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

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ABSTRACT

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

INTRODUCTION

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

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

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

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

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

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

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

Note that, 'subjective value' refers to a personal value assigned to an outcome by an individual. This could be a rating of 'value' on an arbitrary scale from 0-10, the amount of money the individual is willing to pay for the outcome, or a rating of how much the individual ‘likes’ the outcome on consumption. Alternatively, a more ‘objective’ value can be used to investigate valuation processing, e.g. the *number* of chocolates available in a decision. In our study, we quantified subjective value, using participants’ willingness-to-pay money for each reward, as in previous research (Becker et al., 1963; Chib et al., 2009).

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

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

Hypotheses

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

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

We predicted that activity in the vmPFC and bilateral ventral striatum would correlate with subjective cigarette and voucher value, on a trial-by-trial basis. Lastly, based on weaker goal-directed drug-seeking (Everitt and Robbins, 2005, 2016), we predicted that the relationship between subjective value of cigarettes and brain activity would be weaker in dependent smokers than occasional smokers.

MATERIALS AND METHODS

Participants

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

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

Assessments

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

The structure of the task was based on a value-based decision-making task used previously (Chib et al., 2009). The task was divided into two phases: a pre-scanning auction phase and a scanning choice phase. Both phases involved making purchase decisions about cigarettes and 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.

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

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

Pre-scanning auction phase (see figure 1a)

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

Scanning choice phase (see figure 1b)

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

Other assessments

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

Procedure

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

Magnetic resonance image acquisition

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

Behavioural data analyses

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

Demographics and baseline smoking variables for dependent and occasional smokers are described using means, standard deviations, medians and ranges. They were compared using independent t-tests or Mann-Whitney U-tests, depending on whether the data met requirements for parametric analysis.

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

fMRI data analyses

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

First level analyses

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

We modelled the three-second choice events using boxcar functions convolved with the default haemodynamic response function. For the choice-based first-level analyses, the events modelled were: cigarette-choice-purchase, cigarette-choice-don't-purchase, voucher-choice-purchase and voucher-choice-don't-purchase. For each individual we created a cigarette-purchase>cigarette-don't-purchase contrast and a voucher-purchase>voucher-don't-purchase contrast. For the value-based first-level analyses, we modelled all cigarette-choice and voucher-choice events parametrically modulated by the WTP for the reward on offer in that choice. For each participant, we were concerned with the beta associated with the cigarette and voucher parametric modulation term. Movement parameters were also included in all the models, as regressors of no interest.

Second level analysis

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

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

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

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

RESULTS

Demographics of participants (table 2)

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

Behavioural results

Willingness to pay in pre-scanning auction phase

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

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

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

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

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

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

fMRI Results

Choice-based analysis[2]

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

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

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

Difference between groups (figure 4b)

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

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

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.

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

Value-based parametric modulation analysis

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

Across both groups

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

Difference between groups

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

Correlations (figure 6)

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

DISCUSSION

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

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

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

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

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

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

Only one previous study (MacKillop et al., 2014) reported mPFC involvement when the drug (alcohol) was bought. Indeed, Bedi et al. (2015) remarked that this area was a notable omission in their neural signature of cannabis purchase. Here we see that the left vmPFC was activated when buying cigarettes, which we expected given its role in tracking value (Plassmann et al., 2007; Chib et al., 2009; Sescousse et al., 2010). We also found activation in the nucleus accumbens during cigarette purchase. The nucleus accumbens is the terminus of the mesolimbic dopamine pathway and is well-known for its part in reward processing (Ikemoto and Panksepp, 1999; Knutson et al., 2001).

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

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

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

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

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

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

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

Strengths and limitations

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

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

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

Summary

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

Supporting information

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

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Authors' contributions

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

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TABLES

Table 1

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

Region	**x**	**y**	**z**
Left striatum	-6	10	-6
Right striatum	10	12	-6
vmPFC	-2	50	-6

Table 2

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

	Dependent	**Occasional**
Gender (women/men)	3/16	6/13
Age (years) $^{o\ np}$	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*** ^{c}	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^{o}	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]

Table 3

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

Region	***p*(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

FIGURE CAPTIONS

Figure 1

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

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

Figure 2

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

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

Figure 3

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

Figure 4

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

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

Figure 5

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

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

Figure 6

Relationship between expired carbon monoxide (CO) in parts per million (ppm) and overall BOLD response in the significant left amygdala cluster (from the cigarette-purchase>cigarette-don't-purchase contrast), within dependent smokers (r_{17}=-0.667, p=0.003). Lines show line of best fit and 95% confidence intervals.