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Performance Monitoring in Nicotine Dependence: Considering Integration of Recent Reinforcement History

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ABSTRACT

Introduction: Impaired monitoring of errors and conflict (performance monitoring; PM) is well documented in substance dependence (SD) including nicotine dependence and may contribute to continued drug use. Contemporary models of PM and complementary behavioural evidence suggest that PM works by integrating recent reinforcement history rather than evaluating individual behaviours. Despite this, studies of PM in SD have typically used indices derived from reaction to task error or conflict on individual trials. Consequently impaired integration of reinforcement history during action selection tasks requiring behavioural control in SD populations has been underexplored.

Methods: A reinforcement learning task assessed the ability of abstinent, satiated, former and never smokers (N=60) to integrate recent reinforcement history alongside a more typical behavioural index of PM reflecting the degree of reaction time slowing following an error (post-punishment slowing; PPS).

Results: On both indices there was a consistent pattern in PM data: Former smokers had the greatest and satiated smokers the poorest PM. Specifically satiated smokers had poorer reinforcement integration than former ($p=0.005$) and never smokers ($p=0.041$) and had less post-punishment slowing than former ($p<0.001$), never ($p=0.003$) and abstinent smokers ($p=0.026$).

Conclusions: These are the first data examining the effects of smoking status on PM that use an integration of reinforcement history metric. The concordance of the reinforcement integration and PPS data suggest that this could be a promising method to interrogate PM in future studies. PM is influenced by smoking status. As PM is associated with adapting behaviour, poor PM in satiated smokers may contribute towards continued smoking despite negative consequences. Former smokers show elevated PM suggesting this may be a good relapse prevention target for individuals struggling to remain abstinent however prospective and intervention studies are needed. A better understanding of PM deficits in terms of reinforcement integration failure may stimulate development of novel treatment approaches.

Keywords: Abstinence; Addiction; Former Smokers; Nicotine Dependence; Performance Monitoring; Reinforcement Learning

1. INTRODUCTION

Our ability to monitor our own on-going behaviour for errors or conflict (performance monitoring, PM) is an important aspect of adaptive cognition. PM is fundamental to the implementation of top-down control of behaviour so that behavioural adjustments can be made where appropriate and future mistakes or decrements in performance prevented.[1] Hyperactive and hypoactive PM are consistently reported in populations with internalising disorders (e.g. anxiety disorders) and externalising disorders (e.g. substance use disorders) respectively.[2] Impaired PM is documented in populations with various dependencies (e.g. opiate users,[3] cannabis users,[4] cocaine users,[5] alcoholics with a family history of alcohol problems,[6] and those with internet addiction disorder[7]). This suggests that hypoactive PM may be a mechanism by which maladaptive behaviours (such as drug taking) persist despite negative consequences and further, that it may be a transdiagnostic, endophenotypic cognitive marker of addiction.[8]

There is a growing body of research regarding PM and the response to error in tobacco dependence. Electrophysiological and behavioural correlates of PM have been reported in smokers and non-smokers during Flanker tasks.[9,10] In these conflict resolution tasks participants make behavioural selections depending on the identity of a central target that is flanked by either congruent or incongruent distractors.[11] Diminished electrophysiological correlates of PM in smokers compared to non-smokers were found in both studies and one study also found that smokers had a decreased post-error slowing of reaction time compared to non-smokers.[10] Similarly, imaging studies have shown reduced error-related neural activity in smokers compared to non-smokers.[12-14] Interestingly, an increased electrophysiological correlate of PM has been reported in intermittent non-dependent smokers compared to both dependent smokers and non-smokers[15] and greater error-related brain activation during inhibitory control performance was reported in former smokers compared to both current and never smokers.[13] This suggests that intact or enhanced PM may be an important mechanism by which abstinence or reduced consumption is successfully maintained over the long-

term. Other research has previously found a reduced electrophysiological correlate of PM in acutely abstinent compared to satiated smokers.[16]

Common across these studies of PM in nicotine dependence is that indices have focused on reaction to error or conflict on individual trials. However rather than simply detecting and evaluating individual trial error or conflict, there is evidence to suggest that PM involves the use of accumulated evidence and learning over a number of trials. Specifically, behaviour is guided by the integration of recent reinforcement (choice and outcome) history.[17-22] For example, Holroyd and Coles[23] propose a model of PM whereby midbrain dopaminergic learning signals indicating an actual outcome worse than expected (negative prediction error) are carried to the error processing system (the anterior cingulate cortex). This leads to implementation of control, which in turn results in behavioural adjustments that optimise future performance. Using a decision making task where correctness of individual choice was ambiguous, but where amount of reward received depended on response history, Holroyd and Coles[21] showed that this error processing system guides behaviour through the integration of reinforcement information over time, rather than the evaluation of individual responses.

