



Citation for published version:

Lawn, W, Mithchener, L, Freeman, TP, Benattayallah, A, Bisby, JA, Wall, MB, Dodds, CM, Curran, HV & Morgan, CJA 2020, 'Value-based decision-making of cigarette and nondrug rewards in dependent and occasional cigarette smokers: An FMRI study', *Addiction Biology*, vol. 25, no. 4, e12802.
<https://doi.org/10.1111/adb.12802>

DOI:

[10.1111/adb.12802](https://doi.org/10.1111/adb.12802)

Publication date:

2020

Document Version

Peer reviewed version

[Link to publication](#)

Publisher Rights

CC BY-NC

This is the peer reviewed version of the following article: ,Lawn, W, Mithchener, L, Freeman, TP, et al. Value based decisionmaking of cigarette and nondrug rewards in dependent and occasional cigarette smokers: An FMRI study. *Addiction Biology*. 2019; e12802 which has been published in final form at <https://doi.org/10.1111/adb.12802>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

University of Bath

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1 **VALUE-BASED DECISION-MAKING OF CIGARETTE AND NON-DRUG**
2 **REWARDS IN DEPENDENT AND OCCASIONAL CIGARETTE SMOKERS: AN**
3 **FMRI STUDY**

4
5 Lawn, W.^{1*}, Mithchener, L.¹, Freeman, T.P.^{1,2,3}, Benattayallah, A.⁴, Bisby, J.A.⁵, Wall,
6 M.B.^{1,6}, Dodds, C.M.⁷, Curran, H.V.¹ & Morgan, C.J.A.^{1,8}

7 1 Clinical Psychopharmacology Unit, University College London, London, WC1E 7HB,
8 United Kingdom.

9 2 National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King's
10 College London, London, SE5 8BB, United Kingdom.

11 3 Addiction and Mental Health (AIM), Department of Psychology, University of Bath, Bath,
12 BA2 7AY, United Kingdom

13 4 Exeter MR Research Centre, University of Exeter, Exeter, EX1 2LU, United Kingdom

14 5 Institute of Cognitive Neuroscience, University College London, London, WC1N 3AZ,
15 United Kingdom

16 6 Invicro, Invicro London, Burlington Danes Building, Du Cane Road, London, W12 0NN,
17 United Kingdom.

18 7 Department of Psychology, University of Exeter, Exeter, EX4 4QG, United Kingdom

19 8 Psychopharmacology and Addiction Research Centre, University of Exeter, Exeter, EX1
20 2LU, United Kingdom

21 **Key words:** reward, addiction, nicotine, cigarette, decision-making, neuroeconomics

22 **Word count:**

23 Abstract: 248

24 Main body: 5,717

25 **Correspondence to:** Dr Will Lawn¹, will.lawn@ucl.ac.uk

26 **Conflicts of interest:** CJAM and HVC have consulted for Janssen pharmaceuticals. The
27 other authors have no conflicts of interest to declare. MBW's primary employer is Invicro
28 LLC, a private company which performs contract research work for the pharmaceutical and
29 biotechnology industries.

ABSTRACT

31 Little is known about the neural functioning that underpins drug valuation and choice in
32 addiction, including nicotine dependence. Following ad libitum smoking, 19 dependent
33 smokers (smoked ≥ 10 /day) and 19 occasional smokers (smoked 0.5-5/week), completed a
34 decision-making task. First, participants stated how much they were willing-to-pay for
35 various amounts of cigarettes and shop vouchers. Second, during functional magnetic
36 resonance imaging, participants decided if they wanted to buy these cigarettes and vouchers
37 for a set amount of money. We examined decision-making behaviour and brain activity when
38 faced with cigarette and voucher decisions, purchasing (vs. not purchasing) cigarettes and
39 vouchers, and 'value signals' where brain activity correlated with cigarette and voucher
40 value. Dependent smokers had a higher willingness-to-pay for cigarettes and greater activity
41 in the bilateral middle temporal gyrus when faced with cigarette decisions than occasional
42 smokers. Across both groups, the decision to buy cigarettes was associated with activity in
43 the left paracingulate gyrus, right nucleus accumbens and left amygdala. The decision to buy
44 vouchers was associated with activity in the left superior frontal gyrus, but dependent
45 smokers showed weaker activity in the left posterior cingulate gyrus than occasional smokers.
46 Across both groups, cigarette value signals were observed in the left striatum and
47 ventromedial prefrontal cortex. To summarise, nicotine dependence was associated with
48 greater behavioural valuation of cigarettes and brain activity during cigarette decisions. When
49 purchasing cigarettes and vouchers, reward and decision-related brain regions were activated
50 in both groups. For the first time, we identified value signals for cigarettes in the brain.

INTRODUCTION

53 Addiction can be considered a disorder fundamentally caused by maladaptive decision-
54 making (Redish et al., 2008; Schoenbaum and Shaham, 2008; Ekhtiari et al., 2017). Indeed,
55 decisions to continue to use drugs despite interpersonal or psychological and physical health
56 problems are diagnostic criteria for DSM-5 substance use disorders (American Psychiatric
57 Association, 2013). Decisions lie at the heart of our understanding of addiction. However,
58 one critical type of decision that has received scant attention within neuroscientific addiction
59 research is the decision to buy drugs.

60 Initial behavioural economics research on cigarette purchase (Jacobs and Bickel, 1999;
61 MacKillop et al., 2008) showed that, like for other reinforcers, cigarette consumption (i.e. the
62 number purchased) is at its maximum when cost is at its minimum and decreases as cost
63 increases. Furthermore, measures of demand for cigarettes correlate with nicotine dependence
64 (MacKillop et al., 2008; Murphy et al., 2011; Chase et al., 2013), are sensitive to cigarette
65 cues and withdrawal (MacKillop et al., 2012), and predict future smoking behaviour in those
66 attempting to quit (MacKillop et al., 2015). This demonstrates that addiction to cigarettes can
67 be successfully conceptualised in a behavioural economic framework.

68 ‘Neuroeconomics’ was born out of the combination of behavioural economics and cognitive
69 neuroscience (Glimcher and Rustichini, 2004; Glimcher et al., 2009), and studies what
70 happens in the brain when economic decisions are made. Building on the existing behavioural
71 economics work, three ‘neuroeconomics’ studies have examined neural activations associated
72 with decisions to buy drugs. These studies all combined functional magnetic resonance
73 imaging (fMRI) with a drug purchase task with real, financial consequences (MacKillop et
74 al., 2014; Bedi et al., 2015; Gray et al., 2017).

75 MacKillop et al. (2014) used the well-validated ‘alcohol purchase task’ (Murphy and
76 MacKillop, 2006) with 24 heavy alcohol drinkers. The participants made a series of decisions
77 about how many ‘mini-drinks’ they would buy for a range of prices (\$0 to \$15). Decisions to
78 buy alcohol were associated with activation in the medial prefrontal cortex (mPFC), posterior
79 parietal cortex (PPC), dorsolateral prefrontal cortex (dlPFC), posterior cingulate cortex
80 (PCC), and left anterior insula. The authors suggested these regions are specifically involved
81 in attention and intentionality (PPC), decisional balance (mPFC and dlPFC) and craving
82 (insula) (MacKillop et al., 2014).

