



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Duehlmeyer, L;Hester, R

Title:

Impaired learning from punishment of errors in smokers: Differences in dorsolateral prefrontal cortex and sensorimotor cortex blood-oxygen-level dependent responses

Date:

2019-01-01

Citation:

Duehlmeyer, L. & Hester, R. (2019). Impaired learning from punishment of errors in smokers: Differences in dorsolateral prefrontal cortex and sensorimotor cortex blood-oxygen-level dependent responses. *Neuroimage Clinical*, 23, <https://doi.org/10.1016/j.nicl.2019.101819>.

Persistent Link:

<https://hdl.handle.net/11343/251052>

License:

[CC BY-NC-ND](#)



Impaired learning from punishment of errors in smokers: Differences in dorsolateral prefrontal cortex and sensorimotor cortex blood-oxygen-level dependent responses

Leonie Duehlmeier*, Robert Hester

School of Psychological Sciences, University of Melbourne, 12th floor Redmond Barry Building, Parkville Campus, Melbourne, VIC 3010, Australia

ARTICLE INFO

Keywords:

Error-learning
Punishment
Nicotine
Addiction
fMRI

ABSTRACT

Cigarette smokers have shown hypersensitivity to reward and hyposensitivity to punishment, along with impairments in learning from errors. The underlying neural mechanism for this failure to adapt performance following an error, particularly when receiving negative feedback, are unclear. Smokers were hypothesized to have poorer error-learning following monetary punishment, associated with hypoactivation in the insula, dorsal anterior cingulate, and hippocampal cortical regions. Twenty-three smokers (8 females, mean age = 25.48, $SD = 4.46$) and twenty-three healthy controls (13 females, mean age = 24.83, $SD = 5.99$) were administered an associative learning task, providing monetary reward and punishment for recall performance, during fMRI data collection. Compared with controls, smokers had a lower error-correction rate and were less sensitive to punishment magnitude. Hyperactivity during recall was independent of future error correction, but smokers' successful re-encoding appeared related to higher dorsolateral prefrontal cortex activity while controls had equivalent activation for corrected and repeated errors. While controls showed higher deactivation of the sensorimotor cortex during high punishment, smokers showed higher deactivation during low punishment. The present results support smokers having poorer learning from errors and decreased attentional control associated with hyperactivity in the dorsolateral prefrontal cortex. Additionally, smokers exhibited decreased punishment sensitivity that appeared to limit their ability to adapt learning in the face of repeated negative feedback.

1. Introduction

Most societies punish undesirable behaviour, presuming this leads to reduced repetition. While greater punishment leads to greater adaptation (Hester et al., 2010; Martin, 1963), lower punishment sensitivity has been identified in substance use disorder (SUD) (Franken et al., 2010; Luijten et al., 2013; Luijten et al., 2011), with the consequences for behavioural adaptation less clear. Nicotine dependence (ND) is among the most frequent substance dependencies (SD), being the single biggest cause of preventable mortality and morbidity globally (Danaei et al., 2009; Ezzati and Lopez, 2003; Jha et al., 2008; Thorne et al., 2008). Diminished processing of punishment feedback may contribute to lack of adaptation, including disregard of negative health effects and continuation of nicotine use. Greater insight into the dysfunction of neural networks that underlie integration of punishment and learning from negative feedback could contribute to understanding problems of controlling nicotine use and relapse.

Several lines of evidence examining error-related activity in

response inhibition tasks identified error-processing impairments in smokers. Smokers made more errors, coupled with reduced brain activation in the superior frontal gyrus and superior temporal gyrus (Nestor et al., 2011) and showed lower error-related activation in the dorsal anterior cingulate cortex (dACC) (De Ruiter et al., 2012). Ex-smokers showed increased error-related activation compared to both smokers and controls in the ACC, insula, and parahippocampal gyri. Error-related hyperactivity of ex-smokers is difficult to interpret but suggests that such increases may be associated with an increased likelihood of ceasing smoking, or that error-processing deficits observed in smokers are potentially reversible following abstinence.

The high temporal resolution of EEG has fostered a theory that smokers initially detect errors, but do not act on them. Cognitive paradigms administered to smokers to examine executive function have identified lower levels of activity on key neural markers of performance monitoring such as error-related negativity (ERN) and error-positivity (Pe). Hypoactive neural responses were associated with reduced post-error adaptation of behaviour when smoking cues were present (Luijten

* Corresponding author.

E-mail addresses: lduehlmeier@student.unimelb.edu.au (L. Duehlmeier), hesterr@unimelb.edu.au (R. Hester).

et al., 2011). While ERN is thought to reflect initial automatic error detection (Bernstein et al., 1995) and to be generated in the ACC (Gehring and Knight, 2000; Herrmann et al., 2004; Miltner et al., 2003; Ridderinkhof, 2004; Van Veen and Carter, 2002), the Pe is argued to reflect error awareness, their conscious evaluation and motivational significance (Overbeek et al., 2005; Ridderinkhof et al., 2009; Wessel et al., 2011). Another EEG experiment with smokers, assessing error-processing without smoking cues, resulted in equivalent task performance and ERN amplitudes (Franken et al., 2010). However, Pe amplitudes were lower than in controls. The combination of results suggests that error detection may be intact in smokers, when attention is not compromised through smoking cue exposure. More specifically, initial error detection may be intact, but conscious evaluation impaired, contributing to maladaptive learning.

The above described EEG experiments investigated effects of negative feedback (e.g. a – sign) on error processing and learning. However, punishment that evokes negative consequences, for example the deduction of money may be processed differently than negative feedback without consequences and alter its influence on learning. The high spatial resolution of fMRI has fostered theories on specific brain regions in punishment processing. Two monetary punishment magnitudes were applied to healthy participants to assess punishment sensitivity and its effect on associative learning (Hester et al., 2010). Hyperactivation in the dACC predicted future learning, while hyperactivation in the insula predicted learning from the most aversive outcomes. The ACC and insula have previously been found sensitive to increases of punishment magnitude (Seymour et al., 2007; Taylor et al., 2006) and insula dysfunctions appear consistently in studies examining ND (Forget et al., 2010; Naqvi et al., 2014; Scott and Hiroi, 2011; Sutherland et al., 2013), associated with impairment in distinct aspects of error processing. Smokers were found to be more sensitive to monetary reward magnitude, less sensitive to punishment magnitude and equally indifferent to avoidance of punishment compared to receiving reward in associative learning tasks (Duehlmeyer et al., 2018). The independent evidence for impaired error processing and punishment hyposensitivity in smokers emphasize the importance of examining behavioural adaptation following punishment of errors, particularly given its relevance to adaptive behaviour change.