The present study is the first to compare PM in current, former and never smokers which considers the ability to integrate reinforcement information over time. To do this we used a reinforcement learning task (RLT) with acquisition and reversal phases (based on Budhani et al.[24]). In this task participants make timed behavioural choices between two differentially rewarded and punished stimuli. In acquisition phases, participants learn which of the stimuli possess the optimum reinforcement properties and during reversal phases the reinforcement properties of some of the stimuli reverse. The changing reinforcement properties of reversing stimuli during the task provides the PM measure of integration of reinforcement information over time (see Methods section). We also included a traditional behavioural PM index based upon reaction to error on individual trials, post-punishment slowing (PPS) of RLT reaction time. Slowing of reaction time following an error[25] may reflect a mechanism for maintaining response accuracy that results from increased response caution as

a consequence of the engagement of cognitive control.[26] Indeed, studies have shown that the degree of slowing is correlated with electrophysiological measures of PM (error-related negativity and positivity).[27,28] We included both satiated and abstinent smokers in the study as there is some evidence that acute abstinence from smoking reduces PM.[16] We hypothesised that current smokers would have impaired PM compared to both never and former smokers. We further hypothesised that former smokers would have the greatest levels of PM and that abstinent smokers would have reduced PM compared to satiated smokers. Finally we will assess preliminary validity of the integration of reinforcement history measure. We hypothesise that integration ability will correlate with PPS as both purport to index PM. We also hypothesise that the integration measure will be the most sensitive measure given that it fits more closely with theoretical accounts of PM.

2. MATERIALS AND METHODS

2.1 Participants

Sixty healthy participants (30 current smokers, 15 former smokers and 15 never smokers) aged 18-38 years were recruited using the following criteria: current smokers were required to smoke ≥ 10 cigarettes per day for ≥ 12 months, former smokers were required to have had pre-quit smoking levels comparable to the current smoker group and to have remained abstinent for ≥ 6 months. Never smokers were required to have smoked ≤ 5 cigarettes in their lifetime. Participants were required to be medication free (excluding contraceptives), refrain from using illicit drugs for ≥ 1 week and arrive at the laboratory having not consumed alcohol for ≥ 12 hours. Current smokers were required to arrive after overnight abstinence and were randomly assigned to either a satiated or abstinent group to create 4 experimental groups: abstinent smokers, satiated smokers, former smokers and never smokers (n = 15 per group). Group size was based on previous studies measuring PM and inhibitory control in smokers.[10,29] Ethical approval was obtained from the University of Brighton School of Pharmacy and Biomolecular Sciences Research Ethics Committee. Participants gave written informed consent, attended one 1.5 hour laboratory session and received £12 compensation for their time.

2.2 General Procedure

All participants completed an e-mail inclusion criteria screen 0-7 days prior to the laboratory session. Current smokers also completed the Fagerstrom Test for Nicotine Dependence (FTND)[30] to assess severity of dependence. Upon arrival, all participants were subject to breath alcohol (Lion Alcometer SD-40; Lion Laboratories Ltd., Cardiff, UK) and exhaled carbon monoxide (CO) tests (Bedfont Micro Smokerlyzer; Bedfont Scientific Ltd., Kent, UK) for overnight abstinence compliance. Participants were excluded for a breath alcohol reading > 0 g/L or an exhaled CO level > 10 ppm[31]. As general cognitive ability and personality may affect reinforcement learning and PM, participants completed a battery of questionnaires and tests to assess impulsivity (Barratt Impulsiveness Scale, BIS-11[32]), sensitivity to reward and punishment (Behavioural Inhibition System/Behavioural Activation System Scales, BIS/BAS[33]), depression (Beck Depression Inventory, BDI[34]), IQ (The National Adult Reading Test, NART[35]) and short-term memory (immediate word recall, IWR[36]). To reduce smoking/abstinence-related performance expectancies all smokers were told they would smoke at some point during the session, but not when. The satiated group smoked one of their own cigarettes before PM assessment and the abstinent group smoked at the end of the session so they did not leave in a withdrawn state. The effectiveness of the smoking manipulation was assessed with subjective (nicotine-sensitive visual analogue scales (NicVAS) and craving) and physiological (exhaled carbon monoxide (CO) levels). Exhaled CO levels were re-measured before and after PM assessment. NicVAS (based on Perkins et al.[37]) ranged from 0 = 'not at all' to 100 = 'extremely' for the items: 'alert', 'buzzed', 'contented', 'dizzy', 'hungrier than usual', 'impatient', 'irritable', 'jittery', 'relaxed', 'stimulated' and 'thirsty'. NicVAS are known to be sensitive to acute smoking and abstinence[38-40] and were administered upon arrival and immediately before and after PM assessment. Craving (Questionnaire of Smoking Urges-Brief Version, QSU-brief[41]) was also assessed in satiated and abstinent smokers upon arrival, immediately before PM assessment and at the very end of the session (after the abstinent smoker group had also smoked). PM was assessed with a RLT (described below) presented on a laptop computer and programmed in E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA).

