Supplemental Material

Dopaminergic modulation of attentional bias in stimulant dependence: an fMRI study

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1 Additional information on illicit and prescribed drug use in the study sample

Stimulant-dependent individuals (SDI) were non-treatment seeking and recruited from the local community by advertisements and by word-of-mouth. Three amphetamine users were prescribed d-amphetamine as a means of reducing harm associated with amphetamine dependence. One SDI regularly used ibuprofen for back pain. Sixteen of these SDIs also met DSM-IV criteria for nicotine dependence, two for cannabis dependence and five for alcohol abuse. Half of the stimulant users were smoking cannabis regularly (50%) and consumed other drugs sporadically (e.g. ecstasy 33 %, hallucinogens 22%, benzodiazepines 6%, and opiates 6%). The non-dependent volunteers (n=18) were recruited from the volunteer panel of the GlaxoSmithKline (GSK) Clinical Unit Cambridge, UK. Eleven percent of this sample reported recreational cannabis use in the past, 5% were occasional tobacco smokers, and 28% had smoked tobacco in the past. In controls, light cigarette smoking (< 5 cigarettes/week) and recreational cannabis use in the past, as defined by the WHO (http://www.who.int), were tolerated. The two groups were well-matched for age, gender, and ethnicity, and verbal IQ, albeit SDIs had spent less time in education and were less likely to be employed than healthy controls. They also had higher scores on self-reported depressive symptoms than healthy volunteers.

On each study visit, urine samples were analyzed for undeclared drugs and breath tests were also used to screen for acute alcohol intoxication. All urine samples provided by the SDIs tested positive for stimulants, and all urine samples provided by the non-dependent volunteers were negative for all drugs tested. By self-report, SDI participants had last used stimulant drugs about 8.5 hours before testing. A clinical research nurse used a semi-structured interview to evaluate all volunteers with regard to adverse events, including symptoms of acute intoxication and withdrawal.

2 Pharmacokinetics of dopaminergic drugs

The time elapsed between administration of dopaminergic treatment and SDIs' last use of illicit stimulants was not significantly different between the three treatment conditions [placebo: 8.5 hours (±5.6 SD); amisulpride: 10.4 hours (±9.4 SD); pramipexole: 8.6 hours (±5.7 SD); $F_{1.3,22.8}$=0.61, P>0.05]. Identical capsules were used for the study medication (amisulpride and pramipexole) and placebo (lactose), which eliminated the possibility of expectation effects.

Amisulpride is a selective dopamine D2/D3 antagonist that is licensed for treatment of acute psychotic symptoms with a recommended daily dose of 400–800 mg[1]. Amisulpride is rapidly absorbed after oral administration with a bioavailability of about 50%, reaching its peak plasma concentration (C_{max}) at one hour after administration (and it has a second peak about 3 – 4 hours after administration)[2, 3]. The elimination half-life is approximately 12 hours. Pramipexole is a selective dopamine D2/D3 agonist that is licensed for the treatment of parkinsonian symptoms with a maximum recommended daily dose of 5.4 mg[1]. Pramipexole is rapidly absorbed after oral administration, reaching C_{max} at approximately 1–3 hours, and its terminal half-life is about 8 – 12 hours[4]. The scanning was scheduled to start one hour after dosing, to coincide with the peak plasma levels of both drugs. The Stroop task was performed by all volunteers at approximately two hours post dosing. Subjective drug effects were serially assessed using the Bond-Lader Visual Analogue Scale (VAS)[5] administered -0.5 hours, +1 hours, +2.5 and +4 hours after dosing in each treatment session. At these time points, blood samples were also drawn for the assessment of plasma levels of the drug treatments.

The double-blind and counterbalanced randomization of the three drug conditions was unequivocally confirmed by plasma level measurements. Plasma levels of amisulpride and pramipexole were assessed at four different time points (t_1= -0.5 before dosing, t_2= 1 hours after dosing, t_3= 2.5 hours after dosing, t_4=4 hours after dosing). Repeated-measures ANOVA with dopaminergic drug (2 levels: amisulpride, pramipexole) and time points (4 levels: t_1, t_2, t_3, t_4) as the within-subject factors and group (2 levels: controls, SDIs) as the between-subject factor revealed significant main effects of drug ($F_{1,29}$=71.21, P<0.001) and time ($F_{1.6,45.5}$=32.41, P<0.001). The different pharmacokinetic profiles of the two drugs over time were reflected in the significant drug-by-time interaction ($F_{1.6,45.5}$=32.26, P<0.001). No main effect of group ($F_{1,29}$=0.89, P>0.05) or drug-by-group interaction ($F_{1,29}$=0.88, P>0.05) was identified.

