

20 **ABSTRACT**

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

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

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

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

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

47 1. INTRODUCTION

48 Our ability to monitor our own on-going behaviour for errors or conflict (performance monitoring,
49 PM) is an important aspect of adaptive cognition. PM is fundamental to the implementation of top-
50 down control of behaviour so that behavioural adjustments can be made where appropriate and future
51 mistakes or decrements in performance prevented.¹ Hyperactive and hypoactive PM are consistently
52 reported in populations with internalising disorders (e.g. anxiety disorders) and externalising disorders
53 (e.g. substance use disorders) respectively.² Impaired PM is documented in populations with various
54 dependencies (e.g. opiate users,³ cannabis users,⁴ cocaine users,⁵ alcoholics with a family history of
55 alcohol problems,⁶ and those with internet addiction disorder⁷). This suggests that hypoactive PM may
56 be a mechanism by which maladaptive behaviours (such as drug taking) persist despite negative
57 consequences and further, that it may be a transdiagnostic, endophenotypic cognitive marker of
58 addiction.⁸

59
60 There is a growing body of research regarding PM and the response to error in tobacco dependence.
61 Electrophysiological and behavioural correlates of PM have been reported in smokers and non-
62 smokers during Flanker tasks.^{9,10} In these conflict resolution tasks participants make behavioural
63 selections depending on the identity of a central target that is flanked by either congruent or
64 incongruent distractors.¹¹ Diminished electrophysiological correlates of PM in smokers compared to
65 non-smokers were found in both studies and one study also found that smokers had a decreased post-
66 error slowing of reaction time compared to non-smokers.¹⁰ Similarly, imaging studies have shown
67 reduced error-related neural activity in smokers compared to non-smokers.¹²⁻¹⁴ Interestingly, an
68 increased electrophysiological correlate of PM has been reported in intermittent non-dependent
69 smokers compared to both dependent smokers and non-smokers¹⁵ and greater error-related brain
70 activation during inhibitory control performance was reported in former smokers compared to both
71 current and never smokers.¹³ This suggests that intact or enhanced PM may be an important
72 mechanism by which abstinence or reduced consumption is successfully maintained over the long-

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

75

76 Common across these studies of PM in nicotine dependence is that indices have focused on reaction
77 to error or conflict on individual trials. However rather than simply detecting and evaluating
78 individual trial error or conflict, there is evidence to suggest that PM involves the use of accumulated
79 evidence and learning over a number of trials. Specifically, behaviour is guided by the integration of
80 recent reinforcement (choice and outcome) history.¹⁷⁻²² For example, Holroyd and Coles²³ propose a
81 model of PM whereby midbrain dopaminergic learning signals indicating an actual outcome worse
82 than expected (negative prediction error) are carried to the error processing system (the anterior
83 cingulate cortex). This leads to implementation of control, which in turn results in behavioural
84 adjustments that optimise future performance. Using a decision making task where correctness of
85 individual choice was ambiguous, but where amount of reward received depended on response
86 history, Holroyd and Coles²¹ showed that this error processing system guides behaviour through the
87 integration of reinforcement information over time, rather than the evaluation of individual responses.

88

89 The present study is the first to compare PM in current, former and never smokers which considers
90 the ability to integrate reinforcement information over time. To do this we used a reinforcement
91 learning task (RLT) with acquisition and reversal phases (based on Budhani et al.²⁴). In this task
92 participants make timed behavioural choices between two differentially rewarded and punished
93 stimuli. In acquisition phases, participants learn which of the stimuli possess the optimum
94 reinforcement properties and during reversal phases the reinforcement properties of some of the
95 stimuli reverse. The changing reinforcement properties of reversing stimuli during the task provides
96 the PM measure of integration of reinforcement information over time (see Methods section). We also
97 included a traditional behavioural PM index based upon reaction to error on individual trials, post-
98 punishment slowing (PPS) of RLT reaction time. Slowing of reaction time following an error²⁵ may
99 reflect a mechanism for maintaining response accuracy that results from increased response caution as