83 Using an analogous task, the ‘cigarette purchase task’, Gray et al. (2017) examined brain
84 activation when 35 cigarette smokers (who smoked an average of 16 cigarettes per day) made
85 decisions about how many cigarettes they would buy for a range of prices (\$0 to \$10).
86 Decisions to buy cigarettes were associated with activation of the caudate and deactivation of
87 superior parietal lobule. Elastic decision-making (i.e. when consumption is substantially
88 affected by price) was associated with activation of medial frontal gyrus (meFG), middle
89 frontal gyrus (miFG), inferior frontal gyrus (iFG), insula, anterior cingulate cortex (ACC),
90 parietal lobule and dlPFC. The authors suggested that activity in the caudate was due to its
91 role in goal-directed action, meFG activity related to conflict processing and dlPFC activity
92 associated with inhibitory processes (Gray et al., 2017).

93 Bedi et al. (2015) used a slightly different approach in which 21 regular cannabis users made
94 yes/no decisions about whether they wanted to purchase a certain number of cannabis puffs
95 (1 to 12) for a specific price (\$0.25 to \$5). Multivariate analysis was employed to determine
96 which voxels’ activations were associated with decisions to buy cannabis, these were:
97 superior frontal gyrus (sFG), meFG, miFG, PCC, caudate, putamen, insula, inferior parietal
98 lobule and superior parietal lobule. Bedi et al. (2015) noted the similarity between their
99 results and Mackillop et al.’s (2014) results. Bedi et al. (2015) highlighted activation of the
100 bilateral dorsal striatum, which is thought to become more important in directing behaviour
101 towards drugs as addiction severity increases (Everitt and Robbins, 2005, 2016).
102 Furthermore, they linked the insula’s activity with interoception (Naqvi and Bechara, 2009)
103 and the PCC’s activity with subjective value (Clithero and Rangel, 2013).

104 Much *general* neuroeconomics research has focused on finding neural ‘value signals’ for
105 different commodities, i.e. brain regions where activity is directly proportional to the value of
106 the commodity presented (Montague and Berns, 2002; Plassmann et al., 2007; Rangel et al.,
107 2008; Rushworth and Behrens, 2008; Chib et al., 2009; Bartra et al., 2013). This research has
108 highlighted the critical roles of the ventromedial prefrontal cortex (vmPFC) and ventral
109 striatum (amongst others) in valuation processing. Indeed, in a study which directly informed
110 our methodology (Chib et al., 2009), activity in one region of the vmPFC correlated with
111 subjective value for three different types of reward: food, money and ‘trinkets’ (e.g. a hat).

112 Note that, ‘subjective value’ refers to a personal value assigned to an outcome by an
113 individual. This could be a rating of ‘value’ on an arbitrary scale from 0-10, the amount of
114 money the individual is willing to pay for the outcome, or a rating of how much the

115 individual ‘likes’ the outcome on consumption. Alternatively, a more ‘objective’ value can be
116 used to investigate valuation processing, e.g. the *number* of chocolates available in a
117 decision. In our study, we quantified subjective value, using participants’ willingness-to-pay
118 money for each reward, as in previous research (Becker et al., 1963; Chib et al., 2009).

119 Drug-related neuroeconomic research has not yet searched for drug value signals.
120 Furthermore, no comparative rewards have been used to investigate brain activity associated
121 with the valuation and purchase of drugs alongside that of non-drug rewards, despite this
122 strategy being employed in other areas of addiction research (Bühler et al., 2010; Chase et al.,
123 2013; Lawn et al., 2015).

124 Therefore, we do not know: (1) whether nicotine dependence is associated with differential
125 brain activity when purchasing cigarettes and non-drug rewards, (2) if cigarette value signals
126 exist in the expected brain areas, and (3) how the brain responds when valuing and
127 purchasing cigarettes and non-drug rewards within the same paradigm. In order to address
128 these gaps of knowledge, we conducted a cross-sectional fMRI study comparing dependent
129 and occasional cigarette smokers when they made purchase decisions about cigarettes and
130 vouchers.

131 *Hypotheses*

132 We hypothesised that dependent smokers would financially value cigarettes more than
133 occasional smokers. Based on the claim that addiction is underpinned by weakened goal-
134 directed and enhanced habitual drug-seeking (Everitt and Robbins, 2005, 2016), we also
135 hypothesised that dependent smokers would purchase more cigarettes than expected based on
136 the subjective values they assigned to the cigarettes available.

137 We predicted that the decision to purchase cigarettes and vouchers would be associated with
138 activity in reward-related and choice-related regions: mPFC, dlPFC, ACC, PCC, insula,
139 caudate/putamen and mFG/meFG/iFG/sFG. Moreover, we hypothesised that activity in these
140 regions would be greater when purchasing cigarettes and weaker when purchasing vouchers
141 in dependent smokers compared to occasional smokers.

142 We predicted that activity in the vmPFC and bilateral ventral striatum would correlate with
143 subjective cigarette and voucher value, on a trial-by-trial basis. Lastly, based on weaker goal-
144 directed drug-seeking (Everitt and Robbins, 2005, 2016), we predicted that the relationship

145 between subjective value of cigarettes and brain activity would be weaker in dependent
146 smokers than occasional smokers.

147

MATERIALS AND METHODS

148 *Participants*

149 A cross-sectional study design was employed. Nineteen dependent cigarette smokers (three
150 women) and 19 occasional cigarette smokers (six women) took part¹. Inclusion criteria for the
151 dependent smokers were: (1) Fagerstrom Test of Nicotine Dependence (FTND) score ≥ 5 , (2)
152 smoke ≥ 10 cigarettes per day on average. Inclusion criteria for the occasional smokers were:
153 (1) FTND=0, (2) smoke 0.5-5 cigarettes per week on average. Inclusion criteria for all
154 participants were: 18-50 years old, right-handed and normal or corrected-to-normal vision
155 with contact lenses. Exclusion criteria were: (1) seeking treatment for a mental health
156 problem; (2) using psychiatric medication; (3) use of any illicit drug once per week or more;
157 (4) quitting smoking; and (5) any MRI contraindications. Additionally, occasional smokers
158 were excluded if they had ever been a regular, daily cigarette smoker in the past. Participants
159 were told to smoke as normal before the study (i.e. they were *not* required to abstain from
160 smoking).

161 Recruitment was conducted via advertisements on Gumtree, in Exeter town centre and in the
162 University of Exeter. Participants were reimbursed £10/hour. All participants were given full
163 information about the study and provided written informed consent. The study was conducted
164 according to the guidelines of the Declaration of Helsinki and approved by the University of
165 Exeter Ethics Committee.

166 *Assessments*

167 *Value-based decision-making task (Chib et al., 2009)*

168 The structure of the task was based on a value-based decision-making task used previously
169 (Chib et al., 2009). The task was divided into two phases: a pre-scanning auction phase and a
170 scanning choice phase. Both phases involved making purchase decisions about cigarettes and
171 voucher ‘bundles’, i.e. different amounts of cigarettes/vouchers.

¹ We tested 23 dependent smokers and 20 occasional smokers. We excluded four dependent smokers for the following reasons: one smoked cannabis more than once per week, and we only found out during the testing session; one had a missing structural scan; one had an error in all functional data and one had no willingness to pay data recorded. We excluded one occasional smoker because they had an error in all functional scans. Therefore we had 19 participants in each group.

172 The cigarettes on offer were Marlboro, Camel or Lucky Strike and, within a bundle, they
173 varied in number from one to ten, e.g. ‘8 Marlboro cigarettes’ was one cigarette bundle. In
174 total there were 30 cigarette bundles. The vouchers were HMV, Amazon, Waterstones and
175 they varied in amount from one to ten, where one voucher = 20p, e.g. ‘4 Waterstones
176 vouchers’ was one voucher bundle. In total there were 30 voucher bundles. Each phase
177 consisted of 60 purchase decisions.

