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Functional Connectivity During Feedback Learning in Smokers

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Abstract

Background: Although it has been traditionally assumed that dysregulation of psychological processes in smokers results from activity within specific brain regions, an emerging view regards such dysregulation as attributable to aberrant communication between distinct brain regions. These processes can be measured during appropriate task paradigms such as the learning from errors task. This study aims to elucidate interactions between brain regions underlying the process of learning from errors, punishment, and sensitivity to reward in dependent smokers

Methods: Functional MRI data from twenty-three age-matched dependent smokers (8 females, mean age = 25.48, *SD* = 4.46) and twenty-three controls (13 females, mean age = 24.83, *SD* = 5.99) were analysed during a feedback-based associative learning task. Functional connectivity between the dorsal anterior cingulate cortex, nucleus accumbens, and reward/sensorimotor areas was investigated during a feedback learning task.

Results: Behaviorally**,** smokers exhibited lower error-correction rates and were less sensitive to punishment magnitude. Smokers showed increased functional connectivity between dorsal anterior cingulate cortex/nucleus accumbens seed regions and numerous reward-related regions including putamen, anterior cingulate, and orbitofrontal cortex.

Conclusions: Reduced learning from errors and widespread aberrant functional connectivity contribute to the emerging functional characterisation of dependent smokers and may bear significant implications when considering the efficacy of smoking interventions.

Introduction

The consequences of cigarette smoking are the primary cause of mortality and morbidity worldwide[1]. For over one billion smokers, secondary effects of smoking are often serious, irreversible, and commonly pre-empted by milder symptoms.[1,2] However, experiencing these milder negative health symptoms rarely motivates dependent smokers to quit.[2] Besides the impact of physical dependence, disrupted learning from negative feedback may contribute to the continuation of tobacco smoking, despite knowledge of deteriorating health. Indeed, altered cognitive processes have been shown to coincide with altered brain activation[3] yet it is unclear whether this extends to communication between brain regions.

Evidence suggests that smokers are less sensitive to punishment and indifferent to the avoidance of punishment compared to receiving reward in associative learning tasks.[4] For example, smokers inhibited fewer responses to punishing stimuli when fast reactions were required[5] and showed reduced sensitivity to the threat of punishment.[6,7] However, evidence also points to smokers being more sensitive to reward.[4] This conflicting evidence relating to reward sensitivity highlights that this system is complex and may be considered as multiple constructs—*liking*, *wanting* and *anticipating*. The 'wanting versus liking' hypothesis argues that substances can become wanted increasingly *more*, while becoming liked increasingly *less*.[8] While 'wanting' is a form of motivation that is often initiated by cues, 'liking' represents the actual pleasurable effect of a reward.[9] As such, the two states are processed through distinctive neural systems. 'Wanting' is generated within the mesocorticolimbic dopamine system, linking

midbrain dopamine projections to forebrain targets such as the nucleus accumbens (NAcc) and other parts of the striatum. On the other hand, 'liking' is not reliant on dopamine and is generated via a collection of 'interactive hedonic hotspots' within larger limbic structures.[10] Indeed, a ratio of one to nine has been suggested for limbic areas capable of generating 'liking', *versus* those able to generate 'wanting'.[10] Therefore, the experience of heightened 'wanting' may prompt smokers to seek and continue tobacco use, despite this use being aversive.

Reward from substance use is anticipated via memories of initial liking of the use that elicited positive reinforcement in the form of euphoria, happiness, or relaxation. As such, continuously anticipating reward despite experiencing discomfort, without integrating this discomfort into memory (learning from the experience) may exacerbate substance dependence. Moreover, substance-related cues may exacerbate the anticipation of the substance-related reward. These substance-related cue presentations can promote relapse into habitual behavior, as opposed to goal-directed behavior (i.e., sobriety).[11] For example, social events are well-known triggers for relapse behavior, where in the past one may have partaken in, and enjoyed substance use or tobacco smoking (i.e., 'social smoking'). However, the risk of relapse through increased reward anticipation may be equally promoted by decreased punishment anticipation and punishment sensitivity. That is, if an individual does not perceive a punishment as aversive, this punishment will not have as substantive influence on encoding and recall of a memory, resulting in low subsequent anticipation of the punishment. As such, low punishment anticipation and high reward anticipation may promote continued tobacco use. A reduced capacity to adapt after negative feedback and potential increased sensitivity to positive feedback may therefore