To assess neural responses to varying punishment magnitudes and their relationship to learning from errors, we administered an associative learning task (Hester et al., 2010) to smokers and matched controls. Smokers feedback network is expected to be impaired, leading to reduced error-correction rates, particularly in the high punishment condition. Learning from punished errors was previously associated with co-activation of insula, ACC and hippocampal regions. Co-activation of ACC and insula is consistent with the hypothesis that these regions are detecting the significance of an error and then signalling to distal cortical regions critical to task performance, in this task the hippocampus, for increased processing to avoid further punishment. Given previous evidence of insula hypoactivity in smokers, we hypothesized that lower levels of error-correction in smokers would be associated with diminished activity in this region, particularly during the higher punishment (50¢) condition.

2. Material and methods

2.1. Subjects

23 dependent cigarette smokers (8 females; mean age = 25.48 years; range = 19–36 years; years of education = 14.74) and 23 controls (13 females, mean age = 24.74 years; range = 19–40 years; years of education = 14.61) participated in the experiment. Participants were recruited via advertisements at the University of Melbourne and a community website. All participants provided written informed consent, which was approved by Human Ethics Committee of The University of Melbourne and the Royal

Children's Hospital. Participants were classified as dependent smokers if they smoked at least fifteen cigarettes daily, while controls had smoked less than 6 cigarettes in their lifetime. Smokers had been abstinent for a minimum of 3 h before initiation of the experiment. This was confirmed by self-report of last smoked cigarette and breath carbon monoxide (CO) measure. Exclusion criteria for both groups consisted of a history of neurological or psychiatric disorders, current use of psychotropic medication, and current SD (other than nicotine for the smoking group). Groups did not significantly differ on variables of age ($t(44) = 0.475$, $p = .637$, $d = 0.123$) or education ($t(44) = 0.184$, $p = .855$, $d = 0.093$). Fagerstrom Test for Nicotine Dependence (FTND) indicated an average score of 4.7 for smokers, representing a moderate dependence (Heatherton et al., 1991). Self-reported alcohol use was significantly higher in smokers as measured with the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993) (controls = 2, smokers = 9; $t(44) = -6.420$, $p \leq .001$, $d = 1.789$). AUDIT scores, smokers CO, FTND scores, craving as measured with the QSU-brief (Cox et al., 2001), and gender did not correlate with any with dependent variables of interest and were therefore not used as covariates in subsequent analyses.

2.2. Study design

In this spatial paired-associates task, participants experienced learning trials wherein they were required to learn a two-digit number associated with a spatial location within the visual field (Fig. 1). The opportunity to encode the location-number association was followed by two rounds of recall probes, wherein spatial locations were highlighted for number recall. All aspects of stimulus delivery and response recording were controlled by E-Prime software (version 2.0, Psychology Software Tools, Inc. Pittsburgh, PA), running on a Windows PC. The task began with an encoding phase. First, eight gray squares on black background were presented (1 s). The locations of squares were selected in a quasi-random fashion from an 8×8 matrix, with two locations randomly chosen from each of the four quadrants of the display. Each location in turn had superimposed upon it a two-digit number (1.5 s) (encoding epoch), each followed by an interstimulus interval (ISI) (1 s). Each number's digits consisted of 1, 2, 3, or 4. Participants identified the number using a pair of response boxes (Current Designs), holding one response box in each hand. Each response box had two buttons aligned horizontally. Participants could respond with 1 or 2 with the left hand and 3 or 4 with the right hand over a response period of 3 s. Two-digit numbers were used to reduce the probability of guessing the correct answer to 6%. Following the encoding phase, a series of recall trials was presented. One of the eight locations was highlighted in yellow, cueing participants to respond with the associated number-location pair. Participants were required to respond within 3 s, after which a variable ISI was presented (2–4 s). During the ISI, the location remained highlighted by a yellow border. Feedback (2 s) was then provided for validity of the response and magnitude of reward/punishment. The location square turned blue to indicate a correct response or red to indicate an incorrect response. A photo of an Australian 5¢ or 50¢ coin was superimposed over the colored background. Correct responses resulted in the gain of 5¢ or 50¢, and incorrect responses in the loss of 5¢ or 50¢. Feedback magnitude was randomly assigned to each location, did not change throughout the task, and was modelled to ensure equal amounts of 5¢ or 50¢ feedback for correct trials and error trials (separately). Once assigned, feedback magnitude of a location was fixed for round 2 recall trials, ensuring that round 1 feedback predicted future reward and punishment value of a location. Each block's gains and losses were added to an initial credit of AU\$10. Following the feedback epoch, a second ISI was presented (2–4 s), during which the target square remained colored (blue or red, depending on accuracy). Then, the correct two-digit number was presented on the colored location, allowing participants to re-encode the correct answer. When each of the eight locations was highlighted once, recall round 1 was