178 At the start of the pre-scanning phase, participants were given eight pounds in cash. They
179 were told that, across both phases, one of their choices about cigarette bundles and one of
180 their choices about voucher bundles would be *randomly chosen to happen in reality*.
181 Therefore, they should make every decision like it was real. They could spend a maximum of
182 four pounds on vouchers and four pounds on cigarettes, across both phases.

183 *Pre-scanning auction phase (see figure 1a)*

184 The pre-scanning phase was an auction, in which participants decided how much they would
185 like to spend on the total of 60 different cigarette and voucher bundles, ranging from £0.00 to
186 £4.00. The participant had as long as they wanted for each auction decision. The auction was
187 a Becker-DeGroot-Marschack (BDM) auction (Becker et al., 1963; Chib et al., 2009) and a
188 full description can be found in the supplementary materials.

189 *Scanning choice phase (see figure 1b)*

190 Subsequently, the participant entered the scanner and completed the scanning choice phase.
191 The participant faced a series of simple decisions in which they chose whether or not to buy a
192 cigarette or voucher bundle for a set amount of money. The set amount of money (for all
193 trials) was equal to their median willingness-to-pay (WTP) from the pre-scanning auction
194 phase. Each of these choices lasted for three seconds. This three second choice event is the
195 key event for the fMRI analyses in which we investigated value and choice processing across
196 and between the groups. Between the choices there were inter-trial intervals which varied
197 randomly in length from 1 to 10s (with an equal probability for each interval). The 60 trials
198 were fully randomised. The task lasted for nine minutes and 30 seconds. We presented words,
199 rather than images, in the task, in order to reduce cue reactivity.

200 *Other assessments*

201 We also measured depression with the Beck Depression Inventory (Beck et al., 1996),
202 nicotine dependence with the Fagerstrom Test for Nicotine Dependence (Heatherton et al.,
203 1991; Fagerström et al., 2012), tobacco use disorder (TUD) with the Diagnostic and
204 Statistical Manual 5 (American Psychiatric Association, 2013), carbon monoxide using a
205 Bedfont Micro Smokerlyzer (Bedfont Scientific, Harrietsham, UK) and premorbid verbal
206 intelligence with Spot The Word (Baddeley et al., 1993). More details can be found in
207 supplementary materials.

208 ***Procedure***

209 Participants attended one two-hour testing session. Before entering the scanner, they
210 completed the questionnaires, blew into the CO monitor and completed the pre-scanning
211 auction phase of the task. Subsequently, they entered the scanner and completed the scanning
212 choice phase of the task (which started roughly 30 minutes after the pre-scanning auction
213 phase), as well as two other tasks, which will be reported elsewhere (see supplementary
214 materials). After finishing the scanning, one cigarette-related decision and one voucher-
215 related decision from across both phases was selected to happen in reality. At the end of the
216 session, the participant was given their bonus payment of cigarettes, vouchers, and remaining
217 money.

218 ***Magnetic resonance image acquisition***

219 MRI data were collected on a Philips 1.5T scanner with an 8 channel sense head coil. For
220 functional scans, T2*-weighted, echo-planer images were collected using a sequence with the
221 following parameters: repetition time (TR)=3s, echo time (TE)=50ms. T1-weighted images
222 were collected for the structural scan. Further details can be found in the supplementary
223 materials.

224 ***Behavioural data analyses***

225 All behavioural data were analysed using IBM Statistical Package for Social Sciences (IBM
226 SPSS version 21).

227 Demographics and baseline smoking variables for dependent and occasional smokers are
228 described using means, standard deviations, medians and ranges. They were compared using

229 independent t-tests or Mann-Whitney U-tests, depending on whether the data met
230 requirements for parametric analysis.

231 ANOVAs with a between-subjects factor of Group (dependent and occasional) and Reward
232 (cigarette and voucher) were employed to analyse behavioural data. Bonferonni corrections
233 were applied to post hoc comparisons. We winsorized any outcome data above or below 2.5
234 standard deviations from the mean.

235 *fMRI data analyses*

236 Data were analysed using SPM12. Movement correction was carried out using 2nd degree b-
237 spline interpolation to realign all functional volumes to the mean functional volume. No
238 participant was excluded for movement, as all participants moved less than twice the voxel
239 size (6mm) in any direction throughout the task. Each person's structural image was co-
240 registered to their mean functional volume. Subsequently, a slice timing correction was
241 carried out on the functional volumes using SPM12's default settings. Then, the co-registered
242 structural image and the functional volumes were spatially normalised into Montreal
243 Neurological Institute (MNI) space using the SPM standard MNI template and affine
244 regularisation. Finally, the functional volumes were smoothed with an isotropic Gaussian
245 kernel for group analysis (8mm full-width at half-maximum).

246 *First level analyses*

247 Functional data were analysed using general linear models. We conducted two main analyses:
248 one concerning BOLD response when a reward was purchased vs. when it was not, and one
249 concerning the correlation between BOLD response and subjective valuation of reward (i.e.
250 WTP). We also conducted additional analyses investigating all cigarette and voucher choices,
251 regardless of purchase behaviour (reported in the supplementary materials).

252 We modelled the three-second choice events using boxcar functions convolved with the
253 default haemodynamic response function. For the choice-based first-level analyses, the events
254 modelled were: cigarette-choice-purchase, cigarette-choice-don't-purchase, voucher-choice-
255 purchase and voucher-choice-don't-purchase. For each individual we created a cigarette-
256 purchase>cigarette-don't-purchase contrast and a voucher-purchase>voucher-don't-purchase
257 contrast. For the value-based first-level analyses, we modelled all cigarette-choice and
258 voucher-choice events parametrically modulated by the WTP for the reward on offer in that

259 choice. For each participant, we were concerned with the beta associated with the cigarette
260 and voucher parametric modulation term. Movement parameters were also included in all the
261 models, as regressors of no interest.

262 *Second level analysis*

263 Subsequently, second-level random-effects models were used to investigate effects in the
264 entire sample and differences between the dependent and occasional smoker groups. At the
265 second level, we used cluster-based familywise error (FWE) correction to $p < 0.05$, with a
266 cluster defining threshold of $p < 0.005$. First, across both groups, we investigated cigarette-
267 purchase > cigarette-don't-purchase and voucher-purchase > voucher-don't-purchase using one-
268 sample t-tests. Second, we tested whether dependent smokers had greater cigarette-
269 purchase > cigarette-don't-purchase contrasts, and occasional smokers had greater voucher-
270 purchase > voucher-don't-purchase, using independent t-tests. In the supplementary materials,
271 we report these analyses again after excluding participants who made fewer than five
272 purchase or don't-purchase trials.

273 Third, we conducted analyses for 'value signals' for cigarettes and vouchers, using one-
274 sample t-tests on the parametric modulation betas from the first-level. We conducted a
275 regions of interest (ROI) analysis using regions based on a meta-analysis of value processing
276 (Bartra et al., 2013): left and right striatum, and the vmPFC (table 1). The regions were
277 defined using MarsBar (<http://marsbar.sourceforge.net/>) as spheres with co-ordinates in table
278 1 as the centres, and radii of 5mm. The ROIs were combined into a single mask and included
279 in the second level models. We then extracted the betas using MarsBar for each ROI within
280 each participant. One-sample t-tests were used to investigate value signals across groups and
281 independent t-tests to investigate differences between groups, with Bonferroni corrections. In
282 order to evaluate evidence in favour of the null hypothesis, scaled Jeffreys-Zellner-Siow
283 (JZS) Bayes factors were calculated using an online calculator
284 (<http://pcl.missouri.edu/bayesfactor>). We used the recommended scaled-information prior of r
285 $= 1$ (Rouder et al., 2009). A cut-off of three is used as evidence in favour of the null and a
286 cut-off of 1/3 is used as evidence in favour of the alternative hypothesis (Rouder et al., 2009).
287 We also conducted a whole-brain analysis for the value signals using the cluster-based
288 correction described above (reported in supplementary materials).