2.3 Reinforcement Learning Task

The RLT has previously been described elsewhere (see Budhani et al.[24] for further details). Briefly, this task presents a series of two stimuli that are probabilistically rewarded and punished with point gain and loss. Participants must keep selecting the rewarded stimuli even if it is occasionally punishing and only switch responding to the alternative stimulus should they believe it is no longer rewarding them on the majority of occasions. As in Budhani et al. there were acquisition trials where reward and punishment contingencies of stimuli were initially encountered and reversal trials (after 20 or 40 trials) where the contingencies reversed. To prevent participant awareness of when reversals occurred the task includes non-reversing pairs and inter-weaves trials (so participants have to deal with two pairs at a time). In addition we increased the difficulty of our task by changing reward/punishment contingencies from 100/0% and 80/20% to 80/20% and 70/30%. A more difficult task was used as our pilot data with the RLT (un-published) showed that very few errors were made in a version with 100/0% and 80/20% contingencies. The task outcome measures are described below.

2.3.1 Acquisition Errors

As the number of errors/amount of negative feedback and sensitivity to task feedback may influence the degree of PM we recorded the number of errors made in acquisition to serve as an indicator of this potentially confounding factor. Errors were calculated as in Finger et al.[42] (1) lose-stay errors (LSE; perseverative errors), when participants select the incorrect stimulus on trial *n* and are punished for doing so but then also select this stimulus on trial *n+1*; (2) win-maintenance failures (WMF; switch errors), when participants select the correct stimulus on trial *n* but are punished for doing so (false feedback) and then select the incorrect stimulus on trial *n+1*. As these errors relied upon information from the preceding trial all task trials except the very first trial were included in their calculation. LSE and WMF were recorded separately for 80-20% and 70-30% contingency pairs. As in Finger et al. participants had to attain a 6 consecutive correct criterion during acquisition trials to ensure proper

learning of the stimulus-reinforcement associations before reversal trials were analysed. All participants met this criterion for each set of stimuli.

2.3.2 Integration of Recent Reinforcement History

The ability to integrate recent reinforcement history was indexed by calculating change scores for LSE and WMF from acquisition to reversal (i.e. the number of errors made in reversal minus the number of errors made in acquisition). Our pilot data with the RLT (un-published) showed a distinct pattern in these change scores such that more LSE and fewer WMF are made in reversal compared to acquisition. We interpret change in LSE as inappropriate perseveration of previous stimulus-outcome associations with reversing pairs. Thus larger positive LSE change scores indicate poorer flexibility which, at least in part, relies upon ability to integrate feedback over time in order to learn when behavioural adjustment is necessary. We interpret change in WMF as participants' use of false feedback over time. Thus, larger positive WMF change scores indicate poorer integration of reinforcement history over time.

2.3.3 Post-punishment Slowing of Reaction Time

PPS was calculated for each participant using the equation: mean reaction time following punished responses minus mean reaction time following correct, rewarded responses (thus positive values indicated slowing of reaction times after punishment). Reaction times outside 3 standard deviations from the mean and those faster than 250ms were removed;[43] this resulted in removal of less than 10% of the total number of reaction time observations obtained from all participants.

2.4 Sensitivity Analysis

A sensitivity analysis was conducted to determine how well WMF change scores and PPS identified current and former smokers. This preliminary analysis consisted of calculating the percentage of current smokers who had larger, more positive WMF change scores and smaller PPS (poorer PM) than the never smoker mean score for each index and the percentage of former smokers who had

larger, more negative WMF change scores and greater PPS (better PM) than the never smoker mean score for each index.