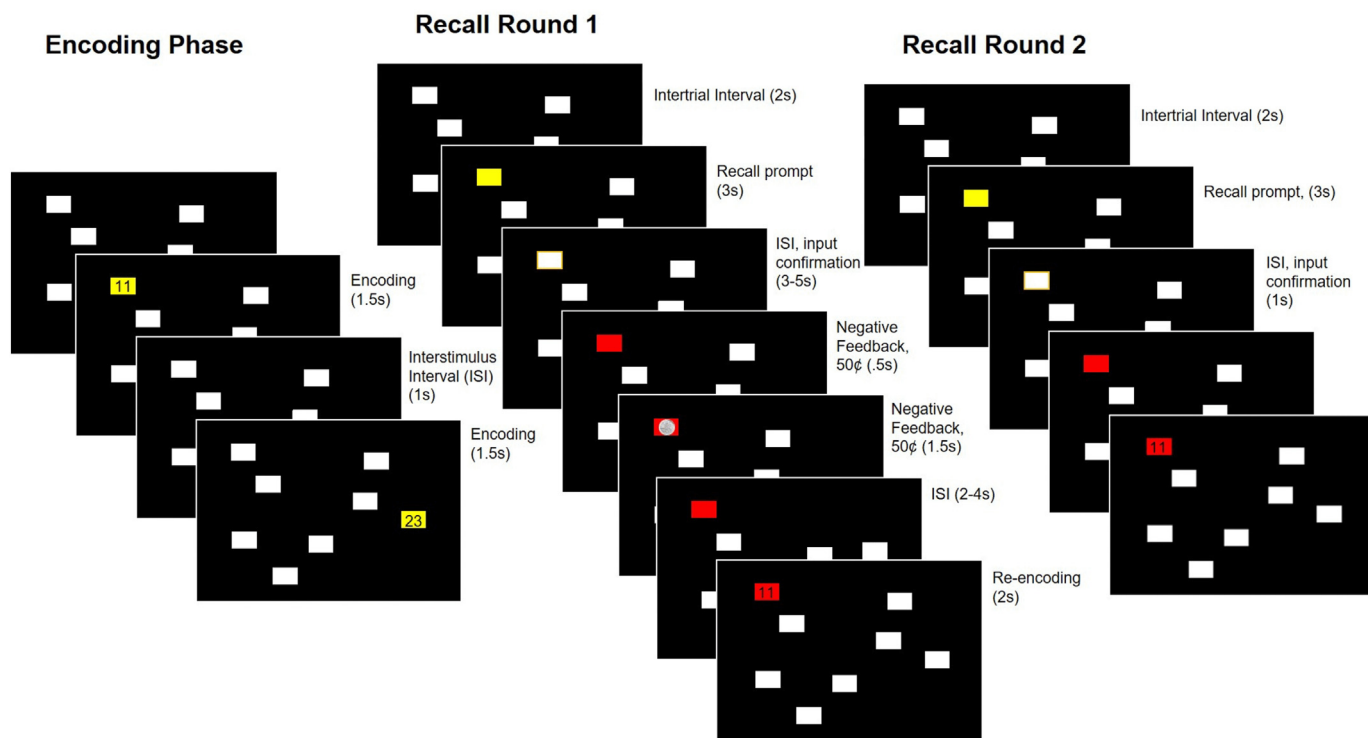


Fig. 1. Divergent Value Learning from Errors task (divVLFE), visualized by screen representations of encoding, recall, and re-encoding events of the task. Each block of trials began with an encoding phase that presented the two-digit number associated with each location (1.5 s) and an intertrial interval display (1 s). All eight number–location associations were presented once during the encoding phase and were immediately followed by the recall phase. A single trial in the recall phase began by highlighting a location in yellow to cue the participant to respond with the two-digit number they associated with the location. Following a variable interstimulus delay, feedback was provided that consisted of presenting the accuracy of the response (red background for an error, blue for correct) and the magnitude of the reward/punishment (an Australian 5¢ or 50¢ coin). Following a second variable interstimulus delay, participants were presented with the accurate number associated with the location to enable encoding of the correct response (re-encoding epoch), regardless of prior recall accuracy. A second round of recall is administered to determine repetition or correction of errors from Recall Round 1.

concluded. Subsequently, each square was highlighted in a different pseudorandom order, constituting recall round 2. Recall trials were pseudorandomly ordered across the two rounds of presentation for a single task block to ensure that the interval between two presentations of any trial was 7–9 trials. The order of locations probed for both encoding and recall trials was consistent across and within blocks. Each block lasted 280 s. Nine blocks of encoding/recall cycle were administered to each participant, with each block involving a different array of number–location pairs. This provided 72 recall round 1 trials within which we could examine feedback and subsequent performance. No location in the array was used more than once throughout the nine blocks, and the two-digit numbers were not repeated on consecutive blocks.

2.3. fMRI data acquisition

Functional MR images were acquired at the Royal Children's Hospital, Melbourne, using a whole-body 3 Tesla Siemens TrioTim with a gradient-echo echoplanar imaging (EPI) sequence (TR = 2 s; TE = 35 ms; flip angle = 90°; 32 contiguous slices of 4 mm thickness, no gap, 64 × 64 matrix, FOV = 230 mm, oblique orientation (through chin)). Lateral padding was used to stabilize the head. Each functional run began with three later discarded volume acquisitions to allow for steady-state tissue magnetization. Nine functional runs per participant were performed, with 140 EPI volumes per run. To localize the task-related physiological changes, activation data were registered to high-resolution T1-weighted isotropic (1mm³) structural MPRAGE images.

2.4. Data analysis

A two-way repeated measures ANOVAs examining recall accuracy performance assessed interactions between the variables of group (controls, smokers) and magnitude (5¢, 50¢). To elucidate differences between groups in sensitivity to positive and negative feedback, a three-way repeated measures ANOVA investigated interactions between the variables of group (controls, smokers), magnitude (5¢, 50¢), and feedback type (reward, punishment).

All analyses were conducted using AFNI software (<http://afni.nimh.nih.gov/afni/>) (Cox et al., 2001) and the Statistical Package for Social Sciences Software (SPSS 23.0) (Norusis, 1990). Following image reconstruction, time-series data were time-shifted using Fourier interpolation to remove differences in slice acquisition times. Motion was corrected using three-dimensional volume registration (least-squares alignment of three translational and three rotational parameters) with the third volume from the first run as a base. Functional data was aligned to corresponding anatomical data and warped to standard MNI space. Activation outside the brain was removed using edge detection techniques. Volumes were blurred using a 4.1 mm full-width half max filter, each voxel was then scaled to a mean of 100 and values over 200 were clipped. Separate hemodynamic response functions at 2 s temporal resolution were calculated using deconvolution techniques for corrected errors and repeated errors. TR pairs were censored where the Euclidian Norm of the motion derivative exceeded 1.0.

Response functions for all regressors' events were included to model the activation related to feedback and re-encoding for correct trials, the recall epoch for errors (before feedback), second round trials, and other inconsequential task events (e.g., instruction screens), to avoid contamination of the baseline and event related activation estimates. These

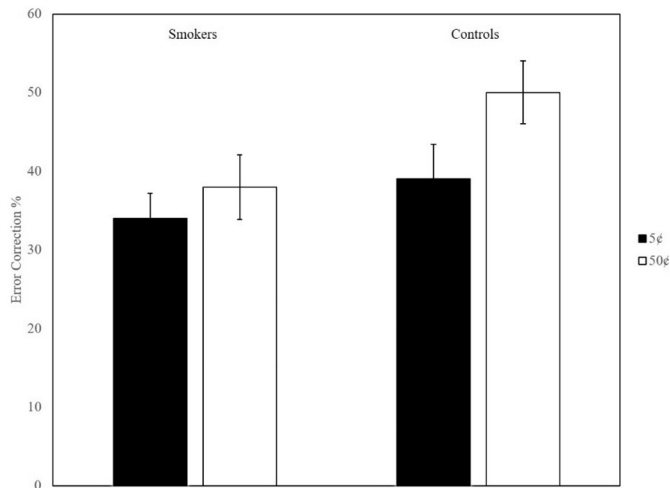


Fig. 2. Error-correction rates for smokers and controls of locations punished with 5¢ and 50¢.

events were not subjected to further analysis. The baseline estimate was the mean activation recorded during the three ISIs per trial, such that activation observed during recall, feedback or re-encoding represented activation over and above that required for the ongoing trial epoch activation. This epoch consisted of viewing the eight gray locations on the screen while waiting for the next memory probe, thus having similar stimulus and memory load requirements as the events of interest. The absence of collinearity between regressors within AFNI X-matrices was confirmed during deconvolution using `xmat_tool.py`. Event-related map voxels for each regressor of interest were extracted, resampled to anatomical data resolution (1 mm³), and masked using a group-averaged EPI mask dataset.