289 Additionally, we investigated main effects and group differences for all-cigarette-choices vs.
290 all-voucher-choices (regardless of behaviour), allowing for drug vs. non-drug reward
291 analyses. We also compared dependent and occasional smokers on all-cigarette-choices and
292 all-voucher-choices separately (see supplementary materials).

293 Finally, we extracted overall betas from the clusters that showed significant activation for
294 cigarette-purchase>cigarette-don't-purchase. Within the dependent smokers, we correlated
295 CO and FTND values with these betas and the value signal betas from the significant pre-
296 specified ROIs. We corrected for the number of correlations; α was reduced to 0.005.

297

298

RESULTS

299 *Demographics of participants (table 2)*

300 As a result of our criteria, dependent smokers by definition smoked more cigarettes/day and
301 had a higher FTND. All dependent smokers had at least mild TUD and the majority had
302 severe tobacco use disorder; only three occasional smokers had mild tobacco use disorder.

303 *Behavioural results*

304 *Willingness to pay in pre-scanning auction phase*

305 For mean WTP in the pre-scanning auction phase, there was a trend Group by Reward
306 interaction ($F_{1, 36}=3.874$, $p=0.057$) [Dependent: Cigarette mean (SD): 1.881 (0.589); Voucher
307 mean (SD): 1.618 (0.652); Occasional: Cigarette mean (SD): 1.004 (0.699); Voucher mean
308 (SD): 1.089 (0.673)]. There was also a main effect of Group ($F_{1, 36}=13.268$, $p=0.001$),
309 whereby dependent smokers had overall higher mean WTP scores than occasional smokers.
310 See supplementary materials for more details.

311 The groups' overall median WTPs differed significantly as well ($t_{34.323}=3.853$, $p<0.001$)
312 [Dependent median mean (SD): 1.716 (0.556); Occasional median mean (SD): 0.929
313 (0.696)].

314 *Number of choices in scanning choice phase (Figure 2a & 2b)*

315 To show that the two phases worked correctly and coherently, we tested the hypothesis that
316 as WTP increased, the proportion of purchases in the scanning choice phase increased. In
317 support of this, we found a significant linear effect of WTP on proportion of purchases
318 ($F_{18}=28.705$, $p<0.001$).

319 For the number of purchases in the scanning phase, there was a Group by Reward interaction
320 ($F_{1, 36}=5.979$, $p=0.020$), and a main effect of Reward ($F_{1, 36}=9.005$, $p=0.005$) with cigarettes
321 bought more than vouchers. On exploration of the interaction, the dependent smokers made
322 cigarette purchases significantly more than voucher purchases ($t_{18}=3.468$, $p=0.006$), while
323 this was not the case for occasional smokers. Occasional smokers made marginally more
324 voucher purchases than dependent smokers ($t_{36}=1.522$, $p=0.078$). There was no evidence of a

325 difference in number of cigarette purchases between the groups. See the supplementary
326 materials for a full description of the distribution of cigarette and voucher choices.

327 Dependent smokers made an unpredictably large number of cigarette purchases based on
328 their individual WTP scores and their set prices ($t_{18}=2.973$, $p=0.032$). In other words, the
329 dependent smokers bought cigarette bundles (in the choice phase) for more money than they
330 thought they were worth (in the auction phase). However, this was not the case for vouchers,
331 or for either reward in the occasional smokers.

332 *fMRI Results*

333 *Choice-based analysis²*

334 *Across both groups (table 3 and figures 3 and 4a)*

335 The cigarette-purchase>cigarette-don't-purchase contrast was associated with greater activity
336 in three clusters, with peak activations in the (1) left paracingulate gyrus, (2) the left
337 amygdala and (3) the right nucleus accumbens. These clusters extended into (1) the left
338 ventromedial prefrontal cortex and left frontal pole; (2) the right hippocampus, right anterior
339 thalamus and across into the left nucleus accumbens and left anterior thalamus; (3) the left
340 hippocampus and left insular cortex.

341 The voucher-purchase>voucher-don't-purchase contrast was associated with activation in the
342 left superior frontal gyrus, which extended into the right superior frontal gyrus.

343 *Difference between groups (figure 4b)*

344 We tested whether dependent smokers compared to the occasional smokers had greater
345 activity for the cigarette-purchase>cigarette-don't-purchase contrast. We found no significant
346 activation for this contrast.

347 We tested whether occasional smokers had greater activity compared to dependent smokers
348 for the voucher-purchase>voucher-don't-purchase. We observed a significant cluster of
349 activation in the left PCC, extending into the left precuneus cortex.

350 *All cigarette and voucher choices (tables S2 & S3; figures S5 and S6)*

² In these choice-based analyses, two dependent smokers were excluded because they never purchased a single voucher bundle, so the modelling would not work. This left 37 participants (17 dependent smokers and 19 occasional smokers). Further exclusions were made in an analysis reported in the supplementary materials.

351 We also investigated overall effects and group differences for the all-cigarette-choices>all-
352 voucher-choices contrast (these included all trials, i.e. when the option – cigarette/voucher –
353 was both purchased and not purchased). The results can be found in the supplementary
354 materials. In summary, across both groups, being faced with a cigarette choice compared with
355 a voucher choice elicited greater activity in the left dorsal anterior cingulate cortex, right
356 angular gyrus, left inferior occipital cortex, left supplementary motor area and left inferior
357 frontal cortex (table S3 & figure S6). Dependent smokers showed greater activity during the
358 cigarette choice than occasional smokers in the bilateral middle temporal gyrus (table S2 &
359 figure S5).

360 *Value-based parametric modulation analysis*

361 *Region of interest analysis (figures 5a & 5b)*

362 *Across both groups*

363 We extracted beta values for the parametric modulation term in the left [-6 10 -6] and right
364 striatum [10 12 -6], and ventromedial prefrontal cortex [-2 50 -6]. We then conducted three
365 Bonferroni-corrected one-sample t-tests. For cigarettes, we found significant value signals in
366 the left striatum ($t_{37}=2.827$, $p=0.024$) and the vmPFC ($t_{37}=3.439$, $p=0.003$). For vouchers, we
367 found no evidence in favour of value signals in these regions.

368 *Difference between groups*

369 We then conducted independent t-tests on the extracted betas for the cigarette parametric
370 modulation terms. We found no significant differences between the groups for the left
371 striatum ($t_{36}=0.410$, $p=0.684$), right striatum ($t_{36}=1.468$, $p=0.159$) and vmPFC ($t_{36}=0.141$,
372 $p=0.889$). A Bayesian analysis provided evidence in favour of there being no group
373 difference in the left striatum (JZS Bayes factor=3.91) and the ventromedial prefrontal cortex
374 (JZS Bayes factor=4.17), but not in the right striatum (JZS Bayes factor=1.67).

375 *Correlations (figure 6)*

376 Within the dependent group, we observed a significant negative correlation between CO and
377 the beta values extracted from the left amygdala cluster in the cigarette-purchase>cigarette-
378 don't-purchase contrast ($r_{17}=-0.667$, $p=0.003$). No other correlations were significant.

