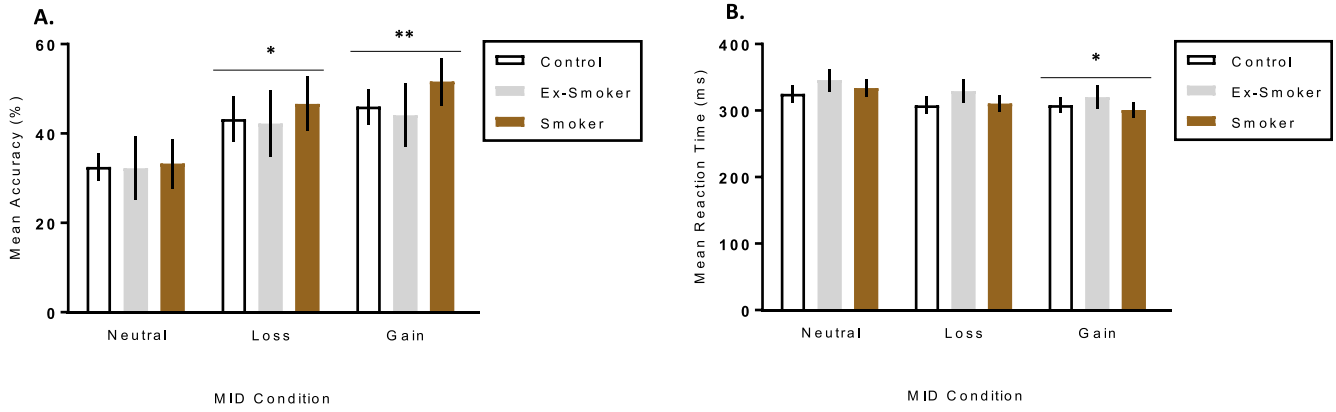

Fig. 1. MID task performance in the control, ex-smoker and current smoker groups showing A) mean percentage accuracy which was greater on the Loss compared to Neutral (*$p < .05$) and Gain compared to Neutral (**$p < .01$) trials; and B) mean reaction time which was faster on the Gain compared to Neutral (*$p < .05$) trials only. Data were analyzed using a 3 (Condition: Neutral vs. Loss vs. Gain) x 3 (Group: Control vs. Ex-smoker vs. Smoker) analysis of variance. Data are expressed as means ± SEM.