contribute to smoking maintenance despite experiencing health detriment. These processes can be examined with task paradigms such as the Learning From Errors task, which measures adaptation following reward and punishment.[12] Within this task, trials feature distinct epochs for (1) recall of the memorized number-location pairs, (2) response feedback, and (3) renewed memorization (re-encoding) of the number-location combination. Two feedback magnitudes (high reward *vs.* low reward and high punishment *vs.* low punishment) allow for investigation into feedback sensitivity while reducing confounding factors. For example, punishment sensitivity can be assessed by comparing responses to low punishment *vs.* high punishment within each group, accounting for potential differences in memory capacity between groups.

As a complementary tool, task-based fMRI can measure the blood oxygenated level dependency (BOLD) signal of specific brain regions during reward/punishment paradigms. For example, healthy individuals exhibit BOLD activity in the dorsal anterior cingulate cortex (dACC) proportional to punishment magnitude[12], and smokers exhibit BOLD hypoactivation in the insula in response to motivational feedback.[13] Although brain activity during monetary feedback task paradigms in smokers has seldom been explored, there is also ample potential for altered hippocampal activity (proposed to be critical for the initial stages of the Learning From Errors task; memorisation and recall)[3] as well as insula activity which can be posited to aid learning from punished errors.[12]

The insula cortex relates to punishment magnitude, and dACC activity is predictive of error correction.[12] In addition, a broader body of literature has implicated the orbitofrontal cortex (OFC) in substance dependent individuals, promoting lack of control, compulsive behavior,

and maladaptive decision-making.[14] Furthermore, it is also important to consider motivation to obtain reward, which has been related to activity within the ventral tegmental area, nucleus accumbens (NAcc), and the dorsolateral prefrontal cortex (dlPFC)[15] with reward anticipation also associated with dorsal striatal function (comprised of caudate and putamen).[16] Altered function of these regions may therefore reflect differences in task performance between smokers and controls. Indeed, when comparing smoking with food cues, smoking cues evoke greater BOLD response in the OFC and supplementary motor area, and weaker activation in the middle frontal gyrus and temporal gyrus.[17] The same study also investigated functional connectivity (FC) between *a priori* selected brain regions (right OFC as seed), reporting increased FC between the somatosensory and lateral inferior parietal lobes in response to smoking cues compared with food cues. When selecting the left insula as a seed, smoking *vs* food cues elicited increased connectivity with the somatosensory cortex, right insula, OFC, and striatum.

Limited evidence during resting-state paradigms converges to report reduced FC between subcortical reward related areas and thalamocortical projections. For example, smokers exhibit reduced FC between the caudate and insula, between the thalamus and dlPFC (which was related to lifetime smoking)[18]. Others found reduced FC in smokers between the OFC and the insula, amygdala, and dorsal striatum.[19] While it has traditionally been assumed that dysregulation of psychological processes in smokers results from activity within specific brain regions, an emerging view regards such dysregulation as also attributable to aberrant communication between distinct brain regions.[20] This notwithstanding, there is relatively little exploration into whether these or other regions exhibit altered communication measures

(i.e., FC) during monetary reward and punishment task paradigms. Therefore, this study aims to measure FC between brain regions underlying the process of learning from errors, during punishment and reward in dependent smokers. We expect smokers will show (i) reduced punishment sensitivity with lower task-based FC between the insula and dACC during feedback presentation and (ii) altered task-based FC between dACC and hippocampus during re-encoding. We also hypothesize that (iii) increased reward anticipation (recall) in smokers will correspond with altered task-based FC between the hippocampus and NAcc during recall of number-location pairs. In response to punishment, we expect smokers will (iv) exhibit altered task-based FC relating to punishment hyposensitivity.

Materials and methods

Subjects

Twenty-three dependent cigarette smokers (8 females; mean age = 25.48 years; range = 19-36 years; years of education = 14.74) and 23 non-smoking controls (13 females; mean age = 24.74 years; range = 19-40 years; years of education = 14.61) were included. Participants were recruited via advertisements at the University of Melbourne and a community website. All participants provided written informed consent, which was approved by the Human Ethics Committee of The University of Melbourne and the Royal Children's Hospital.