379

380

DISCUSSION

381 We conducted a cross-sectional fMRI study to investigate value-based decision-making of
382 cigarettes and vouchers in dependent and occasional cigarette smokers. In support of our first
383 hypothesis, dependent smokers were more willing to spend greater amounts of money to buy
384 cigarettes than occasional smokers; dependent smokers chose to buy more cigarettes than
385 vouchers; and dependent smokers bought more cigarettes than expected based on their
386 individual WTP scores and set prices. Lending some support to our second hypothesis, across
387 both groups, the decision to purchase cigarettes was associated with significant activation in
388 the left paracingulate gyrus, left amygdala and right nucleus accumbens. Dependent smokers
389 had greater activity than occasional smokers in the bilateral middle temporal gyrus when
390 facing a cigarette choice (regardless of whether they purchased it or not). The decision to
391 purchase vouchers was associated with significant activation in the left superior frontal gyrus.
392 Occasional smokers activated the left PCC significantly more than dependent smokers when
393 deciding to purchase vouchers, which suggests the dependent smokers had a blunted response
394 to non-drug reward purchase. Partial support was provided for our third hypothesis: neural
395 value signals for cigarettes were identified in the pre-defined regions of the left striatum and
396 vmPFC, but no group differences were observed, and no value signals for vouchers were
397 identified. We found a negative relationship between CO and BOLD response in the left
398 amygdala when purchasing a cigarette bundle, within the dependent smokers.

399 As predicted, dependent smokers financially valued cigarettes more in the auction phase than
400 occasional smokers. Surprisingly, the dependent smokers were also more willing to spend
401 more money on vouchers than occasional smokers. Previously, we have found no differences
402 in motivation for non-drug rewards between dependent and occasional smokers (Lawn et al.,
403 2015; Lawn et al., 2017). This may be because different methodologies for measuring
404 motivation were employed: physical effort exertion vs. spending money.

405 In the choice phase, participants were more likely to buy a cigarette bundle if they had given
406 it a high WTP score in the auction phase. This correlation showed that the participants'
407 behaviour pre-scanning and during scanning was consistent and demonstrates that both
408 phases of the task worked successfully. Furthermore, in the choice phase, dependent smokers
409 chose to buy cigarette bundles more often than voucher bundles, while this was not the case
410 for occasional smokers. This is consistent with previous choice-based research with heavy vs.

411 light cigarette smokers (Hogarth and Chase, 2011, 2012; Chase et al., 2013; Lawn et al.,
412 2015; Lawn et al., 2017).

413 Notably, dependent smokers chose to buy more cigarette bundles than expected based on
414 their bundles' individual WTP scores and the set monetary price. In other words, even when
415 the cigarette bundle was worth less to them than the price offered, they would still buy it.
416 Behaviourally, this result provides some support theories of addiction which claim that drug-
417 seeking becomes less goal-directed and more habitual as dependence takes hold (Everitt and
418 Robbins, 2005; Goldstein et al., 2007; Everitt and Robbins, 2016). However, one criticism
419 with this logic is that in the time between the auction phase and the choice phase (roughly 30
420 minutes), cigarette subjective value may have increased for dependent smokers, due to further
421 nicotine deprivation. By this logic, the unpredictably large number of cigarette choices could
422 be caused by heightened cigarette value, rather than habitual cigarette purchasing.

423 Across both groups, buying a cigarette bundle compared with not doing so was associated
424 with activation in three clusters, spanning: (1) left paracingulate gyrus, left ventromedial
425 prefrontal cortex and left frontal pole; (2) left amygdala, left nucleus accumbens, left anterior
426 thalamus, right hippocampus and right anterior thalamus; (3) right nucleus accumbens, left
427 hippocampus and left insular cortex. Three of these regions were predicted based on the three
428 previous neuroeconomics of drug purchase studies (MacKillop et al., 2014; Bedi et al., 2015;
429 Gray et al., 2017): the anterior cingulate cortex (i.e. paracingulate gyrus), insula and mPFC.
430 The anterior cingulate has long been linked with reward-related decision-making (Bush et al.,
431 2002; Rogers et al., 2004), while the insula is thought to be important in interoception and
432 conscious urges to use drugs (Naqvi and Bechara, 2009). Indeed, cigarette smokers with
433 damage to the insula appeared to have a greater chance of cessation (Naqvi et al., 2007). Our
434 results here further support the role of the insula in maintaining nicotine dependence, via its
435 importance in the decision to buy cigarettes.

436 Only one previous study (MacKillop et al., 2014) reported mPFC involvement when the drug
437 (alcohol) was bought. Indeed, Bedi et al. (2015) remarked that this area was a notable
438 omission in their neural signature of cannabis purchase. Here we see that the left vmPFC was
439 activated when buying cigarettes, which we expected given its role in tracking value
440 (Plassmann et al., 2007; Chib et al., 2009; Sescousse et al., 2010). We also found activation
441 in the nucleus accumbens during cigarette purchase. The nucleus accumbens is the terminus

442 of the mesolimbic dopamine pathway and is well-known for its part in reward processing
443 (Ikemoto and Panksepp, 1999; Knutson et al., 2001).

444 Dependent smokers showed greater activity than occasional smokers when faced with a
445 cigarette choice (irrespective of their purchase behaviour) in the bilateral middle temporal
446 gyrus. This provides some evidence in favour of an augmented neural sensitivity to drug
447 reward in nicotine dependence. Gray et al. (2017) reported activation in the middle temporal
448 gyrus when participants were making cigarette choices in the ‘inelastic’ and ‘suppressed’
449 stages of economic decision-making. Although the middle temporal cortex is commonly
450 associated with object recognition and semantic processing, there is existing evidence that it
451 is important in decision-making (Krain et al., 2006) and specifically in addiction (Paulus et
452 al., 2005).

453 In this study, participants smoked *ad libitum* before arriving in order to limit the effect of
454 nicotine withdrawal in dependent smokers, which would not have existed in the occasional
455 smokers, had we enforced an abstinence period. However, the dependent smokers differed in
456 CO levels substantially, demonstrating differences in recent intensity of smoking and
457 therefore varying satiation. Contrastingly, the occasional smokers showed little variation.
458 Given satiation should affect neural processing of cigarette reward (McClernon et al., 2009;
459 Sweitzer et al., 2014), we investigated whether CO was negatively associated with activation
460 in regions involved in purchasing cigarette reward in dependent smokers. This was the case
461 in the left amygdala cluster, which extended into the left nucleus accumbens, right
462 hippocampus and bilateral anterior thalamus. The amygdala is thought to encode the current
463 value of reward (Gottfried et al., 2003) and the striatum is sensitive to valuation changes with
464 smoking satiety (McClernon et al., 2009; Sweitzer et al., 2014) and predicts future smoking
465 (Sweitzer et al., 2016). Future research should test whether nicotine deprivation enhances
466 brain activation when purchasing cigarettes.

467 Buying a voucher bundle compared with not buying a voucher bundle was associated with
468 activation in the left and right sFG. For their drug purchase contrasts, Bedi et al. (2015)
469 reported activation in the sFG/mFG/meFG; while Gray et al. (2017) reported activation in the
470 mFG/meFG/iFG. We did not observe any frontal gyrus activation for cigarette purchases, but
471 did for voucher purchases. The reason for this is unknown, but the results of all studies
472 combined support a role for the frontal gyrus in reward-related decision-making.

473 Occasional smokers, relative to dependent smokers, demonstrated greater activity in the left
474 PCC when purchasing a voucher compared to not. This suggests weaker brain activity during
475 the purchase of a non-drug reward in those with nicotine dependence compared to those
476 without. A weakened brain response to non-drug reward processing has sometimes been
477 observed in cigarette smokers (Peters et al., 2011; Rose et al., 2013); our result extends this
478 putatively diminished brain response to a non-drug reward *decision*.

