Dopamine, urges to smoke, and the relative salience of drug versus non-drug reward

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When addicted individuals are exposed to drug-related stimuli, dopamine release is thought to mediate incentive salience attribution, increasing attentional bias, craving and drug seeking. It is unclear whether dopamine acts specifically on drug cues versus other rewards, and if these effects correspond with craving and other forms of cognitive bias. Here, we administered the dopamine D_2/D_3 agonist pramipexole (0.5 mg) to 16 tobacco smokers in a double-blind placebo-controlled crossover design. Visual fixations on smoking and money images were recorded alongside smoking urges and fluency tasks. Pramipexole attenuated a marked bias in initial orienting towards smoking relative to money but did not alter a maintained attentional bias towards smoking. Pramipexole decreased urges to smoke retrospectively after the task but not on a state scale. Fewer smoking words were generated after pramipexole but phonological and semantic fluency were preserved. Although these treatment effects did not correlate with each other, changes in initial orienting towards smoking and money were inversely related to baseline scores. In conclusion, pramipexole can reduce the salience of an addictive drug compared with other rewards and elicit corresponding changes in smoking urges and cognitive bias. These reward-specific and baseline-dependent effects support an 'inverted-U' shaped profile of dopamine in addiction.

INTRODUCTION

Drug addiction is often characterised by an increase in the incentive-motivational properties of the drug alongside a reduction in the salience of other non-drug rewards such as money, food or sex (Anselme, 2009; Bühler *et al.*, 2010; Goldstein and Volkow, 2011). This imbalance may be heightened during exposure to drug-related cues, which are able to overshadow non-drug stimuli that are equally predictive of financial reward (Freeman *et al.*, 2012a). A strong drive to seek out one's drug of choice alongside a lack of motivation to engage in other activities may consign addicted individuals to a recurring cycle of drug use and relapse, especially when they are exposed to previous drug-taking environments. Psychological treatments for addiction which target drug-related and non-drug reward processes can be effective (Petry, 2000; Curran and Drummond, 2005); however, the pharmacological mechanisms through which their relative salience might be shifted are not well understood.

Dopamine release in response to drug-associated stimuli is thought to change how these cues are perceived in addicted individuals, increasing craving and playing a causal role in drug use (Robinson and Berridge, 1993; Franken, 2003). This process of incentive salience attribution can be indexed as the extent to which drug cues capture selective attention, or 'attentional bias' (Franken, 2003; Field and Cox, 2008). Attentional bias to drug cues can predict relapse vulnerability (Waters *et al.*, 2003; Marissen *et al.*, 2006; Janes *et al.*, 2010; Powell *et al.*, 2010; Garland *et al.*, 2012) and offers a viable target for improving the effectiveness of treatment (Schoenmakers *et al.*, 2010). Dopaminergic involvement in attentional bias is supported by a number of experimental studies (Franken *et al.*, 2004; Munafò *et al.*, 2007; Hitsman *et al.*, 2008; Ersche *et al.*, 2010; Luijten *et al.*, 2012). According to a cognitive psychopharmacological

model of drug addiction (Franken, 2003), these effects should be accompanied by corresponding changes in drug-related craving and other cognitive biases; however, empirical support for this is currently lacking (Franken *et al.*, 2004; Munafò *et al.*, 2007; Hitsman *et al.*, 2008; Ersche *et al.*, 2010; Luijten *et al.*, 2012).

Another issue is that previous studies supporting a role of dopamine in drug-related attentional bias (Franken *et al.*, 2004; Munafò *et al.*, 2007; Hitsman *et al.*, 2008; Ersche *et al.*, 2010; Luijten *et al.*, 2012) did not examine the effects of these manipulations on the salience of non-drug reward stimuli such as images of money, which can also elicit attentional bias in drug users (Morgan *et al.*, 2008). These effects might be important clinically because the tendency to show weak responses to pleasant or reward-based images compared with drug-related stimuli is predictive of frequency of drug use at follow-up (Lubman *et al.*, 2009) and chances of relapsing during a subsequent quit attempt (Versace *et al.*, 2011). The implications of these findings are that pharmacological treatments, which aim to reduce the salience of drug-related cues alone may not be optimal, unless they act to redress an imbalance between the salience of the drug relative to that of non-drug rewards (Bühler *et al.*, 2010).

Pramipexole is a dopamine D_2/D_3 agonist used for the treatment of Parkinson's disease and restless leg syndrome. At low doses, its effects are indicative of preferential action at presynaptic autoreceptors rather than post-synaptic receptors (Maj *et al.*, 1997; Pizzagalli *et al.*, 2008). These autoreceptors respond to 'tonic' or background dopamine in a self-regulatory manner, by reducing the short-latency, short-duration 'phasic' dopamine firing that occurs to behaviourally relevant stimuli (Grace, 1991). Low dose pramipexole should therefore, through agonist action at presynaptic autoreceptors, reduce the phasic release of dopamine that occurs upon exposure to drug cues (Phillips *et al.*, 2003). Moreover, pramipexole acutely decreases regional cerebral blood flow in the anterior cingulate cortex and insula (Black *et al.*, 2002), activation of which has been linked to attentional bias in smokers (Janes *et al.*, 2010; Luijten *et al.*, 2011; Vollstädt-Klein *et al.*, 2011). Taken together, this suggests that pramipexole should decrease attentional bias to drug cues in smokers.