Inclusion criteria

To be classified as dependent smokers, individuals had to smoke a minimum of fifteen tobacco cigarettes daily. Non-smoking controls had smoked less than six tobacco cigarettes in their lifetime. Prior to the experiment, smokers were required to be abstinent for at least 3h. This duration had been selected to avoid acute effects of nicotine on task performance while minimising effects of acute withdrawal.[21] Abstinence was confirmed by breath carbon monoxide (CO) measure and self-report of last smoked cigarette. Exclusion criteria for both groups consisted of a history of neurological or psychiatric disorders, current use of psychotropic medication, and current substance dependence (other than nicotine for the smoking group). Groups did not significantly differ on variables of age ($t(44) = .475$, $p = .637$, $d = .123$) or education ($t(44) = .184$, $p = .855$, $d = .093$). Smokers were characterized by moderate dependence as measured with the Fagerstrom Test for Nicotine Dependence (average score = 4.7).[22] Self-reported alcohol use was significantly higher in smokers as measured with

the Alcohol Use Disorder Identification Test (AUDIT)[23] (controls = 2, smokers = 9; $t(44) = -6.420$, $p \leq .001$, $d = 1.789$). The variables of AUDIT scores, smoker's breath carbon monoxide (CO), nicotine dependence scores, craving as measured with the QSU-brief[24] did not correlate with the dependent variables of interest. Gender did not differ significantly between groups. All covariates were measured prior to MRI scanning.

Study Design

A spatial paired-associate learning task was administered to participants (Figure 1). 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 compatible PC. The task began with an encoding phase, presenting participants with eight number-location pairs. 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 in which participants inserted the numbers they associated with the presented location. Feedback was then provided for validity of the response and magnitude of reward/punishment. 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 magnitudes 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. The correct two-digit number was presented

on the coloured location, allowing participants to re-encode the correct answer (for more detail, see the caption corresponding to Figure 1). When each of the eight locations was highlighted once, recall round 1 was concluded. Subsequently, each square was highlighted in a different pseudorandom order, constituting the recall round 2. The recall trials were pseudo-randomly 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 280s. 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.

Behavioral data analysis

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). To focus on error correction, task-based FC analysis included only locations that were answered incorrectly in the first round. In total, 2203 error trials contributed to the averages. We determined conditions in the recall round 1 according to future response in recall round 2. For the recall, feedback, and re-encoding phase, this resulted in four conditions each, categorized as: errors that were subsequently corrected and punished with 5¢ (5¢ corrected errors), errors

that were subsequently corrected and punished with 50¢ (50¢ corrected errors), errors that were repeated and punished with 5¢ (5¢ repeated errors), and errors that were repeated and punished with 50¢ (50¢ repeated errors). Statistical analyses investigated any effect between conditions, effects of magnitude (5¢ corrected errors, 5¢ repeated errors versus 50¢ corrected errors, 50¢ repeated errors), and future performance (5¢ corrected errors, 50¢ corrected errors versus 5¢ repeated errors, 50¢ repeated errors).

fMRI data acquisition

All behavioral measures were conducted prior to MRI data collection. Functional MRI were acquired at the Royal Children's Hospital, Melbourne, using a whole-body 3 Tesla Siemens Trio with a single-band gradient-echo echoplanar imaging sequence (TR = 2s, TE = 35ms, flip angle = 90°, 32 contiguous slices of 4mm thickness (no gap), matrix size = 64 x 64, field of view = 230mm, oblique orientation (angled through chin). T1-weighted isotropic ($1mm^3$) structural MPRAGE images were also acquired. Lateral padding was used to stabilize the head of each participant. The first three volumes of each run were discarded to allow for steady-state tissue magnetization. Nine functional runs per participant were performed, with 140 gradient echoplanar imaging volumes per run (TA = 42min).

fMRI pre-processing

All task-based FC pre-processing analyses were conducted using CONN toolbox (a validated MATLAB toolbox for analysing FC BOLD data).[25] Functional images were realigned using rigid-body registration in reference to the first volume of the first imaging session.