Behavioural data from each participant was used to categorize the recall events into a series of different categories: successful responses, corrected 5¢, corrected 50¢, repeated 5¢, and repeated 50¢ errors. Errors were classified in this way according to responses made on the subsequent presentation of the same number-location pair (Fig. 1). Errors in the second round of presentations could therefore not be included in this analysis because they did not precede another attempt at recall.

Beta weights for correct and incorrect recall trials are calculated again the baseline, where beta weights are equivalent to percent-signal-change as the time-series has been scaled to 100. In other words, group activation maps for the two event types (correct response, round 1; error response, round 1) were determined with one-sample *t*-tests against the null hypothesis of zero event-related activation changes (i.e., change relative to baseline). The purpose of the maps was enabling the contrasting of error-performance, condition-specific effects of the four conditions (errors receiving a 5¢ penalty that were correctly recalled in recall round 2 (corrected 5¢ errors), corrected 50¢ errors; errors receiving a 5¢ penalty that were again incorrectly recalled (repeated 5¢ errors), and repeated 50¢ errors) in the error activity-related map. Significant voxels passed a voxelwise statistical threshold ($t = 4.28$, $p \leq .001$) and were required to be part of a larger 144 μ l cluster of contiguous significant voxels. The combination of probability and cluster thresholding was used to maximize the power of the statistical test while holding the likelihood of false positives to a minimum. Simulation using the 3D ClustSim function in AFNI (AFNI Ver 16.2.11) and an uncorrected voxelwise threshold $p = .0001$, indicated a minimum cluster size, given a threshold of $p = .01$. The activation clusters from whole-brain analyses of errors during either the recall, feedback or re-encoding epoch were utilized for separate epoch-specific regions of interest (ROI) analyses. Significant differences between smokers and controls in the somatosensory cortex during the feedback

epoch, evoked interest in the activity of the somatosensory cortex during recall. ROI analyses were conducted applying a group-averaged mask derived from significant activation during feedback presentation on recall events.

The events of interest for the group epoch maps were the errors from recall round 1. A second analysis was then performed, which entered additional regressors into the deconvolution process to separately estimate activation related to each of the four types of error-related events, relative to baseline. The mean activation for clusters in the separate epoch-specific group maps (recall, feedback, re-encoding) was then calculated for the purposes of a functionally derived ROI analysis, deriving mean activation levels for corrected 5¢, corrected 50¢, repeated 5¢, and repeated 50¢ errors. These estimates were compared using a two-way repeated measures ANOVA, corrected for the number of ROIs via a modified Bonferroni procedure for multiple comparisons (Keppel, 1991). The two-way repeated measure ANOVAs consisted of the variables of group (controls, smokers) X future performance (corrected error, repeated error) and group (controls, smokers) X magnitude (5¢, 50¢).

3. Results

3.1. Behavioural results

A 3 factor mixed ANOVA examining the influence of feedback magnitude (5¢, 50¢), feedback type (reward, punishment) and group on post-feedback (round 2) recall accuracy performance found a significant main effect of feedback magnitude (5¢, 50¢), $F(1,44) = 10.733$, $p = .002$, $\eta_p^2 = 0.196$. Error correction was better in the 50¢ condition (43%) compared to the 5¢ condition (35.5%) (Fig. 2). There were no significant differences between smokers and controls in second round recall rate (main effect of group $F(1,44) = 1.900$, $p = .175$, $\eta_p^2 = 0.041$) and the interaction between group (controls, smokers) and magnitude (5¢, 50¢) ($F(1,44) = 3.208$, $p = .080$, $\eta_p^2 = 0.068$) was also non-significant. The latter non-significant interaction did however suggest a trend towards relatively more frequent error correction of high punished locations versus low punished locations in controls (50¢: controls = 49%, smokers, 37%; 5¢: controls = 37%, smokers = 34%). The three-way interaction between magnitude (5¢, 50¢), feedback type (reward, punishment) and group (controls, smokers) was significant, $F(1,44) = 6.825$, $p = .012$, $\eta_p^2 = 0.134$. Controls appeared more sensitive to learning from small rewards and large punishments than smokers, showing better retention performance in the +5¢ condition and higher error-correction rates in the -50¢ condition.

3.2. MRI BOLD activation

Two-way repeated measures ANOVAs were used to examine changes in BOLD response related to group (controls, smokers) and future performance (corrected error, repeated error), or monetary feedback magnitude (5¢, 50¢). The analysis examined significant clusters of the epoch specific group activation maps. The group map for error-related activity contained twenty-one significant clusters for the recall epoch, sixteen for the feedback epoch, and fifteen for the re-encoding epoch. A significant relationship was identified during the recall epoch, with a main effect of group (controls, smokers) found in the right dorsolateral prefrontal cortex (dlPFC) ($F = 11.52$, $p \leq .001$, $\eta_p^2 = 0.207$), with greater activation in smokers compared to controls (Fig. 4). The centre of mass for this cluster was MNI coordinates $x = 34$, $y = 42$, $z = 31$ (see Fig. 3).