Group comparisons of the mean plasma levels averaged over time points 1 and 2.5 hours post dosing showed no significant difference in plasma levels of amisulpride (t_{34}= -0.91, P=0.371) or plasma levels of pramipexole ($t_{18.64}$= -1.78, P=0.086). However, given the variability in dosing of pramipexole, we included the mean plasma levels of pramipexole as a covariate in all analyses.

3 Functional MRI analysis

3.1 FMRI data pre-processing and response estimation

Full details and validation of the analysis methods are given elsewhere[6-10]. FMRI processing began with generation of a mask of the parenchymal region that constrained subsequent processing. This binary image was generated by segmentation and morphological operations on the mean of the first 16 image volumes[10]. Correction was then made for subject motion assuming the head to be a rigid body, with translations and rotations about its centre of mass. To assess slowly varying head motion, the final (relative to the initial) position was estimated by the correction software. Mean translations were 0.38 mm (range: 0.00 – 0.17mm), 0.54mm (range: 0.00 – 4.52mm), 0.52mm (range: 0.00 – 6.45mm) around the x (left – right), y (anterior – posterior) and z (inferior – superior) axes respectively. A multivariate (x, y, z) mixed model (within-subjects, drug; between-subjects, group) ANOVA did not demonstrate any significant effects (drug: $F_{6,28}$=1.351, P=0.268. group: $F_{3,31}$=0.13, P =0.909. drug-by-group interaction: $F_{6,28}$=0.570, P =0.750). All datasets were successfully corrected for these motions. Rapidly varying (spike) motion was determined not to be sufficient to exclude any datasets. In summary, no datasets were excluded due to participant motion.

Each three-dimensional dataset was registered to the mean, masked image with tri-cubic spline interpolation. Residual spin excitation history effects[11, 12] were corrected by regressing the current (t = 1…T) and lagged (t-1) first and second order displacements at each voxel onto the realigned time series, and the estimated signal change subtracted[6].

Changes in global grey-level scaling during image acquisition were corrected by normalisation to the mean grey-level across all voxels, in all images. Linear trends were estimated and removed by least-

squares regression onto the time-series of corrected global means. Two-dimensional spatial smoothing was applied to each corrected image volume with a Gaussian kernel of standard deviation = 0.5 (in-plane) voxels, convolved via the Fourier domain.

Prior to response estimation, the design matrix was convolved with a canonical haemodynamic response function (HRF) modeling the delay and dispersion of the BOLD effect[13]. Estimates of the BOLD response to the stimuli (contrasts) were made by regression of the GLM onto each mean-zeroed time-series:

(1) $$\mathbf{Y} = \boldsymbol{\beta}\mathbf{X} + \boldsymbol{\varepsilon}$$

where **Y** denotes the pre-processed time-series, $\boldsymbol{\beta}$ denotes the vector of regression coefficients to be estimated and $\boldsymbol{\varepsilon}$ denotes the residuals. Estimates of the coefficients and their standard errors (SE) for each contrast were made by least-squares minimization using singular value decomposition[14].

The voxelwise standardized test statistic for each contrast ($k = 1 \ldots K$) of the design matrix, **X**, was then calculated:

(2) $$F_k^* = \left(\frac{\hat{\beta}_k}{\mathrm{SE}(\hat{\beta}_k)} \right)^2$$

The test statistic was signed by the direction of the correlation of the time-series with the fitted model, $\boldsymbol{\beta}\mathbf{X}$. For a single component HRF this operation reduces to the assignment of the sign of $\hat{\beta}_k$. The image of the test statistic estimated at each intra-cerebral voxel is known as the *observed response map*.

3.2 Statistical inference and hypothesis testing

Statistical testing of the within-group observed response map was made against a null-distribution sampled using a permutation method. Under the null-hypothesis, the power spectrum of the signal is adequately represented as 1/*f*-like noise[8, 15, 16]. In the time domain this is manifest by strong positive autocorrelation or long memory. Under such conditions, the residuals of the general linear model (GLM: Eqn. 1) are correlated and thus render biased estimates of the standard errors of the coefficients. A wavelet-based permutation[8] approach was used to generate surrogate time-series under a simulated null-hypothesis with similar spectral properties as the observed data, leading to nominal type I error control. In more detail, a surrogate time-series under simulated conditions of the null-hypothesis was obtained by permuting (reordering) the wavelet coefficients of the discrete wavelet transform (DWT) of the observed time-series. On reconstituting the signal by the inverse DWT, a new time-series was generated with a disrupted relationship to the applied stimuli, but with similar autocorrelation properties to the observed signal.