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

110

111 **2. MATERIALS AND METHODS**

112 **2.1 Participants**

113 Sixty healthy participants (30 current smokers, 15 former smokers and 15 never smokers) aged 18-38
114 years were recruited using the following criteria: current smokers were required to smoke ≥ 10
115 cigarettes per day for ≥ 12 months, former smokers were required to have had pre-quit smoking levels
116 comparable to the current smoker group and to have remained abstinent for ≥ 6 months. Never
117 smokers were required to have smoked ≤ 5 cigarettes in their lifetime. Participants were required to be
118 medication free (excluding contraceptives), refrain from using illicit drugs for ≥ 1 week and arrive at
119 the laboratory having not consumed alcohol for ≥ 12 hours. Current smokers were required to arrive
120 after overnight abstinence and were randomly assigned to either a satiated or abstinent group to create
121 4 experimental groups: abstinent smokers, satiated smokers, former smokers and never smokers ($n =$
122 15 per group). Group size was based on previous studies measuring PM and inhibitory control in
123 smokers.^{10,29} Ethical approval was obtained from the University of Brighton School of Pharmacy and
124 Biomolecular Sciences Research Ethics Committee. Participants gave written informed consent,
125 attended one 1.5 hour laboratory session and received £12 compensation for their time.

126

127 2.2 General Procedure

128 All participants completed an e-mail inclusion criteria screen 0-7 days prior to the laboratory session.
129 Current smokers also completed the Fagerstrom Test for Nicotine Dependence (FTND)³⁰ to assess
130 severity of dependence. Upon arrival, all participants were subject to breath alcohol (Lion Alcometer
131 SD-40; Lion Laboratories Ltd., Cardiff, UK) and exhaled carbon monoxide (CO) tests (Bedfont Micro
132 Smokerlyzer; Bedfont Scientific Ltd., Kent, UK) for overnight abstinence compliance. Participants
133 were excluded for a breath alcohol reading > 0 g/L or an exhaled CO level > 10 ppm³¹. As general
134 cognitive ability and personality may affect reinforcement learning and PM, participants completed a
135 battery of questionnaires and tests to assess impulsivity (Barratt Impulsiveness Scale, BIS-11³²),
136 sensitivity to reward and punishment (Behavioural Inhibition System/Behavioural Activation System
137 Scales, BIS/BAS³³), depression (Beck Depression Inventory, BDI³⁴), IQ (The National Adult Reading
138 Test, NART³⁵) and short-term memory (immediate word recall, IWR³⁶). To reduce
139 smoking/abstinence-related performance expectancies all smokers were told they would smoke at
140 some point during the session, but not when. The satiated group smoked one of their own cigarettes
141 before PM assessment and the abstinent group smoked at the end of the session so they did not leave
142 in a withdrawn state. The effectiveness of the smoking manipulation was assessed with subjective
143 (nicotine-sensitive visual analogue scales (NicVAS) and craving) and physiological (exhaled carbon
144 monoxide (CO) levels). Exhaled CO levels were re-measured before and after PM assessment.
145 NicVAS (based on Perkins et al.³⁷) ranged from 0 = 'not at all' to 100 = 'extremely' for the items:
146 'alert', 'buzzed', 'contented', 'dizzy', 'hungrier than usual', 'impatient', 'irritable', 'jittery', 'relaxed',
147 'stimulated' and 'thirsty'. NicVAS are known to be sensitive to acute smoking and abstinence³⁸⁻⁴⁰ and
148 were administered upon arrival and immediately before and after PM assessment. Craving
149 (Questionnaire of Smoking Urges-Brief Version, QSU-brief⁴¹) was also assessed in satiated and
150 abstinent smokers upon arrival, immediately before PM assessment and at the very end of the session
151 (after the abstinent smoker group had also smoked). PM was assessed with a RLT (described below)
152 presented on a laptop computer and programmed in E-Prime version 1.1 (Psychology Software Tools
153 Inc., Pittsburgh, PA, USA).

154

155 **2.3 Reinforcement Learning Task**

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

168

169 **2.3.1 Acquisition Errors**

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

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

182

183 **2.3.2 Integration of Recent Reinforcement History**

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

194

195 **2.3.3 Post-punishment Slowing of Reaction Time**

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

201

202 **2.4 Sensitivity Analysis**

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

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

209

210 **2.5 Statistical Analyses**

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

227

228 **3. RESULTS**

229 **3.1 Participants**

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

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

239

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

	Group (n = 15 per group)				Sig.
	AS	SS	FS	NS	
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

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

248

249 3.2 Acquisition Errors

250 The groups did not differ on number of acquisition errors, either for the number of LSE made with 80-
 251 20% or 70-30% contingency pairs (H(3)=4.32, p=0.224; H(3)=1.06, p=0.789, respectively) or the

252 number of WMF made with the 80-20% or 70-30% contingency pairs ($H(3)=4.92$, $p=0.178$;
 253 $H(3)=2.82$, $p=0.426$, respectively). Table 2 shows these data.