Additionally, a significant interaction between group (controls, smokers) and future performance (corrected errors, repeated errors) emerged in the right dlPFC during the re-encoding epoch, $F = 4.123$, $p = .048$, $\eta_p^2 = 0.086$. The centre of mass of this cluster laid posterior of the dlPFC cluster found in the recall epoch, at MNI coordinates $x = 35$,

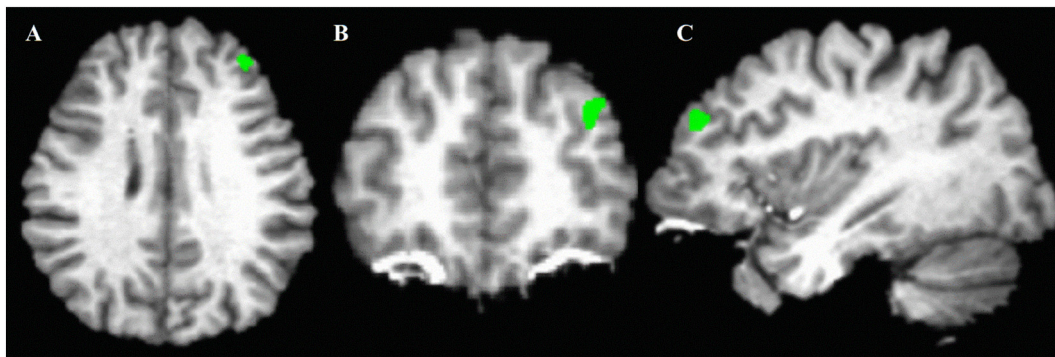


Fig. 3. Three-dimensional rendering from the axial, coronal and sagittal perspective of the right dorsolateral prefrontal cortex (MNI coordinates: $x = 34, y = 42, z = 31$), activated during the recall epoch. The column graphs have been defined by averages of beta weight activation on the second-level map. The group difference is significant irrespective of recall accuracy.

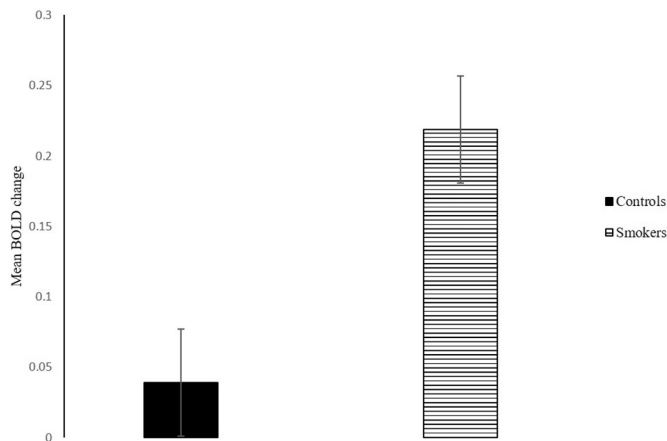


Fig. 4. Estimates of mean percentage change in BOLD activation in the right dorsolateral prefrontal cortex during the recall epoch for controls and smokers. The column graphs have been defined by averages of beta weight activation on the second-level map. The group difference is significant irrespective of recall accuracy.

$y = 29, z = 32$ (Fig. 5). Smokers nearly tripled activation during corrected versus repeated errors (14.5 and 5), while controls' activation was similar across conditions (9.6 and 10.3) (Fig. 6).

In the feedback epoch, a significant interaction between group (controls, smokers) and magnitude (5¢, 50¢) emerged in the left sensorimotor cortex, $F = 4.812, p = .034, \eta_p^2 = 0.099$ (Fig. 7). Smokers showed increased deactivation during the 5¢ condition, while controls showed increased deactivation during the 50¢ condition (Fig. 8). ROI analyses of the sensorimotor cortex in the recall period showed

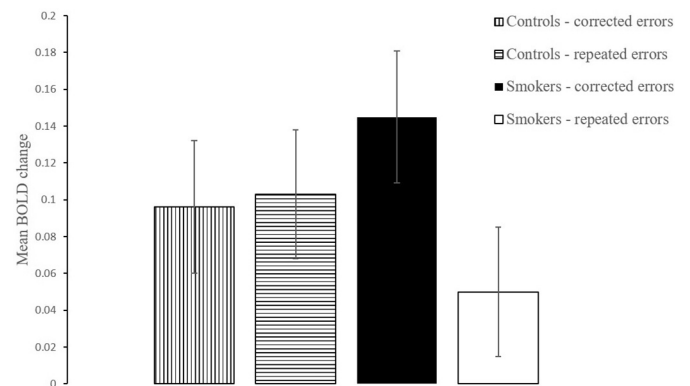


Fig. 6. Estimates of mean percentage change in BOLD activation in the right dorsolateral prefrontal cortex during the re-encoding epoch for corrected and repeated errors. The column graphs have been defined by averages of beta weight activation on the second-level map. The interaction between group (controls, smokers) and future error correction (corrected errors, repeated errors) is significant.

equivalent activation above baseline in smokers and controls, indicating that the observed differences in deactivation were specific to feedback presentation. Brain regions that had been included in the hypotheses (ACC, insula, hippocampus) did not show significant interactions between task conditions but showed significant differences in activation compared with baseline (Table 1).

4. Discussion

Due to reduced punishment sensitivity and error processing,

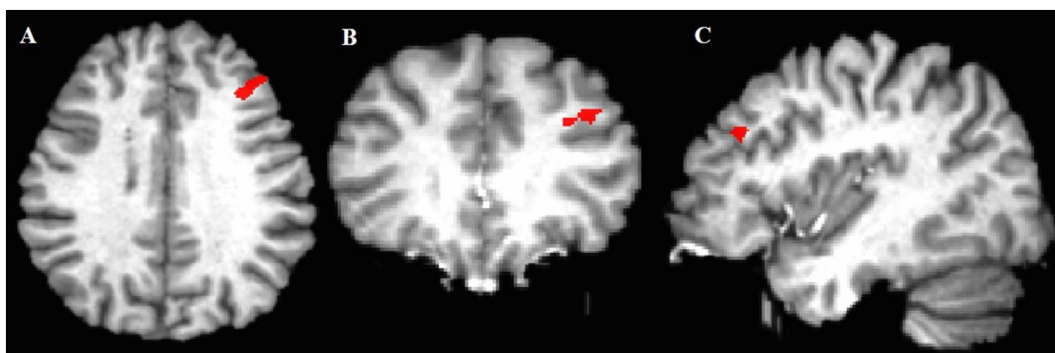


Fig. 5. Three-dimensional rendering from the axial (A), coronal (B) and sagittal (C) perspective of the right dorsolateral prefrontal cortex (MNI coordinates: $x = 35, y = 29, z = 32$), activated during the re-encoding epoch. The column graphs have been defined by averages of beta weight activation on the second-level map. The interaction between group (controls, smokers) and future error correction (corrected errors, repeated errors) is significant.