479 In our three regions of interest (Bartra et al., 2013), we observed significant associations
480 between individual WTP scores and BOLD response in two of them: the left striatum and the
481 vmPFC. This is the first time that value signals for cigarettes have been identified, and they
482 appear in regions known to be critical in the valuation of both monetary and non-monetary
483 rewards (Bartra et al., 2013).

484 Note, in this study, like Chib et al. (2009), we measured subjective value using a behavioural
485 measure: WTP (Becker et al., 1963). We identified brain regions that have ‘value signals’ by
486 finding regions where activity was directly proportional to this subjective value, while
487 decisions were being made. As in Chib et al. (2009), the decisions were ‘do you want to buy
488 a bundle for £X’, where £X remained the same (the median WTP from the pre-scanning
489 auction phase) for every decision. Therefore, we know that a significant result in our
490 parametric modulation analysis means: this brain area has activity that changes linearly with
491 the subjective value of the bundle available.

492 We did not find group differences in these neural value signals, and a Bayesian analysis
493 supported the null hypothesis. This tentatively suggests the relationship between subjective
494 value of cigarettes and brain response is unrelated to nicotine dependence, hence opposing
495 our third hypothesis. Surprisingly, we did not find analogous value signals for vouchers. This
496 therefore precludes a discussion of the relationship between nicotine dependence and the
497 brain’s sensitivity to non-drug reward value.

498 *Strengths and limitations*

499 This study is highly novel; it is the second study to apply neuroeconomics to cigarette use and
500 the first to investigate the relationship between addiction and neural correlates of drug
501 purchase. Furthermore, our procedure had real-world outcomes, in that participants actually
502 earned real cigarettes and vouchers to take away with them. Therefore, one would hope that
503 the participants took the decisions seriously.

504 In comparison to the three most relevant previous studies, our sample of 38 is the largest.
505 However, because each group had only 19 participants, type II errors could have occurred
506 due to smaller individual group size. In retrospect, a more natural comparison reward may
507 have been food, as that is a consummatory reward. However, our concern about nicotine's
508 effects on appetite convinced us against that. The inclusion of an abstinence manipulation
509 would presumably enhance differences in neural activity between dependent and occasional
510 smokers (McClernon et al., 2009; Sweitzer et al., 2014) and should be tested in future work.

511 After excluding participants with a small number of purchase or don't-purchase trials, some
512 of our significant activations in purchase>don't-purchase contrasts became non-significant
513 (see supplementary materials). A further limitation of our study, briefly mentioned above, is
514 that the value assigned to cigarettes may have increased between the auction phase and the
515 choice phase in the dependent smokers, due to nicotine deprivation. Roughly 30 minutes
516 elapsed between these phases; an improvement would have been to measure WTP
517 immediately before the scanning choice phase or to monitor craving/wanting for cigarettes at
518 different times. However, as we found a strong association between bundle WTP and
519 likelihood of purchase, this suggests subjective value did not change dramatically between
520 phases.

521 *Summary*

522 In one of the first studies to apply neuroeconomics to cigarette use, we have identified
523 cigarette value signals in the brain for the first time in dependent and occasional smokers.
524 Additionally, we have highlighted the importance of specific brain regions in purchasing drug
525 (cigarette) and non-drug (voucher) rewards. Our results suggest that dependent smoking is
526 associated with perturbed behavioural valuation and purchase of cigarettes and vouchers.
527 Further, they provide tentative evidence that dependent smoking, in comparison to non-
528 dependent occasional smoking, is associated with altered neural activity when making
529 purchase decisions about drug and non-drug rewards.

530

531 ***Supporting information***

532 Supplementary materials can be found online in the Supporting Information section.

533

534 ***Acknowledgments***

535 We would like to thank Vikram Chib for answering questions about his task and providing
536 general advice.

537

538 ***Authors' contributions***

539 WL, CD, HVC, TF and CJAM designed the study. WL and AB collected the data. WL and
540 LM analysed the data. MBW, CD and JAB assisted with data analysis. WL, LM, CD, JAB,
541 MBW, HVC, TF and CJAM interpreted the results. WL wrote the first draft of the
542 manuscript. WL, TF, CJAM, MBW and JAB provided critical analysis of the manuscript. All
543 authors approved the final version of the manuscript.

544

545 ***Funding***

546 WL was funded by a Biotechnology and Biological Sciences Research Council PhD and is
547 now funded to work on a Medical Research Council grant. TF was funded by a Senior
548 Academic Fellowship from the Society for the Study of Addiction. HVC's research is funded
549 by MRC and by University College London Hospitals National Institute of Health Research
550 Biomedical Research Centre

REFERENCES

- 552 American-Psychiatric-Association (2013) Diagnostic and statistical manual of mental disorders (DSM-
553 5®): American Psychiatric Pub.
- 554 Baddeley A, Emslie H, Nimmo-Smith I (1993) The Spot-the-Word test: A robust estimate of verbal
555 intelligence based on lexical decision. *British Journal of Clinical Psychology* 32:55-65.
- 556 Bartra O, McGuire JT, Kable JW (2013) The valuation system: a coordinate-based meta-analysis of
557 BOLD fMRI experiments examining neural correlates of subjective value. *Neuroimage*
558 76:412-427.
- 559 Beck AT, Steer RA, Brown GK (1996) Beck depression inventory-II. *San Antonio* 78:490-498.
- 560 Becker GM, DeGroot MH, Marschak J (1963) Stochastic models of choice behavior. *Behavioral*
561 *science* 8:41-55.
- 562 Bedi G, Lindquist MA, Haney M (2015) An fMRI-based neural signature of decisions to smoke
563 cannabis. *Neuropsychopharmacology* 40:2657.
- 564 Bühler M, Vollstädt-Klein S, Kobiella A, Budde H, Reed LJ, Braus DF, Büchel C, Smolka MN (2010)
565 Nicotine dependence is characterized by disordered reward processing in a network driving
566 motivation. *Biological psychiatry* 67:745-752.
- 567 Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulate
568 cortex: a role in reward-based decision making. *Proceedings of the National Academy of*
569 *Sciences* 99:523-528.
- 570 Chase HW, MacKillop J, Hogarth L (2013) Isolating behavioural economic indices of demand in
571 relation to nicotine dependence. *Psychopharmacology* 226:371-380.
- 572 Chib VS, Rangel A, Shimojo S, O'Doherty JP (2009) Evidence for a common representation of decision
573 values for dissimilar goods in human ventromedial prefrontal cortex. *Journal of*
574 *Neuroscience* 29:12315-12320.
- 575 Clithero JA, Rangel A (2013) Informatic parcellation of the network involved in the computation of
576 subjective value. *Social cognitive and affective neuroscience* 9:1289-1302.
- 577 Ekhtiari H, Victor TA, Paulus MP (2017) Aberrant decision-making and drug addiction—how strong is
578 the evidence? *Current opinion in behavioral sciences* 13:25-33.
- 579 Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to
580 habits to compulsion. *Nature neuroscience* 8:1481.
- 581 Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years
582 on. *Annual review of psychology* 67:23-50.
- 583 Fagerström K, Russ C, Yu C-R, Yunis C, Foulds J (2012) The Fagerström Test for Nicotine Dependence
584 as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data.
585 *Nicotine & Tobacco Research* 14:1467-1473.
- 586 Glimcher PW, Rustichini A (2004) Neuroeconomics: the consilience of brain and decision. *Science*
587 306:447-452.
- 588 Glimcher PW, Camerer CF, Fehr E, Poldrack RA (2009) Introduction: A brief history of
589 neuroeconomics. In: *Neuroeconomics*, pp 1-12: Elsevier.
- 590 Goldstein RZ, Tomasi D, Alia-Klein N, Cottone LA, Zhang L, Telang F, Volkow ND (2007) Subjective
591 sensitivity to monetary gradients is associated with frontolimbic activation to reward in
592 cocaine abusers. *Drug and alcohol dependence* 87:233-240.
- 593 Gottfried JA, O'doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and
594 orbitofrontal cortex. *Science* 301:1104-1107.
- 595 Gray JC, Amlung MT, Owens M, Acker J, Brown CL, Brody GH, Sweet LH, MacKillop J (2017) The
596 neuroeconomics of tobacco demand: an initial investigation of the neural correlates of
597 cigarette cost-benefit decision making in male smokers. *Scientific Reports* 7:41930.
- 598 Heatherton TF, Kozlowski LT, Frecker RC, FAGERSTROM KO (1991) The Fagerström test for nicotine
599 dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British journal of*
600 *addiction* 86:1119-1127.