2.5 Statistical Analyses

Statistical analyses were conducted using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Parametric statistical tests were used where possible; where data violated parametric assumptions and transformations could not correct this, an appropriate non-parametric alternative was used. Group differences (demographic data, RLT outcome measures) were investigated using Chi Square, one-way analysis of variance (ANOVA), Kruskal-Wallis test, or independent samples t-tests as appropriate. Significant group differences were followed up with appropriate post-hoc pairwise comparisons or Mann-Whitney U tests. Where time was also a factor (exhaled CO levels, NicVAS, craving data) mixed design ANOVA or separate Wilcoxon signed-ranks tests comparing time points for each group separately were used as appropriate. Significant interactions were followed up with post-hoc repeated measures ANOVAs and post-hoc pairwise comparisons as appropriate. As a further smoking manipulation check, craving scores immediately before PM assessment were compared for abstinent and satiated smokers using a Mann-Whitney U test. Correlation between integration of reinforcement history and PPS was assessed with Spearman's rank correlation coefficient (r_s). All statistical tests were two-tailed with alpha set at 0.05. Following the arguments advocated by several independent authors we provide readers with p-values uncorrected for multiple comparisons.[44-48] Effect sizes (Pearson's r) are provided for significant group differences in RLT outcome measures.

3. RESULTS

3.1 Participants

The abstinent, satiated, former and never smoker groups did not significantly differ on the majority of demographic, personality and smoking (where applicable) variables; the groups did differ in gender balance, subjective punishment sensitivity (former and never smokers had higher scores than current smokers) and differences in years of education approached significance. Table 1 shows these data.

Due to these group differences separate parametric analyses of the main outcome variables were conducted using the BIS subscale score of the BIS/BAS and gender as covariates. Significant main effects for PM outcome measures were unchanged by addition of these covariates so all analyses are reported on unadjusted data. Years of education did not correlate with PM outcome measures and was not considered further.

Table 1: Characteristics of the abstinent (AS), satiated (SS), former (FS) and never (NS) smoker groups.

	Group (n = 15 per group)				
	AS	SS	FS	NS	Sig.
Gender (M/F)	11/4	8/7	2/13	2/13	p = 0.001
Age (Years)	24.87 (1.72)	22.20 (1.05)	25.80 (1.50)	24.20 (0.95)	p = 0.287
Years of Education	15.93 (0.78)	15.33 (0.49)	16.67 (0.61)	17.60 (0.48)	p = 0.059
Cigarettes per Day ¥	15.47 (0.76)	14.20 (1.20)	13.07 (1.06)	-	p = 0.261
Age Started Smoking (Years)	14.40 (0.35)	15.73 (0.86)	14.93 (0.84)	-	p = 0.428
FTND Score	5.07 (0.27)	4.87 (0.40)	-	-	p = 0.681
Duration of Abstinence (Months)	-	-	20.47 (4.38)	-	-
Lifetime Cigarettes	-	-	-	1.47 (0.55)	-
NART Errors	14.13 (1.24)	14.80 (0.92)	13.00 (1.33)	14.53 (1.13)	p = 0.709
IWR (Words Recalled)	7.53 (0.51)	7.07 (0.64)	7.80 (0.54)	8.73 (0.49)	p = 0.187
BIS-11 (Total Score)	75.80 (2.16)	72.27 (1.55)	68.87 (3.87)	65.53 (2.69)	p = 0.057
BIS/BAS - Drive #	11.00 (4.00)	11.00 (4.00)	11.00 (2.00)	11.00 (3.00)	p = 0.868
BIS/BAS - Fun Seeking #	11.00 (3.00)	14.00 (3.00)	13.00 (3.00)	12.00 (3.00)	p = 0.173
BIS/BAS - Reward Responsivity #	17.00 (3.00)	17.00 (4.00)	18.00 (4.00)	17.00 (2.00)	p = 0.257
BIS/BAS - BIS ~	18.93 (0.80)	19.73 (1.05)	22.80 (0.81)	20.67 (0.86)	p = 0.020
BDI	7.13 (1.15)	7.13 (1.11)	6.60 (1.34)	3.73 (0.87)	p = 0.113

Data shown are mean and standard error of the mean. Abbreviations: M/F: male/female, FTND: Fagerstrom Test for Nicotine dependence, NART: National Adult Reading Test, IWR: Immediate Word Recall, BIS-11: Barratt Impulsiveness Scale, BIS/BAS: Behavioural Inhibition Scale/Behavioural Activation Scale, BIS/BAS - BIS: Behavioural Inhibition Subscale, BDI: Beck Depression Inventory. ¥ Pre-quit levels for former smokers. # Median and interquartile range shown for data analysed with non-parametric tests. ~ FS > AS, p = 0.003; FS > SS, p = 0.017; NS > AS, p = 0.038; NS > SS, p = 0.038.

3.2 Acquisition Errors

The groups did not differ on number of acquisition errors, either for the number of LSE made with 80-20% or 70-30% contingency pairs (H(3)=4.32, p=0.224; H(3)=1.06, p=0.789, respectively) or the

number of WMF made with the 80-20% or 70-30% contingency pairs (H(3)=4.92, p=0.178; H(3)=2.82, p=0.426, respectively). Table 2 shows these data.