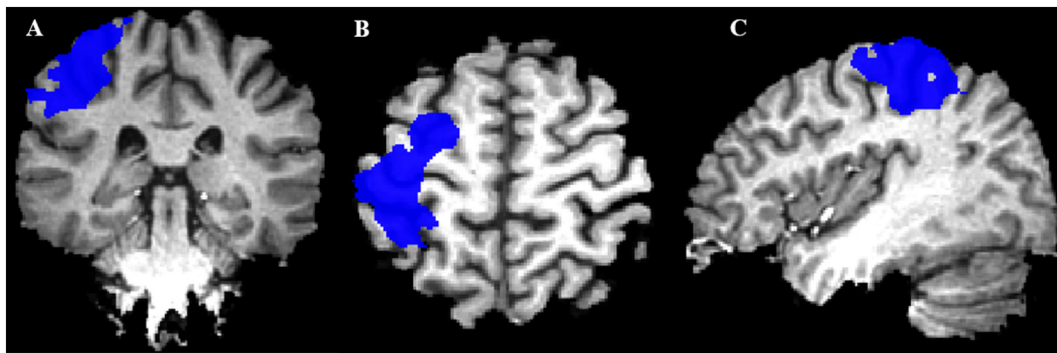


Fig. 7. Three-dimensional rendering from the axial, coronal and sagittal perspective of the left sensorimotor cortex (MNI coordinates: $x = -36, y = -29, z = 54$), deactivated during the feedback epoch. The column graphs have been defined by averages of beta weight activation on the second-level map. The interaction between group (controls, smokers) and negative feedback magnitude ($-5\text{¢}, -50\text{¢}$) is significant stimulates of mean percentage change in BOLD activation in the left sensorimotor cortex during the feedback epoch. The column graphs have been defined by averages of beta weight activation on the second-level map. The interaction between group (controls, smokers) and negative feedback magnitude ($-5\text{¢}, -50\text{¢}$) is significant.

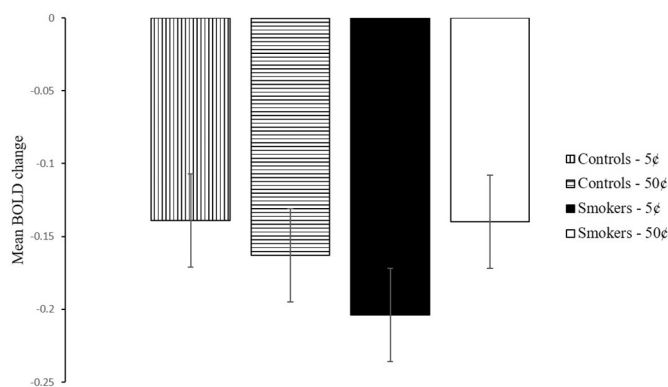


Fig. 8. Stimulates of mean percentage change in BOLD activation in the left sensorimotor cortex during the feedback epoch. The column graphs have been defined by averages of beta weight activation on the second-level map. The interaction between group (controls, smokers) and negative feedback magnitude ($-5\text{¢}, -50\text{¢}$) is significant.

learning from errors was expected to be impaired in smokers, leading to reduced error-correction, particularly under high monetary punishment conditions. Consistent with this hypothesis, smokers corrected their recall errors less than controls, with a significantly lower differentiation between high and low punishment conditions in their error-correction performance. While groups did not differ in activation of brain regions previously associated with performance monitoring, activity in

additional regions, dlPFC and sensorimotor cortex, differed significantly. The dlPFC was hyperactivated in smokers, both during the recall and re-encoding epochs when number-location associations were accurately recalled on the next trial. When number-location pairs were incorrectly recalled in the next trial, smokers showed a lower level of activation in the dlPFC compared with controls.

Successful performance in the LFE requires working memory (WM). According to the multicomponent model of WM, WM consists of at least three structural components: two memory-related storage components and an attentional-control component (Baddeley, 2012; Baddeley and Hitch, 1974). Individual differences in WM have been related to the attentional-control component (Engle and Kane, 2004) and various subcomponents of attentional-control in WM have activated the dlPFC (Esposito et al., 1998; Owen et al., 2005). Of these subcomponents, several are relevant for successful LFE task performance: Manipulation of task-relevant information may support encoding by grouping number-location pairs, for example, memorizing a formation comprised of all numbers in the twenties; Maintaining this representation following the encoding epoch and updating it during re-encoding is critical to subsequent recall performance; Attentional-control is required for feedback-monitoring and incorporation; Upon recall prompt, the previously inserted or presented number may be particularly salient in WM, rendering successful inhibition of inserting one of those numbers and decision-making crucial for accurate recall. Smokers showed impaired response inhibition and punishment hyposensitivity, with hyperactivation in the dlPFC when inhibiting responses in a rewarding and neutral but not in a punishment condition (Luijten et al., 2013).

Table 1

Functionally defined regions of interest resulting from group maps of error-related activity. Presented are only regions that had been included in the hypotheses and that were significantly different to baseline.

Brain region	Volume (μl)	MNI coordinates			Distance to Focus point (mm)	Corrected > Repeated Errors
		x	y	z		
Recall						
L anterior cingulate	51,478	-0	43	25	2	No, deactivation
R insula	7003	44	30	-5	4	Yes, deactivation
R insula	176	29	13	-20	0	No, deactivation
L hippocampus	815	-26	-7	-20	0	No, deactivation
Feedback						
L anterior cingulate	12,454	-3	31	-1	0	Yes, deactivation
R Insula	1816	29	10	5	4	Yes, activity
L hippocampus	448	-13	-20	-22	4	Yes, deactivation
Re-encoding						
R anterior cingulate	2281	24	36	9	7	Yes, activity
Insula	1606	-39	15	14	3	Yes, activity

This suggests greater demand for dlPFC activation by smokers to execute response inhibition when anticipating reward but lower demand when expecting punishment. These findings are consistent with the behavioural results on feedback sensitivity and suggest that response inhibition may contribute to lower error-correction. Smokers' dlPFC hyperactivation during the re-encoding of corrected errors may also suggest a greater need for attentional control, or reduced efficiency in translating dlPFC activation into attentional control. dlPFC activation appears more relevant for smokers' error-correction as re-encoding of corrected-errors was preceded by threefold higher BOLD response compared with repeated errors. In contrast, the control groups' dlPFC activation was approximately equivalent for corrected and repeated errors. However, smokers' dlPFC hyperactivation during the recall phase did not appear to influence recall performance, with lower recall rates in comparison with controls.