Realignment parameters were saved for later detection of movement outliers using the artefact detection tool (ART; http://www.nitrc.org/projects/artifact_detect/). Volumes containing excess movement (>2mm in any direction) were removed. Realigned functional volumes were normalised to MNI-space, using non-linear registration in two steps. Structural images were co-registered to the processed functional images and segmented into grey matter, white matter, and cerebrospinal fluid. The resulting white matter and cerebrospinal fluid masks were used to estimate non-neuronal signal components (e.g., from respiratory, pulsatile or other physiological sources) applying the *aCompCor* approach.[26] These signal components, realignment parameters, and outlier indices were regressed onto each voxel's time series and the residual time-series was used for subsequent analyses. Finally, the data were high-pass filtered at .008Hz before linear detrending was applied.

Task-based FC: post-processing

First, we created 6mm radius gray matter spheres, to be used as seed regions around *a priori* MNI coordinates based on focal points of significant activations that were identified in previous experiments analysing conventional BOLD responses to the Learning From Errors task[27–29] and conventional BOLD response in relation to punishment in this cohort.[3] In the left hemisphere, these regions were within the left dACC (Hester, 2010; -2; 0, 47), hippocampus (-31, -22, -13), insula (-41, 8, 7), NAcc (-13, 9, -8), and sensorimotor cortex (-36, -29, 54). In the right hemisphere, regions were in the dlPFC (34, 42, 31; 35, 29, 32), right dACC (Hester; 2010; 7, 13, 52), NAcc (Hester, 2010; 11, 9, -8). As target regions, we supplemented with cortical and subcortical regions of interest (ROI) relating to feedback/error learning from the Harvard-Oxford and AAL atlases (see Table 1,2,3)

including the bilateral nucleus accumbens, putamen, insula, OFC, medial prefrontal cortex, caudate and sensorimotor area. Thereafter, connectivity matrices were computed from Fisher-transformed pairwise correlation coefficients between ROI BOLD time series. Statistical significance was assessed by first computing a two-sided *p*-value for each edge. Correction for multiple comparisons was performed using the false discovery rate (FDR) as implemented in the CONN toolbox. The FDR rate was set at 5% across all comparisons and FDR-corrected *p*-values were computed for all links. Links with an FDR-corrected $p<.05$ were considered statistically significant.

Results

Behavioral results: Learning from Errors Task (Smokers vs. Control)

Smokers made a total of 1129 errors, with an average of 49 errors per smoker. Controls made a total of 1074 errors, with an average of 47 per control participant. A three-way repeated measures ANOVA between group (smokers, controls), magnitude (5¢, 50¢), and feedback type (corrected errors, repeated errors) found a significant main effect of feedback magnitude (5¢, 50¢), $F(1,44) = 10.733$, $p = .002$, $\eta^2 p = .196$. The main effect of group (controls, smokers) was non-significant ($F(1,44) = 1.900$, $p = .175$, $\eta^2 p = .041$), as was the interaction between group and magnitude ($F(1,44) = 3.208$, $p = .080$, $\eta^2 p = .068$). While smokers showed a trend towards lower error correction of high punished locations versus low punished locations (50¢: controls = 49%, smokers, 37%; 5¢: controls = 37%, smokers = 34%), this effect was not significant. In contrast, the three-way interaction between magnitude, feedback type and group was significant, $F(1,44) = 6.825$, $p = .012$, $\eta^2 p = .134$. As such, smokers showed decreased retention performance in the 5¢-reward condition and lower error-correction rates in the 50¢-punishment condition (Figure 2).

Functional connectivity results: Between groups (Smokers > Controls)

Between groups FC contrasts were performed (Smokers>Control) across each of the feedback conditions (-50¢, -5¢, +5¢ and +50¢) and across all epochs (recall, feedback and re-encoding). We found no significant differences in seed-ROI FC between seeds (dACC;

Hester, 2010; NAcc) and target ROI (see Task-based FC: post-processing for a full list of ROI) in all except the -5¢ feedback condition. In the -5¢ feedback condition, a between groups (seed-ROI) contrast (Smokers>Controls) revealed widespread increased task-based FC in smokers, incident to two seed regions (dACC, NAcc) and target ROI including the putamen, OFC, caudate, medial PFC, insula, sensorimotor area, ACC during repeated error feedback, and low punishment magnitude recall conditions (see Table 1,2,3; Figure 3). Note: MRI group contrasts (Smokers>Controls) were analysed for recall round 1 only (prior to feedback presentation) and therefore feedback magnitude has not been assigned to this epoch. A *post-hoc* multiple regression was performed between FC values and behavioral covariates including carbon monoxide breath measures (CO), cigarette craving scale (QSU-brief) and cigarette dependence scores (Fagerstrom Scale). After False Discovery Rate correction, no significant contribution was found from any of these variables with FC measures in the smokers group.