254

255

256

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

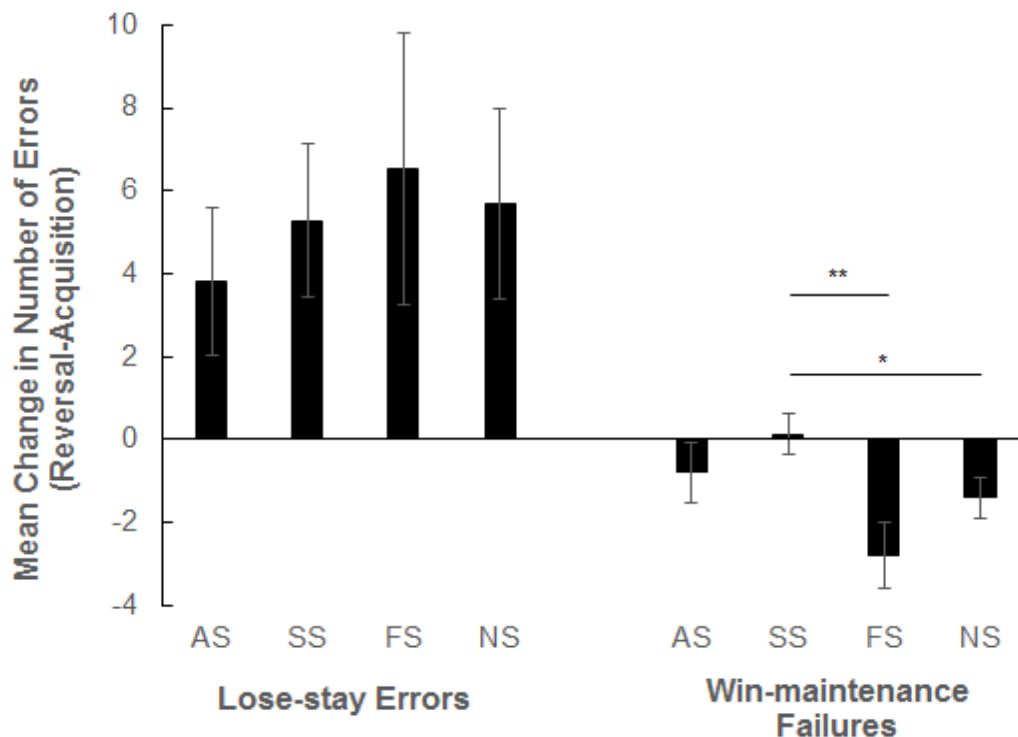
Acquisition Errors	Group (n = 15 per group)				Sig.
	AS	SS	FS	NS	
LSE 80-20 #	2.00 (3.00)	1.00 (2.00)	1.00 (2.00)	1.00 (2.00)	
LSE 70-30 #	3.00 (6.00)	3.00 (5.00)	3.00 (3.00)	2.00 (6.00)	
WMF 80-20 #	1.00 (2.00)	1.00 (2.00)	2.00 (4.00)	2.00 (3.00)	
WMF 70-30 #	3.00 (3.00)	3.00 (5.00)	4.00 (4.00)	2.00 (3.00)	
NicVas					
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↑

259 Data shown are mean and standard error of the mean. Abbreviations: NicVAS: nicotine-sensitive
 260 visual analogue scales, LSE: lose-stay errors, WMF: win-maintenance failures, 80-20 and 70-30 refer
 261 to the reward and punishment contingencies of the task pairs. # Median and interquartile range
 262 shown for data analysed with non-parametric tests. For NicVAS data values are percentage change:
 263 pre-performance monitoring assessment (T2) minus baseline (T1). ↑ = $T2 > T1$, ↓ = $T2 < T1$ (all p-
 264 values < 0.05).
 265