Table 2: Reinforcement Learning Task acquisition errors and NicVAS change scores for abstinent (AS), satiated (SS), former (FS) and never (NS) smokers.

	Group (n = 15 per group)				
Acquisition Errors	AS	SS	FS	NS	
LSE 80-20 #	2.00 (3.00)	1.00 (2.00)	1.00 (2.00)	1.00 (2.00)	
LSE 70-30 #	3.00 (6.00)	3.00 (5.00)	3.00 (3.00)	2.00 (6.00)	
WMF 80-20 #	1.00 (2.00)	1.00 (2.00)	2.00 (4.00)	2.00 (3.00)	
WMF 70-30 #	3.00 (3.00)	3.00 (5.00)	4.00 (4.00)	2.00 (3.00)	
NicVas					Sig.
Alert	-2.40 (0.96)	26.40 (5.59)	2.93 (2.12)	-0.47 (0.43)	SS↑
Buzzed	-0.13 (0.17)	51.57 (6.78)	1.53 (0.66)	-0.07 (0.21)	SS↑
Contented	-5.97 (2.11)	34.07 (5.92)	0.47 (1.31)	-1.43 (0.79)	AS↓, SS↑
Dizzy	0.27 (0.23)	32.70 (7.43)	1.10 (0.52)	-0.03 (0.21)	SS↑
Impatient	9.87 (2.15	-31.90 (8.84)	1.40 (1.22)	0.23 (0.38)	AS↑, SS↓
Irritable	7.67 (2.04)	-26.57 (7.09)	0.90 (1.39)	0.93 (0.60)	AS↑, SS↓
Relaxed	-8.83 (2.82)	33.00 (6.40)	-1.23 (1.54)	-1.13 (0.64)	AS↓, SS↑
Stimulated	-1.10 (0.50)	25.00 (6.19)	2.10 (0.81)	0.23 (0.65)	SS↑

Data shown are mean and standard error of the mean. Abbreviations: NicVAS: nicotine-sensitive visual analogue scales, LSE: lose-stay errors, WMF: win-maintenance failures, 80-20 and 70-30 refer to the reward and punishment contingencies of the task pairs. # Median and interquartile range shown for data analysed with non-parametric tests. For NicVAS data values are percentage change: pre-performance monitoring assessment (T2) minus baseline (T1). ↑ = T2 > T1, ↓ = T2 < T1 (all p-values < 0.05).

3.3 Integration of Recent Reinforcement History

Figure 1 shows the change scores for LSE and WMF from acquisition to reversal for each group. As the number of errors split by contingency (80-20% and 70-30%) were low, group differences in these change scores were investigated irrespective of contingency. The groups did not differ in LSE change scores (H(3)=0.37, p=0.944) but did differ in WMF change scores (H(3)=10.49, p=0.011). WMF change score was significantly greater for former smokers than for satiated smokers (satiated smokers made more errors in reversal; U=46.50, z=-2.77, p=0.005, r=-0.51) and the same was true for never smokers compared to satiated smokers (U=64.50, z=-2.03, p=0.041, r=-0.37). Greater WMF change

scores in former smokers compared to abstinent smokers and in former smokers compared to never smokers were also present, at trend level (U=66.00, z=-1.95, p=0.052 and U=70.00, z=-1.78, p=0.075 respectively). There were no other significant group differences in WMF change score.