Discussion

Main findings

We explored the emerging view that regards learning from errors and negative stimuli as attributable to aberrant communication between distinct brain regions. Smokers exhibited increased pairwise task-based FC between seed regions known to exhibit altered BOLD activity during error learning paradigms (dACC and NAcc) and numerous sub-cortical areas relating to reward processing including the OFC, putamen, caudate and anterior cingulate cortex. This increased FC extended to the sensorimotor cortex which has been reported to exhibit altered BOLD activity during this task paradigm.[27,29]

The role of dopaminergic pathways in reward processing

The pattern of increased task-based FC and decreased error correction rates in smokers is understandable when considering the role of major cortical pathways associated with reward anticipation, dopamine processing and substance dependence.[30] A major finding of this study was increased task-based FC between NAcc and dACC—two brain areas involved in reward-

processing and task-performance. Specifically, the NAcc has been proposed to influence positive reinforcement and reinforcement learning,[31] and to modulate response to monetary reward,[32] and stimuli that are both rewarding and reinforcing.[33] In contrast, dACC activity may also correspond to performance monitoring and selective attention of a given task.[34] Therefore, increased task-based FC between NAcc and dACC during recall may reflect altered communication of expected reward in order to facilitate increased attention and make measured decisions.

Our findings further contribute to literature supporting the notion that increased dACC-insula connectivity is a stable trait in nicotine dependent smokers.[35] Previously, increased dACC-insula connectivity at rest was found to be independent of changes in craving and carbon monoxide measures.[35] The increased resting-state FC was correlated with enhanced smoking cue-reactivity.[35] Our findings suggest that this disposition extends to task-based FC and sustains during negative monetary feedback, inarguably different from appetitive smoking cues. Interestingly, one of the regions of which activation during smoking-cue presentation correlated with increased resting-state dACC-insula connectivity, was described as "putamen extending into the insula". We found increased dACC-putamen FC during the same negative feedback condition as the insula, suggesting the insula and putamen might act together. Altered putamen-ACC and putamen-insula connectivity in smokers has been related to impulse control[36] and impulsivity has been related to increased reward anticipation and NAcc activation.[37] Thus, our results extends upon existing literature by linking altered brain

connectivity with increased impulsivity and reward anticipation, and disrupted learning from negative feedback in nicotine dependent smokers.

Information in the PFC has been suggested to elicit activation in NAcc and ventral tegmental area[38] which may induce dopamine synthesis. This top-down process may be facilitated by thinking into the future and consequences of actions, which may psychologically delineate reward anticipation from reward reception in smokers. In exploration of this theory, hyperactivation was reported within the PFC in smokers during a recall epoch independent of future error correction.[38] This hyperactivation may be explained by increased reward anticipation. Subsequently, increased reward anticipation during the recall epoch in our study may have triggered dopamine release in the ventral tegmental area via the PFC prior to or during the action (i.e., number insertion during recall) that resulted in feedback.[39] However, future research should explore task-based FC in smokers using a task-paradigm that measures reward anticipation without the potential of punishment.

A BOLD-FC relationship in smokers?

We identified increased task-based FC from the dACC relating to incorrect responses. This region is known to exhibit BOLD activity predictive of learning from an error[12]. Together, these findings raise the possibility of a BOLD-FC relationship involving the dACC in smokers. Indeed, our findings suggest an inverse univariate BOLD-FC relationship which may potentially be a compensatory mechanism for underactive brain regions. However, more research is required to shed light into this relationship during monetary reward and