266 3.3 Integration of Recent Reinforcement History

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

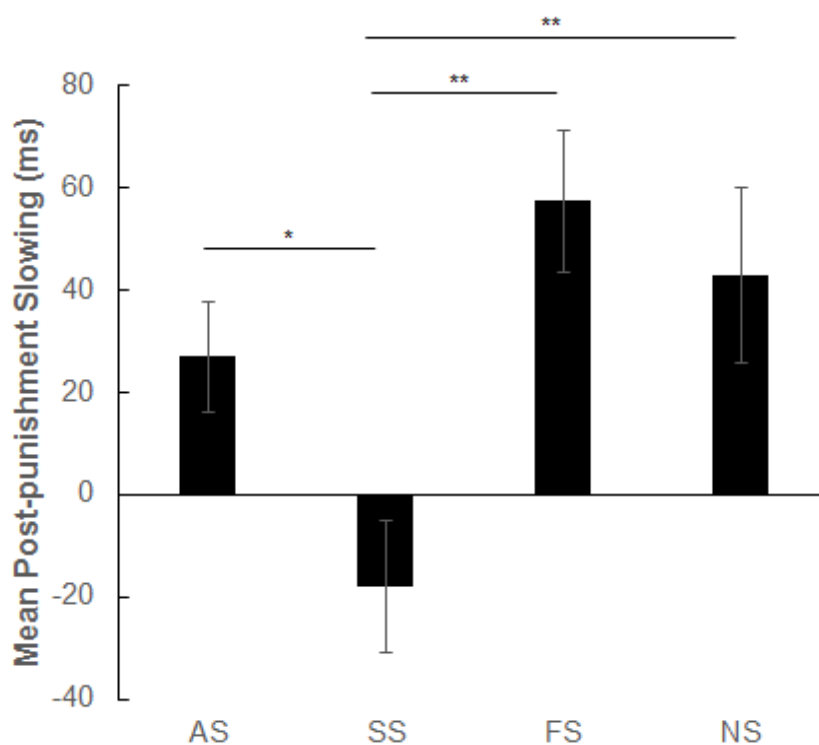
274 scores in former smokers compared to abstinent smokers and in former smokers compared to never
275 smokers were also present, at trend level ($U=66.00$, $z=-1.95$, $p=0.052$ and $U=70.00$, $z=-1.78$, $p=0.075$
276 respectively). There were no other significant group differences in WMF change score.
277



278 **Figure 1: Group differences in change in number of errors from acquisition to reversal.**
279 Data shown are means with error bars representing standard error of the mean. Abbreviations:
280 AS: abstinent smokers, SS: satiated smokers, FS: former smokers, NS: never smokers.
281 Significantly greater change in FS and NS compared to SS ** $p = 0.005$, * $p < 0.05$.
282
283

284 3.4 Post-punishment Slowing of Reaction Time

285 Figure 2 shows the PPS data for each group. The groups significantly differed in PPS ($F(3,56)=5.57$,
286 $p=0.002$). Former, never and abstinent smokers had significantly greater slowing than satiated
287 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
288 significant group differences in PPS.



289

290 **Figure 2: Group differences in post-punishment slowing.**

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

295

296 **3.5 Effectiveness of the Smoking Manipulation**

297 Exhaled CO levels, craving scores and NicVAS all changed in expected directions from baseline
298 consistent with the satiated group having smoked and the abstinent group remaining abstinent. For
299 exhaled CO levels there was a significant time by group interaction ($F(6,112)=95.11$, $p<0.001$) such
300 that immediately before and after PM assessment satiated smokers had higher exhaled CO levels
301 (mean: 12.27ppm, SEM: 0.71 and mean: 12.00ppm, SEM: 0.70 respectively) than abstinent (mean:
302 5.67ppm, SEM: 0.69 and mean: 5.20ppm, SEM: 0.74 respectively), former (mean: 1.40ppm, SEM:
303 0.29 and mean: 1.20ppm, SEM: 0.28 respectively) and never smokers (mean: 1.00ppm, SEM: 0.26
304 and mean: 0.73ppm, SEM: 0.21 respectively; all p -values <0.001). Craving scores in satiated smokers
305 fell significantly after smoking (from median: 4.70, IQR: 1.40 to median: 2.00, IQR: 0.80; $z=-3.41$,

306 p=0.001) and remained significantly lower than baseline at the end of the study (median: 3.00, IQR:
307 1.70; $z=-3.41$, $p=0.001$). In abstinent smokers craving scores increased significantly from baseline
308 (median: 4.70, IQR: 1.30) to immediately prior to PM assessment (median: 5.50, IQR: 1.30; $z=-2.99$;
309 $p=0.003$). Craving scores in abstinent smokers were significantly higher than those of satiated
310 smokers immediately prior to PM assessment ($U=4.50$, $z=-4.49$, $p<0.001$). For clarity Table 2 shows
311 NicVAS change scores (pre-PM assessment minus baseline) for items that significantly changed over
312 time.