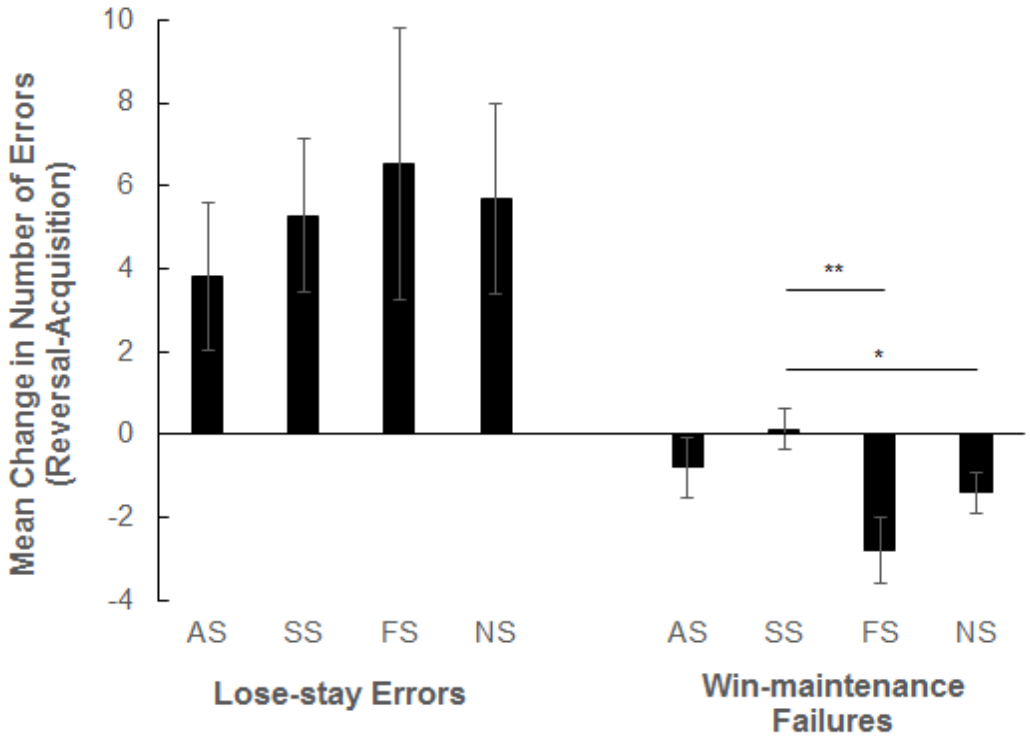

Figure 1: Group differences in change in number of errors from acquisition to reversal.
Data shown are means with error bars representing standard error of the mean. Abbreviations: AS: abstinent smokers, SS: satiated smokers, FS: former smokers, NS: never smokers. Significantly greater change in FS and NS compared to SS ** p = 0.005, * p < 0.05.

3.4 Post-punishment Slowing of Reaction Time

Figure 2 shows the PPS data for each group. The groups significantly differed in PPS ($F(3,56)=5.57$, $p=0.002$). Former, never and abstinent smokers had significantly greater slowing than satiated smokers ($p<0.001$, $r=0.60$; $p=0.003$, $r=0.47$ and $p=0.026$, $r=0.45$ respectively). There were no other significant group differences in PPS.

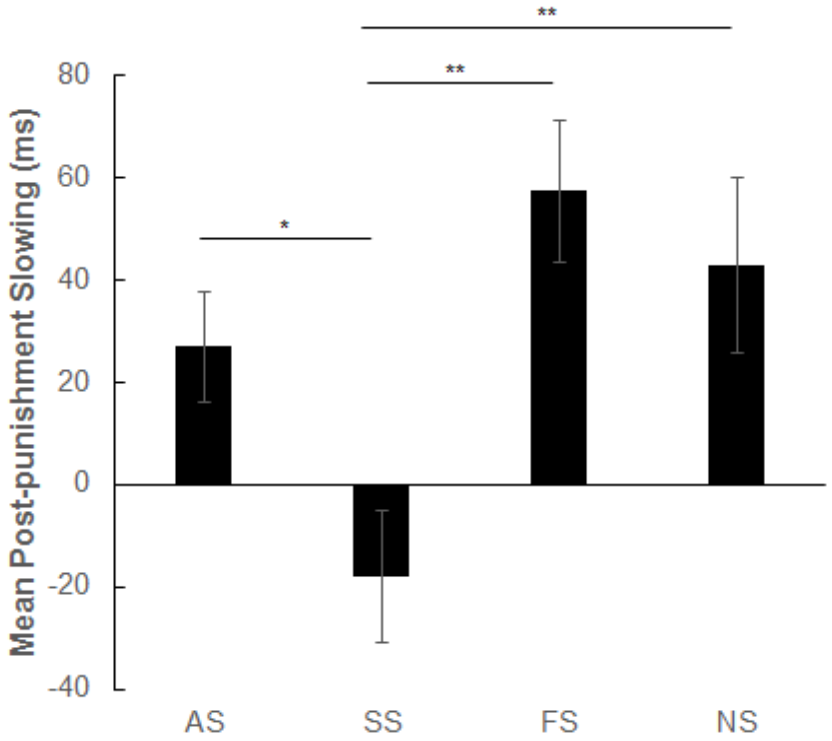

Figure 2: Group differences in post-punishment slowing.
Data shown are means with error bars representing standard error of the mean. Abbreviations: AS: abstinent smokers, SS: satiated smokers, FS: former smokers, NS: never smokers, ms: milliseconds. Significantly greater post-punishment slowing in FS, NS and AS compared to SS ** $p < 0.005$, * $p < 0.05$).