In this study, we examined whether a single low (0.5 mg) dose of pramipexole would reduce attentional bias towards smoking-related

cues. Both initial orienting and maintained attention were recorded because experimental manipulations have produced dissociable effects on these measures in smokers (Field *et al.*, 2004; Bradley *et al.*, 2007). We investigated whether similar or contrasting results would emerge for images of money, because smokers may show an imbalance in the salience of drug versus non-drug reward (Bühler *et al.*, 2010) and effects of dopamine agonists can differ according to baseline performance (Cools and D'Esposito, 2011). Since modification of attentional bias should be accompanied by corresponding changes in craving and other cognitive bias (Franken, 2003), we hypothesised that pramipexole would reduce tobacco craving and urges to smoke, which have previously been reported after treatment with a dopamine agonist (Caskey *et al.*, 1999, 2002; Jarvik *et al.*, 2000) and also 'drug fluency', or the free generation of smoking words from memory, which is theoretically related to attentional bias (Goldstein *et al.*, 2007).

MATERIALS AND METHODS

Design and participants

A randomized double-blind placebo-controlled crossover design was used to assess the effects of 0.5 mg pramipexole in 16 non-treatment-seeking smokers (8 men) recruited from the community. Inclusion criteria were as follows: age 18–40 years, smoking ≥10 cigarettes per day for ≥1 year, smoking a first cigarette ≤1 h after waking, normal or corrected to normal vision and fluent spoken English. Exclusion criteria were current use of any smoking cessation aid, a learning, mental health or substance abuse problem other than nicotine, tumours of the pituitary or adrenal gland, reduced liver or kidney function, pregnancy or breast feeding. All participants provided written, informed consent. This study was approved by the UCL Graduate School Ethics Committee and conducted in accordance with the Declaration of Helsinki. The tasks reported here formed part of a larger battery of tests reported elsewhere (Freeman *et al.*, 2012b).

Assessments

Visual probe task

Overt attention was recorded using an eye tracking device synchronized to a computer-based task. After central fixation, two images were presented side by side on screen. Both were 109-mm wide and 84-mm high, with a distance of 58 mm between their closest edges. They were presented in pairs consisting of a 'reward' image and a 'control' image matched for visual composition. For example in a smoking trial, a woman smoking a cigarette (reward image) was shown next to a woman applying lipstick (control image) and, in a money trial, UK bank notes (reward image) were displayed next to train tickets (control image). Two task versions were created using different stimulus sets to control for changes in novelty across the two testing sessions. Each version employed 8 buffer trials and 192 experimental trials, consisting of 10 pairs of monetary images expanded from a previous stimulus set (Morgan *et al.*, 2008) and 10 pairs of smoking images and 4 pairs of neutral filler images taken from Mogg *et al.* (2003) (Figure 1).

Immediately after stimulus offset, a blank screen was displayed with a probe in the same location as one of the previous images (reward or control). Participants were required to press a key corresponding to its identity (either 'up' or 'down'). No time limit or incentive was provided for responding to the probe. Faster reaction times (RTs) to respond to probes appearing in the same location as a reward image compared with a control image are indicative of attentional bias. Participants were asked to take in both of the images on screen and to respond to the probes as quickly and accurately as possible. Pairs of images were either shown for 250 or 2000 ms to index both initial orienting and maintained attention using RTs (Morgan *et al.*, 2010; Freeman *et al.*, 2012a). Each pair of images was presented four times
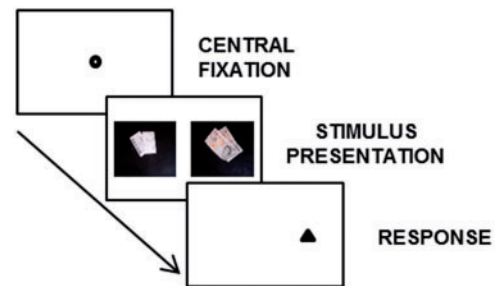

Fig. 1 Visual probe task. Following central fixation, two stimuli were displayed side by side for either 250 or 2000 ms. Experimental trials used smoking-related or money picture pairs, consisting of a reward image (shown here on the right; money) and a matching control image (shown on the left; train tickets). Eye tracking was used to determine the proportion of trials in which a first fixation occurred towards reward versus control images (initial orienting) and the duration of fixations on images across 2000 ms trials (maintained attentional bias). RTs to a probe at stimulus offset were used as a behavioural measure of attentional bias.

for 250 ms and four times for 2000 ms, interspersed throughout the task. Reward/control images appeared equally often on the left and the right and were replaced by the probe on an equal number of trials. Probe identity (up or down) was balanced across trials. Trials were randomised with a maximum of two trials from the same condition (money, smoking or neutral) shown in succession.

Picture rating task

This task presented the same images used in the visual probe task onscreen (109-mm wide and 84-mm high) and required participants to rate them for their pleasantness on a 7-item scale from −3 (very unpleasant) to +3 (very pleasant).

Phonological, semantic and drug fluency

Participants were asked to name as many unique exemplars as possible beginning with the same letter (M; phonological), from the same category (fruit; semantic), and related to smoking (drug fluency) in that order, based on Goldstein *et al.* (2007). Sixty seconds was provided for each variant.