punishment paradigms. To our knowledge, only one study has considered BOLD activity and task-based FC in smokers albeit in a food *vs* smoking cues paradigm.[17] Herein, smokers showed greater activity during food cues in the OFC and sensorimotor area (SMA) and increased connectivity between the OFC-SMA and OFC-lateral parietal lobes. Research has seldom measured both BOLD activity and task-based FC in smokers during Learning From Errors task paradigms, so we can consider first, how BOLD relates to FC *in general*. Simultaneous FDG-PET/fMRI has elucidated that resting-state activity (local neuronal oscillations) are synchronized by power fluctuations on a systems level, and that these are spatially related to resting-state FC.[40] This is supported by simultaneously acquired BOLD fMRI and full-band EEG data whereby scalp potential fluctuations are also directly related to resting-state BOLD signals.[41] In congruence, others have found that BOLD fMRI measures including both regional homogeneity and amplitude of low frequency fluctuation were found to be reliably correlated with cerebral blood flow as derived from arterial spin labelling in most of the cortex.[42] It is therefore possible that our finding of increased FC with numerous regions in both feedback and recall of punishment may reflect dysfunctional propagation of information from an area previously identified as the dACC.[29] Given the extension of this altered FC to numerous distal brain regions, smokers may indeed be exhibiting widespread dysfunctional communication of information relating to both punishment and the anticipation of reward.

This dysfunctional FC we found in our sample of dependent smokers may in part, represent a compensatory effort to satisfy an intrinsically under-active reward system, which is consistent

with research relating to the most replicated marker of smoking—the 'risk allele'. This allele has been associated with weakened resting-state FC between the bilateral ACC and the ventral striatum[43] and marks trait aspects of addiction associated with predisposing individuals to smoking, effectively predicting dependence severity in smokers. However, to understand the complex mechanism underlying BOLD response and both task-based/resting-state FC, we must incorporate these measures into a suitable analytical framework if we are to elucidate if and how altered BOLD activity relates to altered FC in task-negative and positive states.

Future directions

An important challenge remains as to how to reconcile task-based FC and BOLD fMRI measurements into a suitable framework to facilitate advanced statistical analyses between measurements at a whole-brain level. Recent endeavours to incorporate multimodal MRI have utilised multilayer network analysis.[44] Therein, multiple types of MRI information pertaining to each region of the brain (i.e., BOLD activity) as well as the relationships between these regions (i.e., FC) can be represented within whole-brain 'layers' comprising information about each node, or the connections between each node. These layers can then be analysed as a graph using graph theoretic analysis. As such, this framework has the ability to incorporate spatiotemporal information (fMRI/BOLD) and should be considered for clinical cohort studies incorporating multiple fMRI measurements.[45]

Limitations

There are several important limitations here worth mentioning. Firstly, our participant sample was small (23), and was not matched for gender which may have affected task-based FC. Secondly, participants were asked to abstain from smoking for three hours, which may be argued to have invoked withdrawal. However, previous research observed no effects of abstinence from 1-3h, only after 10-24h.[21] Thirdly, cigarette craving was not measured after the MRI scan, so we could not determine level of craving toward the end of the scan. Finally, the cross-sectional characteristic of our study limits conclusions on the pre-existence of altered reward and punishment sensitivity in smokers or whether this occurred as a consequence of cigarette smoking or nicotine dependence.

Conclusions

Smokers show reduced learning from punishment, appear more sensitive to reward, and exhibit widespread increased task-based FC from an area related to error-learning with numerous reward-related regions. These findings contribute to the functional characterisation of smokers and may bear significant implications when considering smoking interventions. Therefore, clinicians may wish to explore a paradigm-shift away from negative behaviour intervention strategies (e.g., aversive images on cigarette packaging), toward positive interventions in an effort to reduce the consumption of tobacco and for individuals to achieve sustained abstinence.

References

1. World health organisation (WHO). *WHO Report on the Global Tobacco Epidemic*.; 2019:209. https://www.who.int/teams/health-promotion/tobacco-control/who-report-on-the-global-tobacco-epidemic-2019

2. 2016 National Drug Strategy Household Survey (AIHW).

3. Duehlmeyer L, Hester R. Impaired learning from punishment of errors in smokers: Differences in dorsolateral prefrontal cortex and sensorimotor cortex blood-oxygen-level dependent responses. *NeuroImage Clin*. 2019;23:101819.