3.5 Effectiveness of the Smoking Manipulation

Exhaled CO levels, craving scores and NicVAS all changed in expected directions from baseline consistent with the satiated group having smoked and the abstinent group remaining abstinent. For exhaled CO levels there was a significant time by group interaction ($F(6,112)=95.11$, $p<0.001$) such that immediately before and after PM assessment satiated smokers had higher exhaled CO levels (mean: 12.27ppm, SEM: 0.71 and mean: 12.00ppm, SEM: 0.70 respectively) than abstinent (mean: 5.67ppm, SEM: 0.69 and mean: 5.20ppm, SEM: 0.74 respectively), former (mean: 1.40ppm, SEM: 0.29 and mean: 1.20ppm, SEM: 0.28 respectively) and never smokers (mean: 1.00ppm, SEM: 0.26 and mean: 0.73ppm, SEM: 0.21 respectively; all p-values<0.001). Craving scores in satiated smokers fell significantly after smoking (from median: 4.70, IQR: 1.40 to median: 2.00, IQR: 0.80; z=-3.41,

p=0.001) and remained significantly lower than baseline at the end of the study (median: 3.00, IQR: 1.70; z=-3.41, p=0.001). In abstinent smokers craving scores increased significantly from baseline (median: 4.70, IQR: 1.30) to immediately prior to PM assessment (median: 5.50, IQR: 1.30; z=-2.99; p=0.003). Craving scores in abstinent smokers were significantly higher than those of satiated smokers immediately prior to PM assessment (U=4.50, z=-4.49, p<0.001). For clarity Table 2 shows NicVAS change scores (pre-PM assessment minus baseline) for items that significantly changed over time.

3.6 Sensitivity Analysis

WMF change score significantly negatively correlated with PPS (r_s = -0.37, p = 0.004) such that a larger, positive WMF change score, indicating poorer integration ability, was associated with less slowing following negative feedback. Furthermore, a sensitivity analysis indicated that the WMF change score correctly identified 83% of the current smokers and 80% of the former smokers while the PPS index correctly identified 80% of the current smokers and 60% of the former smokers.

4. DISCUSSION

Here we report the first study comparing abstinent, satiated, former and never smokers on a behavioural index of PM that measures ability to integrate recent reinforcement history. Group differences in the change in WMF metric suggest that the groups did indeed differ in their ability to integrate recent reinforcement history. Former and never smokers made fewer errors in reversal, compared to acquisition, than did satiated smokers. This suggests former and never smokers have more effective PM and that current smokers have poorer PM. Whether impaired PM is a cause or a consequence of chronic drug taking remains to be fully determined. However, impaired PM during adolescence has been found to pre-date and predict subsequent initiation of tobacco use[49] and the use of animal models using similar behavioural indices (e.g. Jackson et al.[50]) may help to shed light on this. The superior PM shown by former smokers in the present study could equally represent a fundamental group difference that made it easier for this group to be able to maintain abstinence, a

compensatory mechanism that facilitates abstinence, or an indication of recovery from the long-term effects of smoking. The current data do not allow us to discriminate these alternatives.

Successful long-term abstinence appears to be associated with effective PM. Evidence from the cocaine literature suggests that PM may increase as abstinence proceeds.[51,52] Previous work in nicotine dependence has found significantly greater neural activity in prefrontal cortical regions during error monitoring on a response inhibition task in former smokers compared to both current smokers and never smokers.[13] Our data showing the greatest levels of PM in former smokers is consistent with these imaging findings. Together, this suggests PM might prove a useful target for maintaining abstinence. Interestingly, inhibitory control training has been investigated for potential therapeutic benefit in addictive disorders[53] although the precise mechanism by which training reduces inappropriate behaviours is still debated.[54,55] Training of PM may be an implicit component of these interventions, as tasks used in training (e.g. stop-signal, go/no-go) also require PM.[56,57] However, the relative contribution of strengthened inhibitory control or PM in reducing drug use remains to be established. Future research that dissociates inhibition capacity and PM ability before and after inhibitory control training and that directly assesses the potential benefit of training when it is appropriate to implement control (i.e. PM training) may inform future mechanism-driven interventions for nicotine dependence and addictive disorders in general. Studies suggest that reduced PM may lead to increased drug relapse[58-60]. Furthermore, PM can be improved with non-invasive transcranial direct current stimulation (tDCS) of the medial-frontal cortex[61] and tDCS of the nearby dorsolateral prefrontal cortex increases ability to resist smoking.[62] However further prospective studies exploring the relationship between PM, treatment outcomes, relapse and successful long-term abstinence are required.