Mood and physical symptoms scale

This 7-item scale includes 'Depression', 'Irritability', 'Restlessness', 'Hunger' and 'Poor Concentration' which were rated 'at this time' from 0 (not at all) to 4 (extremely) (West and Hajek, 2004). Time Spent with Urges ('How much of the time have you felt the urge to smoke in the past 2 hours?') was rated from 0 (not at all) to 5 (all the time) and Strength of Urges to Smoke (SUTS) ('How strong have these urges been?') was rated from 0 (no urges) to 5 (extremely strong).

Tobacco craving questionnaire-short form

Each of the 12 items on this scale were rated 'right now' from 1 (strongly disagree) to 7 (strongly agree); higher scores reflect stronger tobacco craving (Heishman *et al.*, 2008). It has 4 subscales: Emotionality e.g. 'I would be less irritable now if I could smoke', Expectancy e.g. 'I would enjoy a cigarette right now', Compulsivity e.g. 'If I smoked right now, I would not be able to stop', and Purposefulness e.g. 'If I had a lit cigarette in my hand, I would probably smoke it'.

Fagerström test for nicotine dependence

This scale of nicotine dependence consists of six items that are rated between 0 and 3, with scores ranging from 0 (low dependence) to 10 (high dependence) (Heatherton et al., 1991).

Motivation to stop scale

A single item combining desire and intention to quit smoking. Scores range from 1 (I don't want to stop smoking) to 7 (I REALLY want to stop smoking and intend to in the next month) (Kotz et al., 2012).

Procedure

Following screening, participants attended two 3-h laboratory sessions separated by a washout period lasting between 5 and 9 days. Participants were asked to fast for an hour before attendance, to refrain from caffeine consumption on the day of testing and to avoid driving or using machinery for the remainder of day. After smoking a cigarette, a carbon monoxide (CO) reading (Bedfont Micro Smokerlyzer, UK) and baseline assessments (Mood and Physical Symptoms Scale [MPSS], tobacco craving questionnaire-short form [TCQ-SF]) were taken. This was followed by oral drug administration, which was either 0.5 mg pramipexole (peak plasma levels at 1–3 h) (Wright et al., 1997) or matched placebo. Based on a previous experimental design (Ersche et al., 2010), the peripheral D_2 antagonist domperidone (30 mg) was co-administered on both days to reduce unwanted side effects of dopamine agonist treatment such as nausea and vomiting (Parkes, 1986). Smoking was not permitted for the remainder of each test session, which was enforced by supervision. After drug administration, participants were given trait questionnaires regarding mood and smoking behavior that were split across the two testing days [0–15 min post-drug, including the Fagerström test for nicotine dependence (FTND) and motivation to stop scale (MTSS)] and were encouraged to read magazines or books provided (15–90 min post-drug) before testing began (90 min post-drug). Assessments were conducted in the following order: visual probe (125 min), MPSS and TCQ-SF (150 min), picture rating task (155 min), phonological, semantic and drug fluency (160 min). Participants were reimbursed £7.50 per hour and were able to earn additional money during the testing session (see Freeman et al., 2012b) but were not instructed that they could earn additional money in any of the tasks reported here.

Preparation of eye movement and manual RT data for the visual probe task

Eye movements were recorded at a 1 kHz sampling rate, using a desk-top mounted EyeLink 1000 eye tracking device (SR Research, Ontario, Canada). Participants were seated with their head in a chin/forehead rest 70 cm away from a 19-inch LCD monitor used to present the stimuli. Prior to recording, participants' eye movements were calibrated by fixation on a 3×3 point grid. Drift correction was performed between each trial to ensure participants were attending to the centre of the screen before stimulus onset. Initial orienting of attention was calculated as the proportion of trials in which the first fixation was directed towards the reward image, with 0.5 indicating no bias, and scores above/below 0.5 reflecting increased/decreased bias, respectively. These scores were calculated using all trials in which at least one fixation was made to the reward or control image. Fixations occurring between 0 and 100 ms after stimulus onset were removed (excluding <0.1% of trials) to eliminate any anticipatory eye movements that are not caused by stimulus exposure (e.g. Mogg et al., 2003; Field et al., 2004; Bradley et al., 2007). Mean fixation latencies are typically ~300–400 ms (Mogg et al., 2003), and so data were only available for 21.1% of 250 ms trials, but for 91.9% of 2000 ms trials. Dwell time data were restricted to 2000 ms trials only using the same

criteria (91.9% of trials) and were calculated as the summed duration (ms) of fixation time to each image (reward and control) on each trial. Analysis of behavioural data included RTs from 250 and 2000 ms trials and following previous research (Bradley et al., 2007), these were excluded if an incorrect response was made (11.7% of data), if they were <200 ms, >1000 ms, and then ± 3 s.d. from each participant's mean for each Type and Target (0.7% of data). Bias scores were calculated by subtracting RTs on congruent trials (where the probe replaced a reward image) from incongruent trials (where the probe replaced a control image), with positive/negative scores indicating bias towards/away from reward images, respectively.