Responses under the null-hypothesis were estimated from the surrogate time-series with the GLM (Eqns. 1 and 2). The order of permutation of the coefficients was maintained at each intra-cerebral voxel to retain the spatial autocorrelation in the *permuted response maps*, essential in the subsequent calculation of cluster statistics (see below). For each individual dataset, the permutation was repeated $\Pi = 10$ times to adequately sample the null-distributions.

Observed and permuted response maps from all individual datasets were transformed into the Montreal Neurological Institute (MNI) standard coordinate system. Mappings were calculated from the affine registration of the mean EPI image of a particular dataset onto the ‘EPI’ template (http://www.fil.ion.ucl.ac.uk/spm), maximizing the grey-scale correlation using the Fletcher-

Davison-Powell search algorithm[14]. The optimized mapping parameters were subsequently applied to all response maps from all datasets.

A whole brain voxel-wise analysis was used to generate group activation maps for each contrast. These maps were based on the median value of the individual activation statistics, i.e., the time series regression coefficients, and normalized by their standard errors. Permutation testing was performed on 3-dimentional clusters to make statistical inferences at the cluster level. For each cluster, cluster mass was calculated as the sum of voxel statistics above the cluster defining threshold ($P<0.05$), and the maximum cluster mass was used as a test statistic in a permutation test. To control for multiple comparisons, the probability threshold for significance at cluster level was set at $P=0.00064$; at this level we expect less than one false positive cluster per map under the null hypothesis (full details of this method are given elsewhere[7, 10]).

To test whether behavioral effects were underpinned by functional differences in task-related brain activation, we used the activation map of the drug-word Stroop contrast to define a mask for the regression of the median attentional interference score for each individual on the individual activation statistics at each voxel. This procedure identified a set of voxels which were both generically activated by the task and significantly associated with variability in attentional interference. The mean activation statistics for each activated brain region associated with attentional interference were used as dependent variables in analysis of covariance models which tested the effects of group, drug and drug-by-group on brain activation in these regions. The same regional mean activation statistics were also used as dependent variables in analysis of covariance models which tested the effects of sub-group (e.g., high or low compulsive drug users), drug and sub-group-by-drug on brain activation.

4 Effects of the type of drug words on the response of amphetamine and cocaine users

The drug-word Stroop involved two word lists: amphetamine words and cocaine words, and one may argue that drug users show greater attentional bias for their drug of choice. To test this hypothesis, repeated-measures ANCoVA models were fitted with drug treatment (3 levels: placebo, amisulpride, pramipexole) and word list (2 levels: amphetamine words, cocaine words) as the within-subject factors and sub-group (2 levels: crack/cocaine, amphetamine) as the between-subject factor. Plasma levels of pramipexole were included as a covariate. The ANCoVA did not reveal a significant main effect of the word list ($F_{1,14}$=1.21, P>0.05) but a significant list-by-subgroup interaction ($F_{2,28}$=13.32, P<0.01) as drug users showed greater attentional bias towards those drug words that were related to their drug of choice. However, there was no main effect of sub-group ($F_{1,14}$=1.02, P>0.05), which suggests that the degree of attentional bias for drug-related words was similar in the amphetamine and cocaine user sub-groups.

We also verified that the lists of neutral words which served as a contrast for amphetamine and cocaine words in the calculation of the interference score were not perceived as different. We repeated the analysis with the neutral word lists in all volunteers and in SDIs separately but no main effects of list, group or subgroup and no list-by-group or list-by-subgroup interactions were found. This confirms that the effects of attention bias were caused by the drug-words and not by differences in the perception of the neutral words.