Smokers reduced distinction between correcting high and low punished errors, suggests a reduction in their sensitivity to punishment. The lower sensitivity to punishment in error-correction was associated with an interaction effect between punishment magnitude and group in a large cluster, spanning somatosensory cortex and motor cortex. These cortical areas constitute the sensorimotor cortex, which is responsible for the integration of a wide range of sensory and motor information, for example in speech articulation (Bouchard et al., 2013). Controls showed greater deactivation during high punishment, whereas smokers showed greater deactivation during low punishment (Fig. 6). Two meta-analyses including 11 and 44 studies, respectively, identified the somatosensory cortex and motor cortex to be among the most frequently observed loci in drug-cue reactivity and their activation to correlate with clinical covariates, such as craving (Engelmann et al., 2012; Yalachkov et al., 2012). The present research suggests the sensorimotor cortex may also be engaged for other feedback-related stimuli in a substance using population. Merged data of cocaine dependent individuals and controls showed an effect of punishment magnitude in the sensorimotor cortex, with less activity for small losses, compared with medium and large losses. Controls alone exhibited the least activity for medium losses, implying that the low response to small losses was driven by cocaine dependent individuals (Rose et al., 2017). While these results initially imply a more appropriate comparative response to low punishments in cocaine dependent individuals, they may reflect overall lower punishment sensitivity. It is likely that cocaine dependent individuals exhibited little distinction between the punishment magnitudes, as reflected in the current behavioural and imaging results. Chronic cannabis users also demonstrate greater somatosensory cortex activation when anticipating gain versus loss, compared with controls (Filbey et al., 2013). A reaction to feedback in the sensorimotor cortex may reference the button press as motivated action. Consistent with the notion of deactivation serving as sensorimotor inhibition towards punishment, smokers and controls showed positive activation in the cluster during recall at equivalent levels (Fig. 8). Deactivation of the motor cortex also appears essential for response inhibition (Stevens et al., 2007). This can be life-saving when confronted with threat. For example, inhibiting the motor command for a footstep onto a snake. Decreased sensorimotor cortex deactivation for high punishments in smokers corresponds to the behavioural that shows reduced distinction between low and high punishment. Additionally, impaired inhibition of button press during the high punishment condition supports the notion that impaired response inhibition during recall contributed to smokers' lower error-correction rate via insertion of salient numbers from previous trials.

The cross-sectional design of the study limits conclusions on causality between learning from punishment and dependent smoking. The level of change over time in reward and punishment sensitivity in smokers remains of interest. The absence of significant differences in neural activity between groups in regions previously identified as critical to learning from errors (during the LFE and others), highlights limitations of examining relative levels of functional activity,

particularly during errors (52). While the level of activation may have been similar between groups, communication between regions may be different. Task-based functional connectivity could elucidate dynamic interactions.

In conclusion, the presented findings support previous literature in demonstrating hypersensitivity to reward and hyposensitivity to punishment in smokers. The reduced sensitivity to punishment appeared to contribute to diminished learning from errors. Smokers showed hyperactivation in the right dlPFC during both recall and re-encoding of number-location pairs that were subsequently corrected. Hyperactivation appears to be associated with increased need for attentional control during recall and re-encoding. Monetary punishment was also associated with deactivation in the sensorimotor cortex, potentially linked to the inhibition of motor responses (button presses) associated with monetary loss. Controls exhibited higher deactivation of the sensorimotor cortex during presentation of higher punishment, while smokers showed higher deactivation during presentation of low punishments. These results demonstrate variations in reward and punishment sensitivity extend into other cognitive domains of learning and risk aversion, suggesting the potential to contribute to more established patterns of behaviour seen in substance dependence.

Acknowledgements

This study was supported by USPHS grant from the National Institute on Drug Abuse [grant number DA01865-01], Australian Research Council Future Fellowship [grant number (RH) FT110100088]. Neither funding agency had any further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Dr. Bianca Levis assisted in collecting a subset of the control data.

Disclosures

Ms. Duehlmeier and Dr. Hester reported no biomedical financial interests or potential conflicts of interest.

References

- Baddeley, A., 2012. Working memory: theories, models, and controversies. *Annu. Rev. Psychol.* 63, 1–29. <https://doi.org/10.1146/annurev-psych-120710-100422>.
- Baddeley, A.D., Hitch, G., 1974. Working memory. *Psychol. Learn. Motiv. Adv. Res. theory.* [https://doi.org/10.1016/S0079-7421\(08\)60452-1](https://doi.org/10.1016/S0079-7421(08)60452-1).
- Bernstein, P.S., Scheffers, M.K., Coles, M.G.H., 1995. "Where did I go wrong?" a psychophysiological analysis of error detection. *J. Exp. Psychol. Hum. Percept. Perform.* 21, 1312–1322. <https://doi.org/10.1037/0096-1523.21.6.1312>.
- Bouchard, K., Mesgarani, N., Johnson, K., Chang, E., 2013. Functional organization of human sensorimotor cortex for speech articulation. *Nature.* <https://doi.org/10.1038/nature11911>.
- Cox, L., Tiffany, S., Christen, A., 2001. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob. Res.* 3, 7–16.
- Danaei, G., Ding, E., Mozaffarian, D., Taylor, B., 2009. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS med.* 6, e1000058.
- De Ruiter, M.B., Oosterlaan, J., Veltman, D.J., Van Den Brink, W., Goudriaan, A.E., 2012. Similar hyposensitiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend.* 121, 81–89. <https://doi.org/10.1016/j.drugalcdep.2011.08.010>.
- Duehlmeier, L., Levis, B., Hester, R., 2018. Effects of reward and punishment on learning from errors in smokers. *Drug Alcohol Depend.* 188, 32–38. <https://doi.org/10.1016/j.drugalcdep.2018.03.028>.
- Engelmann, J.M., Versace, F., Robinson, J.D., Minnix, J.A., Lam, C.Y., Cui, Y., Brown, V.L., Cinciripini, P.M., 2012. Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *Neuroimage* 60, 252–262. <https://doi.org/10.1016/j.neuroimage.2011.12.024>.
- Engle, R.W., Kane, M.J., 2004. Executive attention, working memory capacity, and a two-factor theory of cognitive control.
- Espósito, M.D., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K., Lease, J., 1998. Functional MRI studies of spatial and nonspatial working memory.
- Ezzati, M., Lopez, A., 2003. Estimates of global mortality attributable to smoking in 2000. *Lancet* 362, 847–852.
- Filbey, F.M., Dunlop, J., Myers, U.S., 2013. Neural effects of positive and negative