601 Hogarth L, Chase HW (2011) Parallel goal-directed and habitual control of human drug-seeking:
602 Implications for dependence vulnerability. *Journal of Experimental Psychology: Animal*
603 *Behavior Processes* 37:261.

604 Hogarth L, Chase HW (2012) Evaluating psychological markers for human nicotine dependence:
605 Tobacco choice, extinction, and Pavlovian-to-instrumental transfer. *Experimental and clinical*
606 *psychopharmacology* 20:213.

607 Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a
608 unifying interpretation with special reference to reward-seeking. *Brain Research Reviews*
609 31:6-41.

610 Jacobs EA, Bickel WK (1999) Modeling drug consumption in the clinic using simulation procedures:
611 demand for heroin and cigarettes in opioid-dependent outpatients. *Experimental and clinical*
612 *psychopharmacology* 7:412.

613 Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward
614 selectively recruits nucleus accumbens. *Journal of Neuroscience* 21:RC159-RC159.

615 Krain AL, Wilson AM, Arbuckle R, Castellanos FX, Milham MP (2006) Distinct neural mechanisms of
616 risk and ambiguity: a meta-analysis of decision-making. *Neuroimage* 32:477-484.

617 Lawn W, Freeman T, Hindocha C, Mokrysz C, Das R, Morgan C, Curran H (2015) The effects of
618 nicotine dependence and acute abstinence on the processing of drug and non-drug rewards.
619 *Psychopharmacology* 232:2503-2517.

620 Lawn W, Freeman TP, East K, Gaule A, Aston ER, Bloomfield MA, Das RK, Morgan CJ, Curran HV
621 (2017) The acute effects of a dopamine D3 receptor preferring agonist on motivation for
622 cigarettes in dependent and occasional cigarette smokers. *Nicotine and Tobacco Research*
623 20:800-809.

624 MacKillop J, Brown CL, Stojek MK, Murphy CM, Sweet L, Niaura RS (2012) Behavioral economic
625 analysis of withdrawal-and cue-elicited craving for tobacco: an initial investigation. *Nicotine*
626 *& Tobacco Research* 14:1426-1434.

627 MacKillop J, Murphy JG, Ray LA, Eisenberg DT, Lisman SA, Lum JK, Wilson DS (2008) Further
628 validation of a cigarette purchase task for assessing the relative reinforcing efficacy of
629 nicotine in college smokers. *Experimental and clinical psychopharmacology* 16:57.

630 MacKillop J, Murphy CM, Martin RA, Stojek M, Tidey JW, Colby SM, Rohsenow DJ (2015) Predictive
631 validity of a cigarette purchase task in a randomized controlled trial of contingent vouchers
632 for smoking in individuals with substance use disorders. *Nicotine & Tobacco Research*
633 18:531-537.

634 MacKillop J, Amlung MT, Acker J, Gray JC, Brown CL, Murphy JG, Ray LA, Sweet LH (2014) The
635 Neuroeconomics of Alcohol Demand: An Initial Investigation of the Neural Correlates of
636 Alcohol Cost–Benefit Decision Making in Heavy Drinking Men. *Neuropsychopharmacology*
637 39:1988.

638 McClernon FJ, Kozink RV, Lutz AM, Rose JE (2009) 24-h smoking abstinence potentiates fMRI-BOLD
639 activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology*
640 204:25-35.

641 Montague PR, Berns GS (2002) Neural economics and the biological substrates of valuation. *Neuron*
642 36:265-284.

643 Murphy JG, MacKillop J (2006) Relative reinforcing efficacy of alcohol among college student
644 drinkers. *Experimental and clinical psychopharmacology* 14:219.

645 Murphy JG, MacKillop J, Tidey JW, Brazil LA, Colby SM (2011) Validity of a demand curve measure of
646 nicotine reinforcement with adolescent smokers. *Drug and alcohol dependence* 113:207-
647 214.

648 Naqvi NH, Bechara A (2009) The hidden island of addiction: the insula. *Trends in neurosciences*
649 32:56-67.

650 Naqvi NH, Rudrauf D, Damasio H, Bechara A (2007) Damage to the insula disrupts addiction to
651 cigarette smoking. *Science* 315:531-534.

652 Paulus MP, Tapert SF, Schuckit MA (2005) Neural activation patterns of methamphetamine-
653 dependent subjects during decision making predict relapse. *Archives of general psychiatry*
654 62:761-768.

655 Peters J, Bromberg U, Schneider S, Brassens S, Menz M, Banaschewski T, Conrod PJ, Flor H, Gallinat J,
656 Garavan H (2011) Lower ventral striatal activation during reward anticipation in adolescent
657 smokers. *American Journal of Psychiatry* 168:540-549.

658 Plassmann H, O'Doherty J, Rangel A (2007) Orbitofrontal cortex encodes willingness to pay in
659 everyday economic transactions. *Journal of neuroscience* 27:9984-9988.

660 Rangel A, Camerer C, Montague PR (2008) A framework for studying the neurobiology of value-
661 based decision making. *Nature reviews neuroscience* 9:545.

662 Redish AD, Jensen S, Johnson A (2008) Addiction as vulnerabilities in the decision process. *Behavioral*
663 *and Brain Sciences* 31:461-487.

664 Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, Smith SM (2004) Distinct portions
665 of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing
666 in separable phases of decision-making cognition. *Biological psychiatry* 55:594-602.

667 Rose EJ, Ross TJ, Salmeron BJ, Lee M, Shakleya DM, Huestis MA, Stein EA (2013) Acute nicotine
668 differentially impacts anticipatory valence-and magnitude-related striatal activity. *Biological*
669 *psychiatry* 73:280-288.

670 Rouder JN, Speckman PL, Sun D, Morey RD, Iverson G (2009) Bayesian t tests for accepting and
671 rejecting the null hypothesis. *Psychonomic bulletin & review* 16:225-237.

672 Rushworth MF, Behrens TE (2008) Choice, uncertainty and value in prefrontal and cingulate cortex.
673 *Nature neuroscience* 11:389.

674 Schoenbaum G, Shaham Y (2008) The role of orbitofrontal cortex in drug addiction: a review of
675 preclinical studies. *Biological psychiatry* 63:256-262.

676 Sescousse G, Redouté J, Dreher J-C (2010) The architecture of reward value coding in the human
677 orbitofrontal cortex. *Journal of neuroscience* 30:13095-13104.