5 Effects of recent consumption of non-stimulant drugs on attentional bias for stimulant words

Attentional bias in drug dependence is a phenomenon that is known to be highly specific to cues relating to the individual's current concern such as their drug of dependence, i.e., individuals dependent solely on alcohol are not expected to demonstrate attentional interference in response to cocaine-related cues. Bearing this in mind, we used drug words that were related to stimulant drugs to investigate attentional interference in this sample of stimulant-dependent individuals. The specificity of the attentional interference phenomenon anticipates that behavioral response to stimulant-related words will not be strongly affected by concomitant use of other drugs. However, we have confirmed this expectation empirically by additional analysis. We split the SDI group according to their urine screen (see Table S7) and tested for differences in attentional interference scores between sub-groups that had tested positive for various non-stimulant drugs of abuse. We did not find sub-group differences in SDIs with and without a positive urine test for cannabis ($F_{1,16}$=1.51, P=0.236), opiates ($F_{1,16}$=1.51, P=0.461), benzodiazepines ($F_{1,16}$=1.51, P=0.901), or tricyclic antidepressants ($F_{1,16}$=1.51, P=0.814). Thus we conclude that concomitant use of non-stimulant drugs did not significantly affect attentional interference elicited by stimulant drug-related cues.

6 Ratings of stimulant craving before and after the Stroop task

Acute Stroop-induced stimulant cravings were measured immediately before and after the Stroop task by asking the drug users to verbally rate their current feelings of stimulant craving on a scale from 0 (none) to 100 (severe). Self-reported craving did not increase over the course of the Stroop paradigms ($F_{1,15}$=3.78, *P*=0.095) and the main effect of drug ($F_{2,30}$=2.24, *P*=0.124) and the drug-by-time interaction ($F_{2,30}$=0.16, *P*=0.856) were non-significant. Likewise, no significant main effects of group ($F_{1,14}$=1.11, *P*=0.309) and drug ($F_{1.3,18.9}$=2.40, *P*=0.132) and no significant drug-by-time interaction ($F_{1.6,22.3}$=0.26, *P*=0.727) were identified in the high and low compulsivity subgroups.

7 Correlational analysis of attentional bias and impulsivity/compulsivity

Within the stimulant-dependent group, impulsivity and compulsivity of drug use were *not* significantly correlated with each other (*r* = 0.30, *P*>0.05) or with mood ($r_{impulsivity}$*=-0.16, P>0.5;* $r_{compulsivity}$*=0.07, P>0.5).* Within the control group, there were also no significant relationships between impulsivity and mood (*r* = -0.25, *P*>0.05).

Correlational analyses between the task-related activation associated with attentional bias for drug words and the BIS-11 revealed a significant relationship in all participants (r=0.37, *P*<0.05). Separate analysis in controls and drug users showed a marginal significant relationship in controls (r=0.46, *P*=0.054) and no relationship in drug users (r=0.034, *P*> 0.5). Correspondingly, there was no significant task-related brain activation associated with attentional bias correlated with compulsivity (OCDUS total score) in SDIs (r=0.10, *P*>0.5). Separate correlations in high (r=0.06, *P*>0.5) and low (r= -0.19, *P*>0.5) compulsivity sub-groups showed different directions; but both were non-significant.

8 Methodological issues concerning the assessment of compulsivity

We decided to measure compulsivity using different measures in healthy controls and SDIs because compulsivity is specifically linked to aspects of drug use in the context of dependence, and it therefore seemed appropriate to use the OCDUS scale for the SDI group and the YBOCS scale for the non-drug using control group. The OCDUS scale is based on the YBOCS but directly interrogates drug-related aspects of compulsivity, whereas the YBOCS is a more general measure of compulsivity. There are currently no well-established objective measures of compulsivity in humans that could be used instead of self-report measures, which require subjective insight and are potentially compromised by recall and social desirability bias. For impulsivity, however, previous studies have shown that self-rated BIS-11 scores are mildly correlated with more objective, behavioral measures of impulsivity[17, 18].

The standardized norms for the 10-item YBOCS measure (range of total scores: 0 – 40) are as follows[19]: 0 – 7 subclinical, 8 – 15 mild, 16 – 23 moderate, 24 – 31 severe, and 32 – 40 extreme obsessive-compulsive symptom severity. The healthy volunteers in the present study scored on average 0.1 (±0.5 SD), indicating no obsessive-compulsive symptoms. The OCDUS is derived from the YBOCS and measures obsessive thoughts and compulsive drive to use drugs within a time frame of 1 week[20]. The scoring of the 13-item OCDUS measure (range of total scores: 0 – 52) is identical to the scoring of the YBOCS, i.e. each item is rated on a 5-point Likert scale ranging from 0, none, to 4, extreme. To the best of our knowledge, the OCDUS is not used in clinical practice, and no standardized scores have yet been published. We consider that there might not be a single instrument that is ideally suited to measuring low levels of compulsivity in healthy volunteers and that also suitable for measuring high levels of drug-related compulsivity in SDIs. We would however suggest

that the PADUA inventory[21], which measures the symptom spectrum of compulsivity in a non-drug related context might be more sensitive than the YBOCS which measures symptom severity.