- incentives during marijuana withdrawal. *PLoS One*. <https://doi.org/10.1371/journal.pone.0061470>.
- Forget, B., Pushparaj, A., Le Foll, B., 2010. Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. *Biol. Psychiatry* 68, 265–271. <https://doi.org/10.1016/j.biopsych.2010.01.029>.
- Franken, I.H.A., van Strien, J.W., Kuijpers, I., 2010. Evidence for a deficit in the salience attribution to errors in smokers. *Drug Alcohol Depend.* 106, 181–185. <https://doi.org/10.1016/j.drugalcdep.2009.08.014>.
- Gehring, W.J., Knight, R.T., 2000. Prefrontal-cingulate interactions in action monitoring. *Nat. Neurosci.* 3, 516–520. <https://doi.org/10.1038/74899>.
- Heatherton, T., Kozlowski, L., Frecker, R., 1991. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire.
- Herrmann, M.J., R?mmler, J., Ehlis, A.C., Heidrich, A., Fallgatter, A.J., 2004. Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). *Cogn. Brain Res.* 20, 294–299. <https://doi.org/10.1016/j.cogbrainres.2004.02.013>.
- Hester, R., Murphy, K., Brown, F.L., Skilleter, A.J., 2010. Punishing an error improves learning: the influence of punishment magnitude on error-related neural activity and subsequent learning. *J. Neurosci.* 30, 15600–15607. <https://doi.org/10.1523/JNEUROSCI.2565-10.2010>.
- Jha, P., Jacob, B., Gajalakshmi, V., Gupta, P., 2008. A nationally representative case–control study of smoking and death in India. *Engl. J.* 358, 1137–1147.
- Keppel, G., 1991. Design and analysis: a researcher's handbook. autor:Keppel - Google Scholar [WWW Document] In: *Des. Anal. A Res. Handb.*
- Luijten, M., Van Meel, C.S., Franken, I.H.A., 2011. Diminished error processing in smokers during smoking cue exposure. *Pharmacol. Biochem. Behav.* 97, 514–520. <https://doi.org/10.1016/j.pbb.2010.10.012>.
- Luijten, M., O'Connor, D.A., Rossiter, S., Franken, I.H.A., Hester, R., 2013. Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers. *Addiction* 108, 1969–1978. <https://doi.org/10.1111/add.12276>.
- Martin, B., 1963. Reward and punishment associated with the same goal response: a factor in the learning of motives. *Psychol. Bull.* 60, 441.
- Miltner, W.H.R., Lemke, U., Weiss, T., Holroyd, C., Scheffers, M.K., Coles, M.G.H., 2003. Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biol. Psychol.* 64, 157–166. [https://doi.org/10.1016/S0301-0511\(03\)00107-8](https://doi.org/10.1016/S0301-0511(03)00107-8).
- Naqvi, N.H., Gazznick, N., Tranel, D., Bechara, A., 2014. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. *Ann. N. Y. Acad. Sci.* 1316, 53–70. <https://doi.org/10.1111/nyas.12415>.
- Nestor, L., McCabe, E., Jones, J., Clancy, L., Garavan, H., 2011. 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*. <https://doi.org/10.1016/j.neuroimage.2011.03.054>.
- Norusis, M., 1990. *SPSS-X Advanced Statistics Guide*.
- Overbeek, T.J.M., Nieuwenhuis, S., Ridderinkhof, K.R., 2005. Dissociable components of error processing: on the functional significance of the Pe vis-à-vis the ERN/Ne. *J. Psychophysiol.* <https://doi.org/10.1027/0269-8803.19.4.319>.
- Owen, A.M., Mcmillan, K.M., Laird, A.R., 2005. N-Back Working Memory Paradigm : A Meta-Analysis of Normative Functional Neuroimaging Studies. vol. 59. pp. 46–59. <https://doi.org/10.1002/hbm.20131>.
- Ridderinkhof, K.R., 2004. The role of the medial frontal cortex in cognitive control. *Science (80-)* 306, 443–447. <https://doi.org/10.1126/science.1100301>.
- Ridderinkhof, K.R., Ramautar, J.R., Wijnen, J.G., 2009. To P E or not to P E: A P3-like ERP component reflecting the processing of response errors. 46. pp. 531–538. <https://doi.org/10.1111/j.1469-8986.2009.00790.x>.
- Rose, E.J., Salmeron, B.J., Ross, T.J., Waltz, J., Schweitzer, J.B., Stein, E.A., 2017. Dissociable effects of cocaine dependence on reward processes: the role of acute cocaine and craving. *Neuropsychopharmacology* 42, 736–747. <https://doi.org/10.1038/npp.2016.161>.
- Saunders, J., Aasland, O., Babor, T., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II.
- Scott, D., Hiroi, N., 2011. Deconstructing craving: dissociable cortical control of Cue reactivity in nicotine addiction. *Biol. Psychiatry* 69, 1052–1059. <https://doi.org/10.1016/j.biopsych.2011.01.023>.
- Seymour, B., Singer, T., Dolan, R., 2007. The neurobiology of punishment. *Nat. Rev. Neurosci.* 8, 300–311. <https://doi.org/10.1038/nrn2119>.
- Stevens, M.C., Kiehl, K.A., Pearlson, G.D., Calhoun, V.D., 2007. Functional neural networks underlying response inhibition in adolescents and adults. *Behav. Brain Res.* 181, 12–22. <https://doi.org/10.1016/j.bbr.2007.03.023>.
- Sutherland, M.T., Carroll, A.J., Salmeron, B.J., Ross, T.J., Hong, L.E., Stein, E.A., 2013. Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. *Biol. Psychiatry* 74, 538–546. <https://doi.org/10.1016/j.biopsych.2013.01.035>.
- Taylor, S.F., Martis, B., Fitzgerald, K.D., Welsh, R.C., Abelson, J.L., Liberzon, I., Himle, J.A., Gehring, W.J., 2006. Medial frontal cortex activity and loss-related responses to errors. *J. Neurosci.* 26, 4063–4070. <https://doi.org/10.1523/JNEUROSCI.4709-05.2006>.
- Thorne, S., Malarcher, A., Maurice, E., 2008. Cigarette smoking among adults in the United States. *Oncol. Times* 30, 26–30.
- Van Veen, V., Carter, C.S., 2002. The anterior cingulate as a conflict monitor: FMRI and ERP studies. *Physiol. Behav.* 77, 477–482. [https://doi.org/10.1016/S0031-9384\(02\)00930-7](https://doi.org/10.1016/S0031-9384(02)00930-7).
- Wessel, J.R., Danielmeier, C., Ullsperger, M., 2011. Error awareness revisited: accumulation of multimodal evidence from central and autonomic nervous systems. *J. Cogn. Neurosci.* 23, 3021–3036. <https://doi.org/10.1162/jocn.2011.21635>.
- Yalachkov, Y., Kaiser, J., Naumer, M.J., 2012. Functional neuroimaging studies in addiction: multisensory drug stimuli and neural cue reactivity. *Neurosci. Biobehav. Rev.* 36, 825–835. <https://doi.org/10.1016/j.neubiorev.2011.12.004>.