4. Duehlmeyer L, Levis B, Hester R. Effects of reward and punishment on learning from errors in smokers. *Drug Alcohol Depend*. 2018;188. doi:10.1016/j.drugalcdep.2018.03.028

5. Luijten M, Van Meel CS, Franken IHA. Diminished error processing in smokers during smoking cue exposure. *Pharmacol Biochem Behav*. 2011;97(3):514-520. doi:10.1016/j.pbb.2010.10.012

6. Luijten M, O'Connor DA, Rossiter S, Franken IHA, Hester R. Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers. *Addiction*. 2013;108(11):1969-1978. doi:10.1111/add.12276

7. De Ruiter MB, Oosterlaan J, Veltman DJ, Van Den Brink W, Goudriaan AE. Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend*. 2012;121(1-2):81-89. doi:10.1016/j.drugalcdep.2011.08.010

8. Robinson TE, Berridge KC. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res Rev*. Published online 1993. doi:10.1016/0165-0173(93)90013-P

9. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol*. 2016;71(8):670-679. doi:10.1037/amp0000059

10. Berridge KC, Kringelbach ML. Pleasure Systems in the Brain. *Neuron*. 2015;86(3):646-664. doi:10.1016/j.neuron.2015.02.018

11. Everitt B, Robbins T. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci*. Published online 2005.

12. Hester R, Murphy K, Brown FL, Skilleter AJ. Punishing an error improves learning: the influence of punishment magnitude on error-related neural activity and subsequent learning. *J Neurosci Off J Soc Neurosci*. 2010;30(46):15600-15607. doi:10.1523/JNEUROSCI.2565-10.2010

13. Ruiter M De, Veltman D. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. Published online 2009.

14. Schoenbaum G, Roesch MR, Stalnaker TA. Orbitofrontal cortex, decision-making and drug addiction. *Trends Neurosci*. 2006;29(2):116-124. doi:10.1016/j.tins.2005.12.006

15. Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci*. Published online 2004. doi:10.1038/nrn1406

16. Haruno M, Kawato M. Different Neural Correlates of Reward Expectation and Reward Expectation Error in the Putamen and Caudate Nucleus During Stimulus-Action-Reward Association Learning. *J Neurophysiol*. 2006;95(2):948-959. doi:10.1152/jn.00382.2005

17. Claus ED, Blaine SK, Filbey FM, Mayer AR, Hutchison KE. Association Between Nicotine Dependence Severity, BOLD Response to Smoking Cues, and Functional Connectivity. *Neuropsychopharmacology*. 2013;38(12):2363-2372. doi:10.1038/npp.2013.134

18. Wang C, Bai J, Wang C, von Deneen KM, Yuan K, Cheng J. Altered thalamo-cortical resting state functional connectivity in smokers. *Neurosci Lett*. 2017;653:120-125. doi:10.1016/j.neulet.2017.05.038

19. Bi Y, Yuan K, Guan Y, et al. Altered resting state functional connectivity of anterior insula in young smokers. *Brain Imaging Behav*. 2017;11(1):155-165. doi:10.1007/s11682-016-9511-z

20. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35(1):217-238. doi:10.1038/npp.2009.110

21. Xu J, Mendrek A, Cohen MS, et al. Brain activity in cigarette smokers performing a working memory task: Effect of smoking abstinence. *Biol Psychiatry*. 2005;58(2):143-150. doi:10.1016/j.biopsych.2005.03.028

22. Heatherton T, Kozlowski L, Frecker R. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Published online 1991.

23. Saunders J, Aasland O, Babor T. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Published online 1993.

24. Cox L, Tiffany S, Christen A. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res*. Published online 2001.

25. Whitfield-Gabrieli S, Nieto-Castanon A. *Conn* : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connect*. 2012;2(3):125-141. doi:10.1089/brain.2012.0073

26. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*. 2007;37(1):90-101. doi:10.1016/J.NEUROIMAGE.2007.04.042

27. Carey SE, Nestor L, Jones J, Garavan H, Hester R. Impaired learning from errors in cannabis users: Dorsal anterior cingulate cortex and hippocampus hypoactivity. *Drug Alcohol Depend*. 2015;155:175-182. doi:10.1016/j.drugalcdep.2015.07.671

28. Hester R, Barre N, Murphy K, Silk TJ, Mattingley JB. Human medial frontal cortex activity predicts learning from errors. *Cereb Cortex*. 2008;18(8):1933-1940. doi:10.1093/cercor/bhm219

29. Hester R, Murphy K, Brown FL, Skilleter AJ. Punishing an error improves learning: the influence of punishment magnitude on error-related neural activity and subsequent learning. *J Neurosci Off J Soc Neurosci*. 2010;30(46):15600-15607. doi:10.1523/JNEUROSCI.2565-10.2010

30. Volkow ND. Imaging the addicted brain: from molecules to behavior. *J Nucl Med Off Publ Soc Nucl Med*. 2004;45(11):13N-16N, 19N-20N, 22N passim. doi:10.1109/IEMBS.2006.259770

31. Wenzel JM, Rauscher NA, Cheer JF, Oleson EB. A role for phasic dopamine release within the nucleus accumbens in encoding aversion: A review of the neurochemical literature. *ACS Chem Neurosci*. 2015;6(1):16-26. doi:10.1021/cn500255p

32. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*. Published online 2001.