The findings in the present study have disclosed the need for the construct of compulsivity to be validated. At present, different self-report scales, all based on the YBOCS in obsessive-compulsive disorder, are used in various clinical groups (e.g. alcoholism[22], drug dependence[20], compulsive gambling[23], compulsive buying[24]) but have not been cross-validated with objective tests.

9 Methodological issues concerning the Stroop paradigm

As in the original study by Compton et al[25] and other studies[26-29], we did not use congruent words in the color-word Stroop, but contrasted the color words, which were always incongruent with their font colors, against neutral words. This contrast was chosen because it matches best the contrast used for the drug-word Stroop (drug words against neutral words). Although the most common contrast on the color-word Stroop is 'incongruent color words versus congruent color words', there are also studies that used the contrast 'incongruent color words versus neutral words', and these studies also found activation in the anterior cingulate cortex[26, 30]. The reason why in the present study the anterior cingulate cortex showed no activation but significant de-activation in all participants, may result from repeated task exposure over the three testing sessions, including the additional rehearsal during the practice trial[31]. It is also possible that the duplication of the eight color words in the color-word Stroop task facilitated habituation. However, given that most color-word Stroop tasks only include the four color words *(red, blue, yellow, green)* which are repeated several times during the task, it seems less likely that the repeated exposure of eight color words which was used to match the list of 16 drug words, solely accounts for the deactivation in the anterior cingulate cortex. The fact that we did not use congruent color words in the color-word Stroop, and consequently calculated the interference score by subtracting response latencies to incongruent color words from response latencies to neutral words, is unlikely to account for non-significant behavioral result. It is of note that previous research that used both incongruent and congruent color words, also did not find group differences between cocaine users and healthy controls[32, 33].

Overall, brain activation patterns elicited by both Stroop paradigms were broadly consistent with comparable prior reports, i.e. inferior frontal activations have been found in various disorder-related Stroop paradigms[34-36], and involvement of the cerebellum and reduced activation in the anterior cingulate during color-word Stroop performance has been associated with effects of practice[31, 37].

There were also some points of difference in our results: e.g., greater lateralization of frontal activation, which may reflect our adoption of a blocked periodic rather than event-related fMRI design[38], or the use of drug words instead of drug pictures[39].

10 Methodological issues concerning the fMRI analysis

10.1 Head rotation

It might be suggested that large displacements are indicative of subject motion at time-scales less than the volume acquisition, which retrospective motion correction algorithms may well have difficulty in correcting. We do not have evidence for such motion in this dataset. In fact, multivariate tests of the set of final displacements and rotations did not demonstrate any differences between group ($F_{6,28}$=1.43, P>0.05) or drug ($F_{12,22}$=1.30, P>0.05) conditions, or group-by-drug interactions ($F_{12,22}$=0.86, P>0.05).

In general, increases in variance serve to obscure the effect interest and thus reduce the power of the experiment. False positives arise when there is stimulus correlated motion. The pre-processing pipeline deployed in this study uses an auto-regressive model to remove intensity artefacts that arise due to motion (that is, spin excitation history[6, 10, 40]), that serves to ameliorate this issue. In any case, as we have seen, there is no observable difference in motion parameters between factors and thus there is no evidence for inflation of type I error in between-group from this source.

10.2 Regional task-related activation in prefrontal cortex and cerebellum

Attentional bias for drug words was significantly associated with activation in the left prefrontal cortex and right cerebellum. In addition to the analysis describe in the manuscript, we also fitted extended ANOVA models which include an additional term for region. The ANCoVA comparing SDIs and controls showed no significant main effects of drug ($F_{1.9,60.6}$=0.45, *P*>05) or region ($F_{1.9,60.6}$=0.28, *P*>0.05), and no significant two-way interactions between region and diagnostic group ($F_{1.9,60.6}$=1.58, *P*>0. 05) or drug and diagnostic group ($F_{1.6,50.2}$=0.04, *P*>05). The main effect of group ($F_{1,31}$=5.71, *P*<0.05), however was significant.