678 Sweitzer MM, Geier CF, Joel DL, McGurrian P, Denlinger RL, Forbes EE, Donny EC (2014) Dissociated
679 effects of anticipating smoking versus monetary reward in the caudate as a function of
680 smoking abstinence. *Biological psychiatry* 76:681-688.

681 Sweitzer MM, Geier CF, Denlinger R, Forbes EE, Raiff BR, Dallery J, McClernon F, Donny EC (2016)
682 Blunted striatal response to monetary reward anticipation during smoking abstinence
683 predicts lapse during a contingency-managed quit attempt. *Psychopharmacology* 233:751-
684 760.

685

686

687

TABLES

688 Table 1

689 We used regions from a meta-analysis of value processing (Bartra et al., 2013), which
690 combined monetary and non-monetary rewards: left and right striatum, and the ventromedial
691 prefrontal cortex (vmPFC). We used the centres found in the meta-analysis and used radii of
692 5mm.

693

Region	x	y	z
<i>Left striatum</i>	-6	10	-6
<i>Right striatum</i>	10	12	-6
<i>vmPFC</i>	-2	50	-6

696 Table 2

697 Demographics of participants. Dependent smokers and occasional smokers did not differ
 698 significantly on age, BDI or verbal intelligence, although there were trend differences for age
 699 and BDI, with dependent smokers slightly older and more depressed. Occasional smokers had
 700 spent significantly more time in formal education than dependent smokers. Dependent
 701 smokers smoked more cigarettes/day and had a higher FTND. All dependent smokers had at
 702 least mild tobacco use disorder (TUD) and the majority had severe tobacco use disorder; only
 703 three occasional smokers had mild tobacco use disorder. Mean (SD) [median, range].
 704 FTND=Fagerstrom test for nicotine dependence, DSM-TUD=Diagnostic and statistical
 705 manual of mental disorders–5 tobacco use disorder. CO=carbon monoxide. BDI=Beck
 706 depression inventory. ***p<0.001, °p<0.1, np non-parametric test used, °divided
 707 #cigarettes/week by seven for #cigarettes/day for the occasional smokers.

	Dependent	Occasional
Gender (women/men)	3/16	6/13
Age (years) ° np	29.5 (10.7) [24, 18-49]	22.7 (4.4) [21, 19-34]
FTND*** np	6.2 (1.0) [6, 5-8]	0.0 (0.0)
DSM-TUD (none/mild/moderate/severe)	0/4/4/11	9/7/2/1
# cigarettes/day*** °	18.7 (5.9) [17, 10-30]	0.5 (0.2) [0.6, 0.1-0.8]
CO (ppm)***	12.3 (7.1) [10, 2-30]	2.3 (1.7) [0-6]
BDI°	10.2 (8.7) [9, 0-34]	5.2 [3, 0-17]
Years in education***	12.3 (3.0) [16, 11-20]	16.3 (2.7) [11, 7-19]
Spot the word (# correct)	46.8 (5.6) [48.5, 37-55]	48.7 (6.5) [50, 33-56]

708

709 Table 3

710 Brain activation for the cigarette-purchase>cigarette-don't-purchase contrast across both
711 groups. The table shows: brain regions; cluster-corrected p values for each cluster; k (cluster
712 size) and peaks of each cluster in Montreal Neurological Institute co-ordinates.

Region	<i>p</i>(FWE-corr)	k	Peak co-ordinates in cluster [MNI, mm]
Left paracingulate gyrus	<0.001	211	-3 44 -4
Right nucleus accumbens	0.001	156	12 5 -13
Left amygdala	0.046	82	-27 -4 -19

713

714

FIGURE CAPTIONS

715 Figure 1

716 (a) Example of a pre-scanning auction trial. The participant was asked how much they were
717 willing to pay for a cigarette or voucher bundle (from £0.00 to £4.00). In this example, the
718 bundle is '4 Amazon vouchers'. Each voucher was worth 20p, and a cigarette was worth
719 approximately 20p in the UK at the time the study was conducted (2014). This phase of the
720 task provides an individual WTP score for each voucher and cigarette bundle for every
721 participant. The participant could take as long as they wanted for each trial. There were 60 of
722 these trials.

723 (b) Example of a scanning choice trial. The participant chose whether they would like to buy
724 a cigarette or voucher bundle for a set amount of money, which was equal to their median
725 WTP from the pre-scanning auction phase. If the participant wanted to buy the bundle, in this
726 example 6 Marlboro cigarettes for 70p, they selected the bundle option. If the participant did
727 not want to buy the bundle and did not want to spend any money, they selected the money
728 option. They had 3 seconds to make this choice. Then there was an inter-trial interval for 1-
729 10s. There were 60 of these trials. Across both phases, there were 120 decisions. Two of them
730 were chosen to happen in reality – one cigarette-related decision and one voucher-related
731 decision.

732

733 Figure 2

734 (a) The percentage of the bundles purchased in the scanning choice phase, as a function of the
735 bundles' WTP, across both groups and both rewards (cigarettes and vouchers). Error bars
736 represent standard error.

737 (b) Mean number of purchases for cigarette and voucher bundles in the scanning choice
738 phase. There was a significant interaction between Group and Reward ($p=0.020$), explained
739 by a significant difference between the number of cigarette and voucher purchases in the
740 dependent smokers ($p=0.006$) but not the occasional smokers. Furthermore, dependent
741 smokers bought an unpredictably high number of cigarette bundles based on the individual
742 WTP scores and the set price ($p=0.032$). Error bars represent standard error. $*p<0.05$;
743 $**p<0.01$.

744 Figure 3

745 Brain activation for the contrast cigarette-purchase>cigarette-don't-purchase, across both
746 groups in the vmPFC, left amygdala and right nucleus accumbens. Images are in the sagittal
747 view, in the following planes: left: x=-3, middle: x=12, right: x=-27. The colours represent z
748 values. The background image is a high-resolution version of the MNI152T1 template.

749

750 Figure 4

751 (a) Brain activation in the left superior frontal gyrus for the contrast voucher-
752 purchase>voucher-don't-purchase, across both groups. The cluster peak was at [-6 23 50],
753 and the cluster had 108 voxels with $p(\text{FWE-corr})=0.014$. Sagittal view in plane of x=-6,
754 coronal view in plane of y=23 and axial view in plane of z=50. The background image is a
755 high-resolution version of the MNI152T1 template.

756 (b) Occasional smokers showed greater activation than dependent smokers for the voucher-
757 purchase>voucher-don't-purchase, in the left posterior cingulate cortex. The cluster peak
758 was at [-21 -55 32], and the cluster had 86 voxels with $p(\text{FWE-corr})=0.041$. Sagittal view in
759 plane of x=-9, coronal view in plane of y=-55 and axial view in plane of z=32. The
760 background image is a high-resolution version of the MNI152T1 template.

761

762 Figure 5

763 (a) Extracted beta values for the parametric modulation term (by WTP) for the three ROIs:
764 left striatum, right striatum and ventromedial prefrontal cortex (vmPFC). Regions were
765 defined with centres from Bartra et al. (2013) and radii of 5mm. One-sample t-tests with
766 Bonferroni correction were conducted. Error bars represent standard errors. * $p<0.05$.

767 (b) Spheres show the regions of interest from which the betas were extracted from.

768

769 Figure 6

770 Relationship between expired carbon monoxide (CO) in parts per million (ppm) and overall
771 BOLD response in the significant left amygdala cluster (from the cigarette-

772 purchase>cigarette-don't-purchase contrast), within dependent smokers ($r_{17}=-0.667$,
773 $p=0.003$). Lines show line of best fit and 95% confidence intervals.

774

775