313

314 **3.6 Sensitivity Analysis**

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

320

321 **4. DISCUSSION**

322 Here we report the first study comparing abstinent, satiated, former and never smokers on a
323 behavioural index of PM that measures ability to integrate recent reinforcement history. Group
324 differences in the change in WMF metric suggest that the groups did indeed differ in their ability to
325 integrate recent reinforcement history. Former and never smokers made fewer errors in reversal,
326 compared to acquisition, than did satiated smokers. This suggests former and never smokers have
327 more effective PM and that current smokers have poorer PM. Whether impaired PM is a cause or a
328 consequence of chronic drug taking remains to be fully determined. However, impaired PM during
329 adolescence has been found to pre-date and predict subsequent initiation of tobacco use⁴⁹ and the use
330 of animal models using similar behavioural indices (e.g. Jackson et al.⁵⁰) may help to shed light on
331 this. The superior PM shown by former smokers in the present study could equally represent a
332 fundamental group difference that made it easier for this group to be able to maintain abstinence, a

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

335

336 Successful long-term abstinence appears to be associated with effective PM. Evidence from the
337 cocaine literature suggests that PM may increase as abstinence proceeds.^{51,52} Previous work in
338 nicotine dependence has found significantly greater neural activity in prefrontal cortical regions
339 during error monitoring on a response inhibition task in former smokers compared to both current
340 smokers and never smokers.¹³ Our data showing the greatest levels of PM in former smokers is
341 consistent with these imaging findings. Together, this suggests PM might prove a useful target for
342 maintaining abstinence. Interestingly, inhibitory control training has been investigated for potential
343 therapeutic benefit in addictive disorders⁵³ although the precise mechanism by which training reduces
344 inappropriate behaviours is still debated.^{54,55} Training of PM may be an implicit component of these
345 interventions, as tasks used in training (e.g. stop-signal, go/no-go) also require PM.^{56,57} However, the
346 relative contribution of strengthened inhibitory control or PM in reducing drug use remains to be
347 established. Future research that dissociates inhibition capacity and PM ability before and after
348 inhibitory control training and that directly assesses the potential benefit of training when it is
349 appropriate to implement control (i.e. PM training) may inform future mechanism-driven
350 interventions for nicotine dependence and addictive disorders in general. Studies suggest that reduced
351 PM may lead to increased drug relapse⁵⁸⁻⁶⁰. Furthermore, PM can be improved with non-invasive
352 transcranial direct current stimulation (tDCS) of the medial-frontal cortex⁶¹ and tDCS of the nearby
353 dorsolateral prefrontal cortex increases ability to resist smoking.⁶² However further prospective
354 studies exploring the relationship between PM, treatment outcomes, relapse and successful long-term
355 abstinence are required.

356

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

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

371

372 There are several strands of evidence that are indirectly supportive of poorer PM in satiated smokers.
373 Firstly smoking a cigarette causes the release of striatal and cortical dopamine.⁶³⁻⁶⁵ This smoking-
374 induced dopamine release, that is non-contingent with task performance, may therefore interfere with
375 the integration of error signals by masking the phasic decrease in dopamine that normally
376 accompanies events that are worse than expected.⁶⁶ In concordance with this poorer PM (reduced
377 post-error slowing, calculated in a similar manner to our PPS index) has been found in healthy
378 participants administered amphetamine.⁶⁷ Although improved PM (assessed electrophysiologically)
379 has also been found with amphetamine administration.⁶⁸ Secondly, reduced PM might be expected to
380 lead to deficient implementation of cognitive control and impairments in adapting behaviour. Indeed
381 increased impulsive action and impulsive choice and impairments in cognitive flexibility following
382 nicotine administration in rats⁶⁹⁻⁷⁵ or following smoking in humans^{40,76} have been reported. Although
383 baseline dopamine levels⁷⁷ and impulsivity⁷⁸ may influence these effects.

384

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

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

395

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

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

419

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

433

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437

438 **DECLARATION OF INTERESTS**

439 None declared.

440

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445

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