The ANCoVA in high and low compulsivity drug users showed no significant main effects of drug ($F_{2,30}$=0.84, *P*>0.01) or region ($F_{1.8,26.8}$=1.43, *P*>0.05), and no significant two-way interaction between region and compulsivity ($F_{1.8,26.8}$=0.38, *P*>0.05) and no significant three-way interaction between region, compulsivity and dopaminergic treatment ($F_{2.7,41.0}$=0.94, *P*>0.05). The two-way interaction between dopaminergic treatment and compulsivity ($F_{2,30}$=3.61, *P*<0.05), however, was significant. An implication of these results is that there is no evidence for significant difference between cerebellar and prefrontal regions in their pattern of response to factorial effects of interest.

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Figure 1: Overview of the design of the pharmacological fMRI study

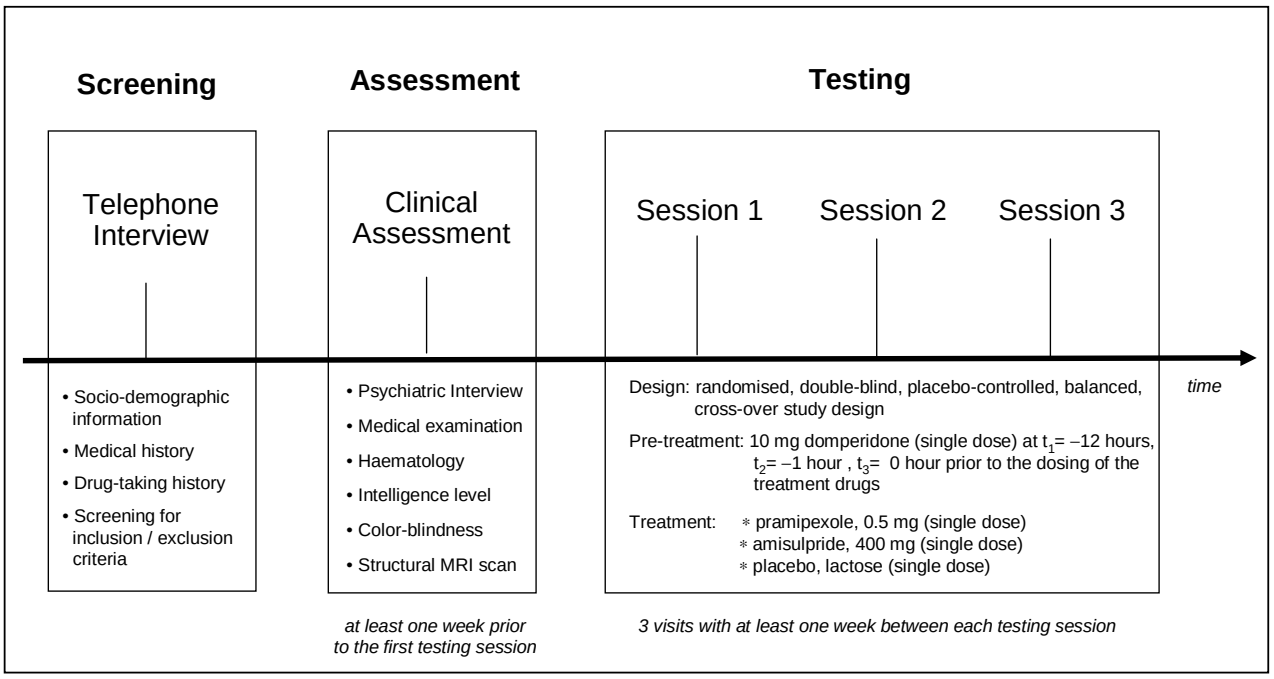

Figure 2: Pattern of task-related brain activation (indicated in red) and de-activation (indicated in blue) during the drug-word Stroop test (contrast: drug words versus neutral words) for all participants on all three treatment conditions. Overlaid onto the T1-weighted MNI template for anatomical visualization.