33. Haber SN, Knutson B. The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*. 2010;35(1):4-26. doi:10.1038/npp.2009.129

34. Ridderinkhof KR. The Role of the Medial Frontal Cortex in Cognitive Control. *Science*. 2004;306(5695):443-447. doi:10.1126/science.1100301

35. Janes AC, Farmer S, Peechatka AL, Frederick B de B, Lukas SE. Insula–Dorsal Anterior Cingulate Cortex Coupling is Associated with Enhanced Brain Reactivity to Smoking Cues. *Neuropsychopharmacology*. 2015;40(7):1561-1568. doi:10.1038/npp.2015.9

36. Akkermans SEA, Luijten M, van Rooij D, Franken IHA, Buitelaar JK. Putamen functional connectivity during inhibitory control in smokers and non-smokers: Putamen functional connectivity in smokers. *Addict Biol*. 2018;23(1):359-368. doi:10.1111/adb.12482

37. Hammond CJ, Krishnan-Sarin S, Mayes LC, Potenza MN, Crowley MJ. Associations of Cannabis- and Tobacco-Related Problem Severity with Reward and Punishment

Sensitivity and Impulsivity in Adolescent Daily Cigarette Smokers. *Int J Ment Health Addict*. Published online May 15, 2020. doi:10.1007/s11469-020-00292-2

38. Ballard IC, Murty VP, Carter RM, MacInnes JJ, Huettel SA, Adcock RA. Dorsolateral Prefrontal Cortex Drives Mesolimbic Dopaminergic Regions to Initiate Motivated Behavior. *J Neurosci*. Published online 2011. doi:10.1523/JNEUROSCI.0895-11.2011

39. Hayashi T, Ko JH, Strafella AP, Dagher A. Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proc Natl Acad Sci*. 2013;110(11):4422-4427. doi:10.1073/pnas.1212185110

40. Riedl V, Bienkowska K, Strobel C, et al. Local Activity Determines Functional Connectivity in the Resting Human Brain: A Simultaneous FDG-PET/fMRI Study. *J Neurosci*. 2014;34(18):6260-6266. doi:10.1523/JNEUROSCI.0492-14.2014

41. Hiltunen T, Kantola J, Abou Elseoud A, et al. Infra-Slow EEG Fluctuations Are Correlated with Resting-State Network Dynamics in fMRI. *J Neurosci*. 2014;34(2):356-362. doi:10.1523/JNEUROSCI.0276-13.2014

42. Li Z, Zhu Y, Childress AR, Detre JA, Wang Z. Relations between BOLD fMRI-Derived Resting Brain Activity and Cerebral Blood Flow. Stamatakis EA, ed. *PLoS ONE*. 2012;7(9):e44556. doi:10.1371/journal.pone.0044556

43. Hong LE, Hodgkinson CA, Yang Y, et al. A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. *Proc Natl Acad Sci*. 2010;107(30):13509-13514. doi:10.1073/pnas.1004745107

44. Vaiana M, Muldoon SF. Multilayer Brain Networks. *J Nonlinear Sci*. 2020;30(5):2147-2169. doi:10.1007/s00332-017-9436-8

45. Suárez LE, Markello RD, Betzel RF, Misic B. Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn Sci*. 2020;24(4):302-315. doi:10.1016/j.tics.2020.01.008

46. Lerman C, Gu H, Loughead J, Ruparel K, Yang Y, Stein EA. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry*. 2014;71(5):523-530. doi:10.1001/jamapsychiatry.2013.4091

47. Mendrek A, Monterosso J, Simon SL, et al. Working memory in cigarette smokers: Comparison to non-smokers and effects of abstinence. *Addict Behav*. 2006;31(5):833-844. doi:10.1016/j.addbeh.2005.06.009