Statistical analysis

Paired sample t-tests and repeated measures analysis of variance (ANOVA) models were used to assess effects of Treatment (prami-pexole, placebo). Fluency tasks were analysed using planned orthogonal contrasts comparing (i) drug-related (smoking) with non-drug (phonological and semantic) fluency, (ii) phonological and semantic fluency. All analysis of the visual probe data included an extra within-subject factor of Type (smoking, money) with additional factors of Stimulus (reward, control) for dwell time and picture rating, and Trial (250 and 2000 ms) for RT bias scores. Time (pre, post) was a within-subject factor for analysis of the MPSS and the TCQ-SF. One sample t-tests were used to assess whether biases in initial orienting occurred towards smoking or money reward images versus control images, using a test value of 0.5 (no bias), and were also used to assess any significant RT bias scores using test value of 0 (no bias). Post hoc t-tests and Pearson correlation analyses were two-tailed unless stated and a Bonferroni correction was applied locally within each ANOVA model. Baseline dependency refers to an inverse relationship between basal scores (placebo) and the direction and magnitude of treatment effects (scores on pramipexole—scores on placebo) and was investigated using Pearson correlational analyses. In the absence of test–retest reliability scores (Teicher et al., 2003), we investigated whether these effects were robust to regression to the mean artefacts using a method described by Myrtek and Foerster (1986). This approach has previously been used to establish baseline dependency in experimental studies of this kind (Mehta et al., 2004) and is evidenced by a significant t statistic. In all tables and figures, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, and error bars show SEM.

RESULTS

Participants and smoking behaviour

Participants' mean ($\pm$s.d.) age was 24.81 (± 4.92) years. They reported smoking for 8.25 (± 5.21) years and were currently smoking 13.25 (± 4.64) cigarettes per day. FTND scores were 4.81 (± 1.17) indicating moderate levels of nicotine dependence. MTSS scores were 4.38 (± 1.15) reflecting intermediate motivation to stop (e.g. 'I REALLY want to stop smoking but I don't know when I will'). Expired CO levels (Parts Per Million) did not differ before treatment with placebo (15.63 ± 6.75) and pramipexole (15.75 ± 4.63). Fidelity of the blind was maintained with neither participant nor experimenter guesses differing from chance on either day (all χ^2_1's < 1.1, all P's > 0.3). For data on subjective effects, see Freeman et al. (2012b). Briefly, pramipexole administration was associated with an increase in drowsiness, and a more pronounced reduction in Positive Affect than that seen on placebo. These effects are consistent with previous findings in healthy volunteers at this dose (e.g. Hamidovic, King and de Wit, 2008).

Visual probe task

For initial orienting (Figure 2), a Treatment × Type interaction ($F_{1,15} = 6.197$, $P = 0.025$, $\eta_p^2 = 0.292$) emerged as well as a main effect
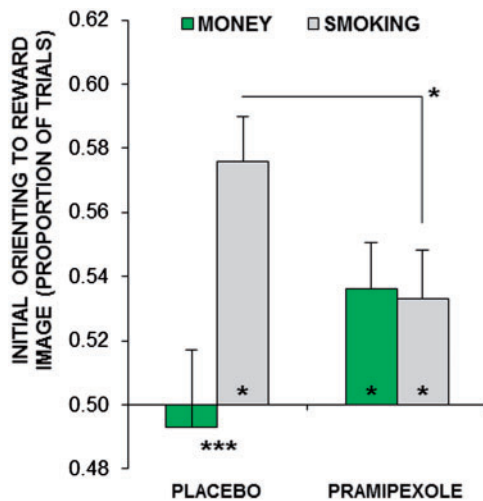
Fig. 2 Initial orienting towards reward-based images. Pramipexole decreased attentional bias towards smoking images, redressing an imbalance between the salience of drug versus non-drug reward. Significant bias scores are marked with an asterisk above the *x* axis.
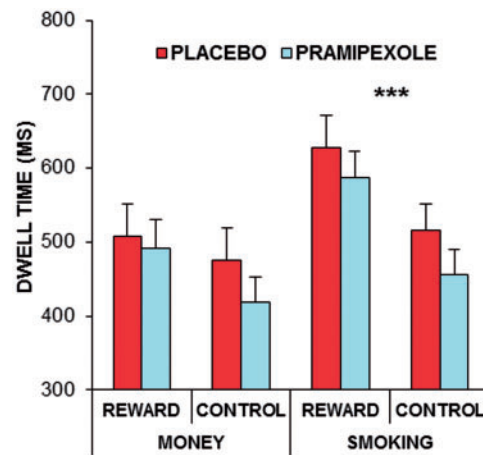

Fig. 3 Maintained attentional bias. Smokers showed longer dwell time towards reward images compared with control images on smoking trials, but equivalent dwell time was observed towards both types of image on money trials.

of Type ($F_{1,15} = 9.294$, $P = 0.008$, $\eta_p^2 = 0.383$). Pramipexole reduced attentional bias on smoking trials ($t_{15} = 1.866$, $P = 0.041$, one-tailed as hypothesised) but not money trials ($t_{15} = 1.632$, $P = 0.124$). Further exploration of the interaction showed that on placebo, a greater bias in orienting towards reward images was shown on smoking compared with money trials ($t_{15} = 3.911$, $P < 0.001$) but after pramipexole no difference was evident between these two trial types ($t_{15} = 0.147$, $P = 0.885$). Significant bias scores (i.e. different from 0.5) were shown towards smoking reward images ($t_{15} = 5.561$, $P < 0.001$) but not money reward images ($t_{15} = 0.295$, $P = 0.772$) on placebo. After pramipexole, significant bias scores were found for both smoking ($t_{15} = 2.180$, $P = 0.046$) and money ($t_{15} = 2.546$, $P = 0.022$) reward images.