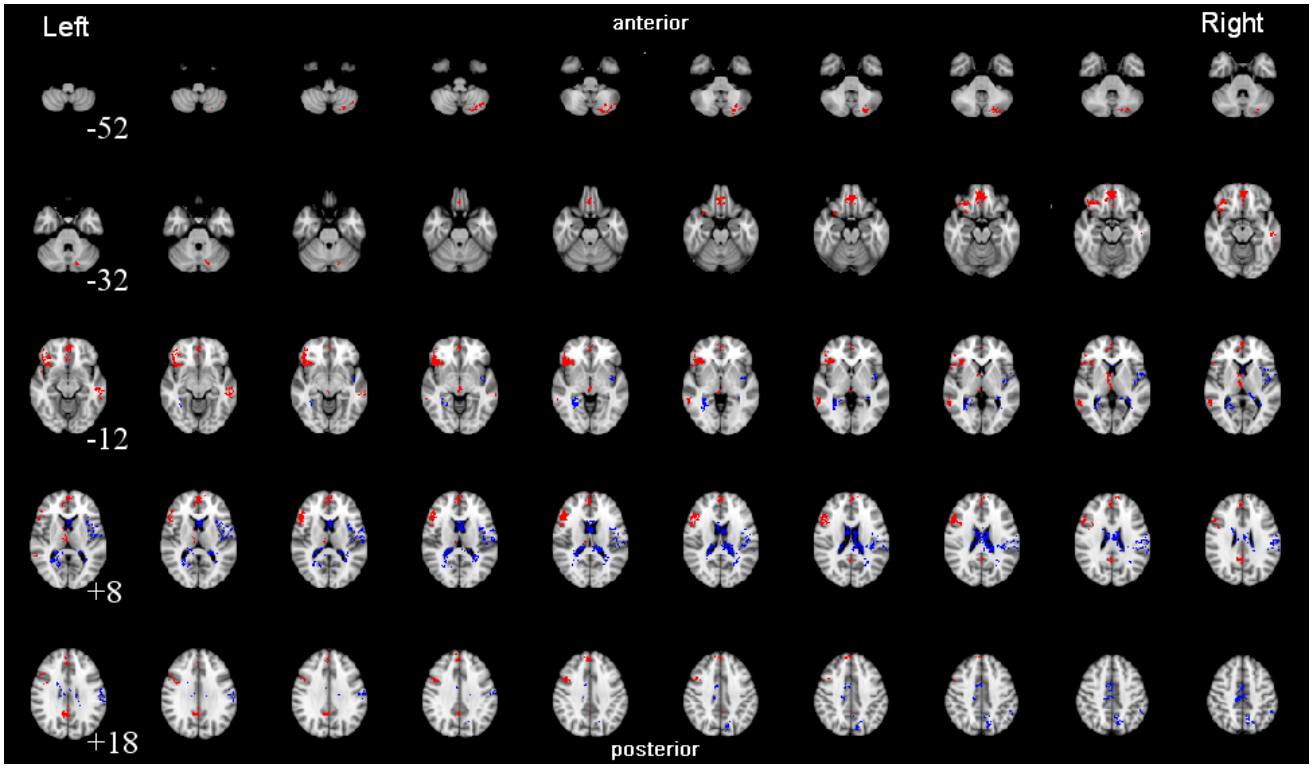

Figure 3: Pattern of task-related brain activation (indicated in red) and de-activation (indicated in blue) during the color-word Stroop test (contrast: incongruent color words versus neutral words) in all participants on all three treatment conditions. Overlaid onto the T1-weighted MNI template for anatomical visualization.