Results for abstinent compared to satiated smokers were not as predicted. Similar to the present findings, previous research has reported reduced PM in current smokers although there are a number of differences between the previous work and our own. For example Luijten et al.[10] found a reduced

electrophysiological correlate of PM and reduced post-error slowing of reaction times in minimally deprived abstinent smokers compared to never smokers. The study did not include satiated smokers, but it is possible that non-deprived smokers would have shown further reductions in PM. In apparent contrast to our results, showing the poorest PM in satiated as opposed to abstinent smokers, Schlienz et al.[16] found reduced PM after overnight abstinence relative to satiation. However the participants in that study were older (mean age: 40 years), had more years of smoking (mean: 23 years), used more cigarettes per day (mean: 22) and were more dependent (mean FTND score: 5.6). In addition they used an electrophysiological approach and assessed PM during an Eriksen flanker task so the studies also differed in experimental techniques and task-related demands on various aspects of cognitive control. They also asked smokers to smoke as usual prior to testing, so there may have been dosing differences between the two studies.

There are several strands of evidence that are indirectly supportive of poorer PM in satiated smokers. Firstly smoking a cigarette causes the release of striatal and cortical dopamine.[63-65] This smoking-induced dopamine release, that is non-contingent with task performance, may therefore interfere with the integration of error signals by masking the phasic decrease in dopamine that normally accompanies events that are worse than expected.[66] In concordance with this poorer PM (reduced post-error slowing, calculated in a similar manner to our PPS index) has been found in healthy participants administered amphetamine.[67] Although improved PM (assessed electrophysiologically) has also been found with amphetamine administration.[68] Secondly, reduced PM might be expected to lead to deficient implementation of cognitive control and impairments in adapting behaviour. Indeed increased impulsive action and impulsive choice and impairments in cognitive flexibility following nicotine administration in rats[69-75] or following smoking in humans[40,76] have been reported. Although baseline dopamine levels[77] and impulsivity[78] may influence these effects.

We did not find any significant group differences in change in LSE. We interpreted change in LSE as reflecting inappropriate perseveration. Although integration of information over time is likely to

influence perseveration, the amount of perseveration an individual displays may also depend on other factors such as the ability to inhibit previously learned information (in this case previously learned stimulus-outcome associations). Thus, change in LSE may be a less sensitive index of integration of information over time than change in WMF, where we saw group differences emerging. We also found that change in WMF scores correlated with PPS which we suggest is because both are assessing processes that are relevant for effective PM. In addition, a preliminary sensitivity analysis indicated that the integration metric was as good, if not better, than a traditional behavioural PM metric at determining current and former smoker status.

There are a number of strengths to this study. The inclusion of both abstinent and satiated smokers, accommodation of natural smoking preferences: smokers used their own cigarettes, as opposed to 'study cigarettes', so they could smoke to satiation as they would in a natural setting; also, the smoking manipulation was validated by physiological and subjective measures. The lack of group differences in acquisition errors means that the number of errors/amount of negative feedback received does not confound our findings. There were also some limitations to this study. The moderate nicotine dependence of the current smokers and the relatively young age of participants across groups are important considerations; we cannot say for certain that the present findings would generalise to older and/or more severely dependent populations where abstinence could potentially lead to withdrawal-induced behavioural impairment. Current and former smoker groups were not matched with respect to FTND scores meaning that there could have been differences in dependence/prior dependence levels. However retrospective assessment of dependence can be inaccurate due to problems with recall and bias. For this reason, we chose to match groups with respect to number of cigarettes smoked per day which has previously been found to account for a high degree of variance in dependence questionnaire scores.[79,80] The association between use and dependence is logical given that greater use is likely to increase dependence risk and greater dependence is likely to drive further use. A small sample size and a small number of RLT errors mean that the findings reported here need to be replicated in a larger sample, possibly with more difficult

contingencies. It should be noted, however, that despite the current sample size, group differences with medium effect sizes were found across two different PM indices. Replication should also consider matching participants more closely particularly with regard to gender as previous studies report gender differences in PM.[81,82] However covariate analysis suggests that this did not affect our results.

Notwithstanding limitations we report medium effect sizes for the significant group differences in PM. The groups differed for both the integration of reinforcement history index (change in WMF) and a more traditional behavioural index of PM (PPS) with a consistent pattern across both indices, such that former smokers > never smokers > abstinent smokers > satiated smokers. As far as we are aware this is the first study to consider PM in terms of reinforcement integration in a substance dependent population. This is important because an integration metric more closely fits theoretical accounts of PM and on a practical level it offers researchers an alternative behavioural index. In sum our findings in combination with existing literature suggest that current smokers, particularly those that have recently smoked have impaired PM compared to former and never smokers. Furthermore intact or even superior PM in former smokers provides further support for its importance in long-term abstinence, but both prospective and intervention studies are needed to examine the relationship between PM and successful long-term abstinence and to further ascertain PM's suitability as a target for relapse prevention.

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DECLARATION OF INTERESTS

None declared.

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