Analysis of dwell time (Figure 3) revealed a trend for a Type × Stimulus interaction ($F_{1,15} = 4.282$, $P = 0.056$, $\eta_p^2 = 0.222$) as well as main effects of Type ($F_{1,15} = 51.181$, $P < 0.001$, $\eta_p^2 = 0.773$) and Stimulus ($F_{1,15} = 11.530$, $P = 0.004$, $\eta_p^2 = 0.435$). Exploration of the interaction revealed significantly greater dwell time for reward versus control images on smoking trials ($t_{15} = 3.898$, $P < 0.001$) but not on money trials ($t_{15} = 1.742$, $P = 0.102$). Manual RT bias scores were missing for one participant on the placebo day due to use of incorrect response keys on the task. Analysis of RT bias in the remaining 15 participants (Table 1) did not reveal any significant interactions or effects of Day, Type or Trial, and none of the bias scores were significantly different from 0. Although RT bias scores were only calculated from trials in which a correct response to the probe was made, exploratory analysis indicated that significantly more errors were made on pramipexole ($14.83 \pm 7.94\%$) compared with placebo ($8.63 \pm 4.19\%$), $t_{15} = 3.919$, $P = 0.002$. Controlling for differences in probe response errors by including it as a covariate in each of the previous models (initial fixation, dwell time, RT bias) did not change any of the results, and did not reveal any new effects or interactions. This suggests that variation in probe accuracy did not influence these results.

Picture rating task

A significant Type × Stimulus interaction emerged ($F_{1,15} = 8.517$, $P = 0.011$, $\eta_p^2 = 0.362$), as well as a main effect of Stimulus ($F_{1,15} = 39.009$, $P < 0.001$, $\eta_p^2 = 0.722$) and a trend for a main effect of Type ($F_{1,15} = 4.183$, $P = 0.059$, $\eta_p^2 = 0.218$) (Table 1). No Treatment × Type × Stimulus interaction was found ($F_{1,15} = 1.582$,

Table 1 Mean (s.d.) scores for behavioural data from the visual probe and picture rating tasks

	Placebo	Pramipexole
Visual probe RT bias		
Money		
250 ms	1.57 (19.54)	6.61 (22.52)
2000 ms	−0.33 (24.46)	9.00 (27.98)
Smoking		
250 ms	−1.01 (23.20)	2.75 (26.66)
2000 ms	3.46 (22.14)	−3.20 (28.24)
Picture rating		
Money		
Control	0.11 (0.72)	0.11 (0.60)
Reward	1.75 (0.85)	1.66 (0.82)
Smoking		
Control	0.21 (0.38)	0.33 (0.35)
Reward	1.26 (1.06)	0.68 (1.36)

$P = 0.228$, $\eta_p^2 = 0.095$). The Type × Stimulus interaction indicated that equal pleasantness ratings were given towards smoking and money control images ($t_{15} = 1.041$, $P = 0.314$) but higher pleasantness ratings were made towards money relative to smoking reward images ($t_{15} = 2.899$, $P = 0.011$).

Fluency tasks

A significant interaction was found between Treatment and the contrast comparing drug fluency with non-drug fluency performance ($F_{1,15} = 5.363$, $P = 0.035$, $\eta_p^2 = 0.263$) (Figure 4). Phonological and semantic fluency scores did not differ from each other or interact with Treatment. The only other effect to emerge was a trend for lower drug fluency compared with non-drug fluency on both testing days ($F_{1,15} = 4.051$, $P = 0.062$, $\eta_p^2 = 0.213$). Exploration of the interaction showed that performance on the phonological and semantic fluency tasks did not differ across the two testing days ($t_{15} = 0.404$, $P = 0.692$) but fewer smoking-related words were generated after pramipexole compared with placebo ($t_{15} = 2.705$, $P = 0.008$, one-tailed as hypothesised).

Mood, physical symptoms and tobacco craving

Analysis of the MPSS revealed significant effects of Time for 'Irritable', 'Restless', 'Hungry' and 'Poor concentration', reflecting increased severity of symptoms post-drug compared with pre-drug (Table 2). Analysis of Strength of Urges to Smoke (SUTS) revealed a significant Time × Treatment interaction ($\eta_p^2 = 0.327$); SUTS decreased from pre- to post-pramipexole treatment ($t_{15} = 2.334$, $P = 0.017$ one-tailed as hypothesised) but tended to increase with Time on the placebo day ($t_{15} = 1.952$, $P = 0.035$ one-tailed).

For the Tobacco Craving Questionnaire, significant effects of Time emerged for 'Emotionality', 'Expectancy', 'Purposefulness' and total scores, reflecting elevated craving scores post-drug compared with pre-drug. For Compulsivity, main effects of Time and Day were found. Although a significant Time × Treatment interaction did not emerge for the Compulsivity subscale, lower craving scores on the pramipexole day compared with placebo appeared to be driven by post-treatment ratings ($t_{15} = 2.389$, $P = 0.030$) whereas pre-treatment scores did not differ across the two testing days ($t_{15} = 1.497$, $P = 0.155$).

Exploring individual variability in drug effects

Pearson correlational analyses were carried out between treatment effects (pramipexole minus placebo scores) on the following variables: initial orienting to money reward images, initial orienting to smoking reward images, drug fluency and the changes in SUTS across the testing session. No significant correlations emerged. Furthermore, none of these variables correlated with treatment effects on side effects experienced (increases in drowsiness and decreases in Positive Affect). Thus, the observed results cannot be accounted for by these side effects. Additionally, independent sample t-tests indicated that treatment effects were equivalent in both male and female volunteers.

Baseline dependency (the relationship between initial scores and changes scores) was also investigated. Placebo scores were inversely related to the direction and magnitude of effects for initial orienting to money reward images ($r = -0.848$, $P < 0.001$), initial orienting to smoking reward images ($r = -0.777$, $P < 0.001$), and the changes in SUTS across the testing session ($r = -0.828$, $P < 0.001$) but not drug fluency ($r = -0.482$, $P = 0.059$). Using a method described by Myrtek and Foerster (1986) to control for regression to the mean artefacts, these findings were robust for initial orienting towards money ($t_{15} = 31.571$, $P < 0.001$; Figure 5a) and smoking ($t_{15} = 13.245$, $P < 0.001$; Figure 5b) but not SUTS ($t_{15} = 0.846$, $P = 0.409$).

DISCUSSION

In tobacco smokers, a single 0.5 mg dose of pramipexole attenuated a bias in initial orienting towards images of smoking relative to money, redressing an imbalance between the salience of drug versus non-drug reward. No effects were found for dwell time, which accords with previous within-subject manipulations in smokers producing dissociable effects for initial and maintained attentional bias (Field et al., 2004; Bradley et al., 2007). Furthermore, RT bias was lacking altogether, perhaps due to the poorer internal reliability of these indirect measures (Ataya et al., 2011; Field and Christiansen, 2012). Decreases in retrospective urges to smoke, and smoking-related word production were also found, but state tobacco craving scores were unaffected by pramipexole. Although these effects did not correlate with each other, they provide the first evidence that manipulating the dopamine system can elicit reward-specific effects on attentional bias and produce corresponding changes in drug-related urges and cognitive bias.

Initial orienting towards smoking images decreased after pramipexole, in line with its agonist action at presynaptic autoreceptors (Maj et al., 1997; Pizzagalli et al., 2008), causing a reduction in phasic dopamine firing to drug cues (Phillips et al., 2003). However, the contrasting effects on money stimuli—a non-significant increase—cannot be
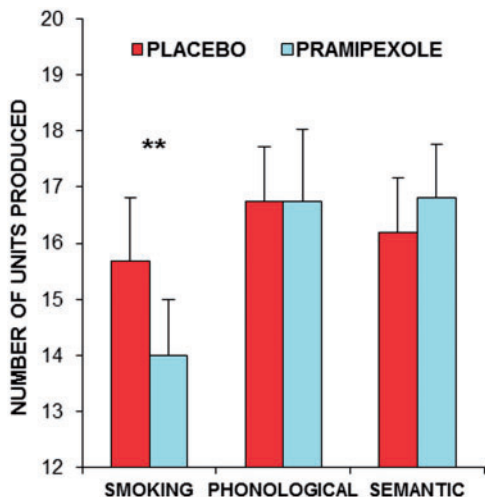

Fig. 4 Fluency tasks. Fewer smoking-related words were generated for the drug fluency task on pramipexole compared with placebo, but non-drug (phonological and semantic) fluency did not differ across treatment days.

Table 2 Mean (s.d.) scores for mood and physical symptoms, smoking urges and craving at baseline and 150 min after treatment

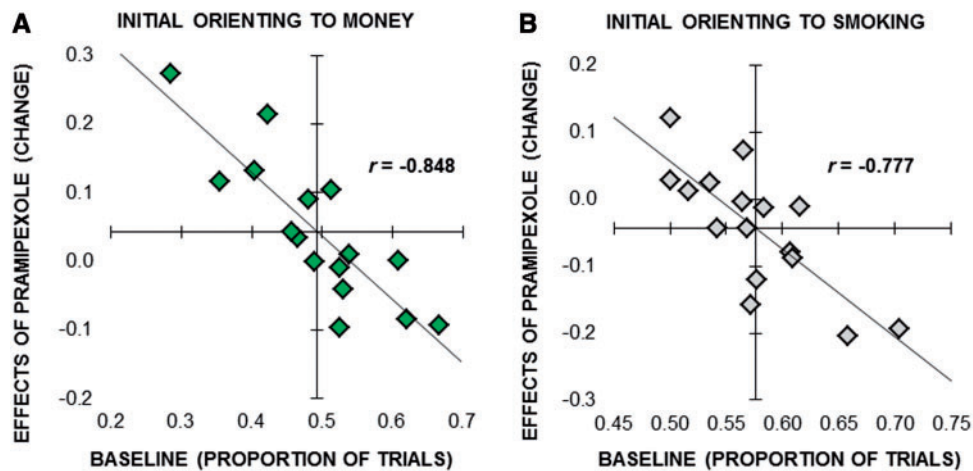|	Placebo		Pramipexole		Time × Treatment $F_{(1,15)}$	Time $F_{(1,15)}$	Treatment $F_{(1,15)}$
	Pre	Post	Pre	Post			
MPSS depressed	0.19 (0.40)	0.06 (0.25)	0.31 (0.60)	0.13 (0.34)	0.319	4.310	0.808
MPSS irritable	0.06 (0.25)	0.25 (0.58)	0.19 (0.54)	0.44 (0.63)	0.072	4.623*	1.518
MPSS restless	0.38 (0.50)	1.06 (0.68)	0.50 (0.73)	1.19 (1.17)	0.000	12.020**	0.484
MPSS hungry	0.57 (0.63)	1.81 (0.83)	0.57 (0.63)	1.81 (0.91)	0.000	31.250***	0.00
MPSS poor concentration	0.44 (0.63)	1.13 (0.81)	0.44 (0.51)	1.38 (0.81)	0.652	18.778***	0.484
MPSS time spent with urges	2.06 (0.85)	1.94 (1.29)	2.06 (0.68)	1.69 (0.70)	0.319	2.500	0.385
MPSS SUTS	1.94 (0.85)	2.50 (1.32)	2.44 (0.73)	1.88 (0.72)	7.275*	0.00	0.048
TCQ emotionality	8.66 (3.94)	10.72 (5.87)	7.60 (3.93)	10.06 (5.63)	0.078	5.249*	0.718
TCQ expectancy	14.03 (4.28)	18.06 (3.33)	13.28 (3.97)	15.53 (4.54)	1.575	17.833***	1.903
TCQ compulsivity	8.25 (4.86)	11.94 (6.05)	6.41 (3.04)	8.91 (4.50)	0.951	18.490***	4.985*
TCQ purposefulness	12.28 (4.97)	14.66 (4.83)	11.94 (3.23)	13.66 (3.99)	1.390	7.080*	0.501
TCQ total	43.22 (14.05)	55.38 (17.61)	39.22 (10.22)	48.16 (15.34)	0.921	13.995**	2.268

Fig. 5 Baseline dependency. Variation in individuals' performance on the placebo day was predictive of the direction and magnitude of drug effects for initial orienting to (A) money and (B) smoking. These effects were reliable when controlling for regression to the mean.

easily explained in this way. Perturbations of the dopamine system can have differential effects on cognition that are dependent on baseline state and motivation (Aarts et al., 2011; Cools and D'Esposito, 2011). Attentional bias towards smoking images was markedly evident on placebo, reflecting the strong incentive-motivational properties of drug cues in addicted individuals (Robinson and Berridge, 1993). If they were able to elicit phasic dopamine release because of their behavioural relevance (Grace, 1991), these cues should also be sensitive to autoreceptor self-regulation by a dopamine agonist, decreasing attentional bias. In contrast, there was no evidence of bias towards money on placebo, perhaps due to a low level of motivation towards this non-drug reward (Anselme, 2009; Bühler et al., 2010; Goldstein and Volkow, 2011). If these images were unable to elicit phasic dopamine release to start with, this may have rendered them ineffective to self-regulation by pramipexole.

Exploration of individual differences showed that the direction and magnitude of treatment effects on attentional bias were inversely related to scores on placebo, after controlling for regression to the mean. Thus, orienting towards smoking images decreased most in those with the strongest bias on placebo, but conversely increased in those with no bias to begin with. At the same time, money bias underwent the greatest increase in people who oriented away from it on placebo, but diminished in those who were initially biased towards it. This suggests that dopamine has an 'inverted U-shaped' profile in addiction (as reported for working memory and cognitive control; Cools and D'Esposito, 2011), with separate curves for drug and non-drug reward. Thus, dopaminergic pharmacotherapies might worsen or improve outcomes in addiction depending on the dose and the individual. This could explain why bupropion, an effective dopaminergic treatment for smoking cessation, can paradoxically increase smoking in people who are not motivated to quit (Cousins et al., 2001). Opposite effects of dopaminergic agents may be caused by changes in the sensitivity of pre-synaptic and post-synaptic dopamine receptors (Cools and D'Esposito, 2011), perhaps mediating reductions and increases in attentional bias respectively following a D_2/D_3 agonist in this study. However, the mechanisms responsible for our results are speculative, and future studies should employ additional doses in order to dissociate pre-synaptic and post-synaptic effects (Maj et al., 1997).

In people seeking treatment for addiction, preferential reactivity to drug-related compared with other rewarding or pleasant stimuli predicts poorer outcomes at follow up (Lubman et al., 2009; Versace et al., 2011). As baseline attentional bias was inversely related to drug effects,

this may indicate that people with the severest imbalance between drug and non-drug reward might benefit most from drugs such as pramipexole. One qualification of the claim that pramipexole redressed this imbalance is that we did not place smoking and money images alongside each other during the visual probe task. However, because drug cues can overshadow other reward-predicting stimuli (Freeman et al., 2012a) one might expect that interventions such as pramipexole could be most effective in contexts where drug and non-drug reward cues are in direct competition with each other. Based on the findings reported here, drugs such as pramipexole might be particularly useful for acutely reducing reactivity to drug-associated cues, a quality that may be lacking in current smoking cessation pharmacotherapies (Hitsman et al., 2012). In contrast to previous work (Munafò et al., 2007), we found equivalent results in male and female volunteers.

The results of this study add to previous evidence highlighting the potential of dopamine agonists for smoking cessation (Caskey et al., 1999, 2002; Jarvik et al., 2000). Additionally, a substantially lower rate of smoking (<50%) was seen at antenatal booking in those who used the dopamine D_2 agonist bromocriptine to aid conception versus other methods or no treatment (Murphy et al., 2002). However, it should be noted that nausea and drowsiness are common side effects of these drugs and based on previous research (Ersche et al., 2010), we administered a single low (0.5 mg) dose of pramipexole with the peripheral dopamine antagonist domperidone (30 mg). This was effective in alleviating any increases in nausea but drug treatment did enhance drowsiness and potentiated a general reduction in Positive Affect in the sample of smokers tested here (see Freeman et al., 2012b). Moreover, pramipexole reduced overall accuracy for responses on the visual probe task. Although these side effects and impairments were not associated with any of the other treatment effects found in this study, future work should investigate the consequences of extended dosing with drugs such as pramipexole, at even lower doses which may not induce side effects (Hamidovic et al., 2008) and in smokers who are motivated to quit.

Participants were required to remain abstinent during each testing session in this study, but despite this manipulation and in contrast to placebo, pramipexole-treated smokers showed a reduction in SUTS. The SUTS item is thought to be especially sensitive to peak craving experiences such as smoking cue exposure due to its retrospective nature (Ferguson et al., 2011) and a single rating on this item from a day's smoking is highly predictive of cessation success 6 months later (Fidler et al., 2011).

Because this item was rated retrospectively after the visual probe task, an enhanced sensitivity to peak craving experiences (Ferguson et al., 2011) might offer some explanation for this effect, in the absence of changes on 'in the moment' scores from the Tobacco Craving Questionnaire. On the other hand, reductions in urges to smoke and tobacco craving have been reported following dopamine agonist treatment in the absence of experimental smoking cues (Caskey et al., 1999, 2002; Jarvik et al., 2000). These issues could be explored further by manipulating both dopaminergic function and cue presentation in a factorial design.

Another finding of this study was that pramipexole reduced drug fluency, which is theoretically related to attentional bias (Goldstein et al., 2007) and correlates with drug-cue elicited BOLD activation in dopamine innervated mesotelencephalic brain regions (Goldstein et al., 2009). Incentive salience theory provides a strong theoretical background to attentional bias research (Field and Cox, 2008) and the parallel decreases in initial orienting, drug fluency, and smoking urges suggest that drug-related 'wanting' and attentional bias are subserved by a common dopaminergic system (Robinson and Berridge, 1993). In contrast to previous studies on dopamine and attentional bias (Franken et al., 2004; Munafò et al., 2007; Hitsman et al., 2008; Ersche et al., 2010; Luijten et al., 2012), our study is the first to our knowledge showing that these effects may be accompanied by corresponding changes in urges and drug-related cognition, as predicted by Franken (2003). Additionally, results from the picture rating task indicated that money images were rated as more pleasant than smoking images; the contrasting results for these ratings and overt attention to the same cues supports a dissociation between motivational 'wanting' and hedonic 'liking' processes in addiction (Robinson and Berridge, 1993).

On the other hand, pramipexole did not influence maintained attentional bias or state tobacco craving, and the effects on initial orienting, drug fluency and smoking urges did not correlate. Thus, not all of these results support a unitary underlying mechanism, and suggest these processes might be independent or at least dissociable. Furthermore, they could be interpreted in other ways. One major alternative hypothesis is that phasic dopamine release follows the difference between expected and actual reward delivery and acts as a teaching signal in reinforcement learning (Schultz et al., 1997). One way to distinguish between 'motivational' and 'learning' based accounts of dopamine might be to test whether the effects we observed are moderated by state physiological changes (Berridge, 2012) such as tobacco abstinence, which can increase attentional bias to smoking cues (Field et al., 2004; Freeman et al., 2012a).

STUDY LIMITATIONS

We acknowledge that the use of 'smoking' and 'money' images can only provide a crude index of reward processing that may be dependent on the nature of specific images and individual differences across volunteers. Although the interactive effects of treatment and picture type in this design cannot be attributed to these cross-sectional factors, future studies should aim to investigate these effects using a range of other reward-based stimuli. Furthermore, similar to other studies of this kind (Franken et al., 2004; Munafò et al., 2007; Hitsman et al., 2008; Ersche et al., 2010), the relatively small sample size in this study is an important limitation. Finally, volunteers were prohibited from smoking during the testing session, therefore we cannot ascertain whether similar effects would be shown under different conditions of nicotine deprivation. Future studies should investigate the effects of pramipexole in larger samples, at different levels of tobacco abstinence, and in different subgroups of smokers.

CONCLUSIONS

A single dose of pramipexole can alleviate a bias in initial orienting to drug cues versus other rewards in smokers. These effects were inversely related to baseline scores, supporting an 'inverted U' profile of dopamine in addiction. State tobacco craving was unaffected, but simultaneous reductions were found for SUTS and drug-related fluency. These findings highlight an important role for D_2/D_3 receptor function in nicotine dependence and its treatment.

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