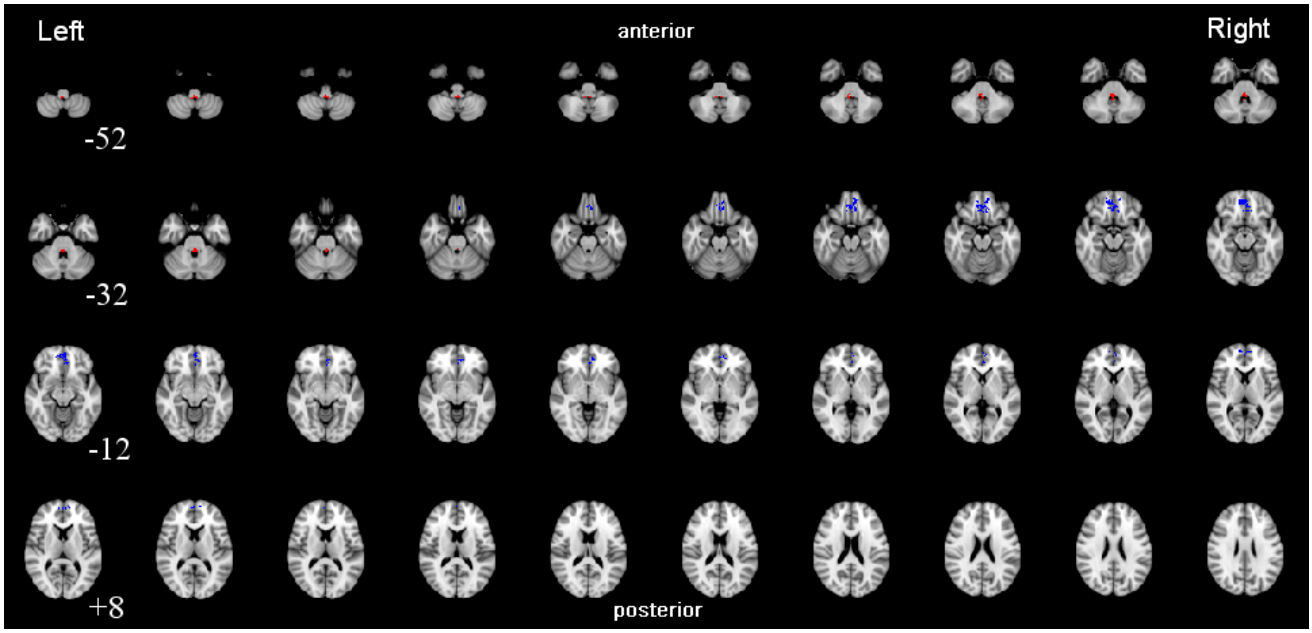

Figure 4: The four-button response box used during fMRI scanning manufactured at the MRC Cognition and Brain Sciences Unit, Cambridge, U.K using Mec UnimecTM silver low temperature keyboard switches. Each button was pressed by a different finger of the volunteer's right hand. Each finger-press corresponded to a font color: index finger (red), middle finger (blue), ring finger (yellow,) and little finger (green). Volunteers received practice on the button box before each testing session to ensure that they were familiar with the color-finger associations.

Table 1: Current nicotine use has not significantly affected the behavioral results. We analyzed the interference and error data with current smoking status (2 levels: smoker/non-smoker) as a second between-subject factor (in addition to the between-subject factor group) in the repeated-measures ANCoVA. No factorial effects of smoking status were found. However, since 98% of drug users and 5% of controls smoked tobacco, it is possible that chronic nicotine exposure might have had a confounding effect on performance and task-related brain activation in the SDI group.

	Dependent variables	Effect	df	F	P
Drug- word Stroop	Attentional Interference score (median latency)	drug x smoking	2,60	0.35	0.965
		smoking	1,30	1.46	0.236
	Attentional Interference score (mean latency)	drug x smoking	2,60	0.77	0.926
		smoking	1,30	2.18	0.150
	Error rate (%)	drug x group	2,60	3.55	0.035
		smoking	1,30	0.57	0.813
Color-word Stroop	Attentional Interference score (median latency)	drug x smoking	2,58	0.23	0.978
		smoking	1,29	0.01	0.953
	Attentional Interference score (mean latency)	drug x smoking	2,60	0.80	0.455
		smoking	1,30	0.45	0.507
	Error rate (%)	drug x smoking	2,60	0.74	0.480
		smoking	1,30	0.41	0.528

Table 2: The type of stimulant abused did not significantly affect Stroop performance. We analyzed the interference and error data with stimulant sub-group (2 levels: cocaine/crack users, amphetamine users) as the between-subject factor in the repeated-measures ANCoVA; plasma levels of pramipexole were included as a covariate. No factorial effects were found.

	Dependent variables	Effect	df	F	P
Drug-word Stroop	Attentional Interference score (median latency)	drug	2,30	1.96	0.158
		drug x stimulant	2,30	1.82	0.179
		group	1,15	0.84	0.374
	Attentional Interference score (mean latency)	drug	2,30	3.12	0.059
		drug x stimulant	2,30	1.21	0.339
		group	1,15	0.20	0.661
	Error rate (%)	drug	2,30	1.65	0.326
		drug x stimulant	2,30	0.14	0.872
		stimulant	1,15	0.54	0.476
Color-word Stroop	Attentional Interference score (median latency)	drug	2,28	0.18	0.841
		drug x stimulant	2,28	0.22	0.841
		stimulant	1,14	0.07	0.800
	Attentional Interference score (mean latency)	drug	2,30	0.30	0.745
		drug x stimulant	2,30	0.68	0.513
		stimulant	1,15	0.05	0.833
	Error rate (%)	drug	2,30	1.38	0.334
		drug x stimulant	2,30	0.05	0.956
		stimulant	1,15	0.48	0.498

Table 3: Demographic, psychological, clinical and baseline personality measures for the sub-groups of high impulsivity (N=9) and low impulsivity (N=9) stimulant dependent individuals.

	low impulsivity stimulant dependent individuals	high impulsivity stimulant dependent individuals	**F**	**df**	**p**
Age (years)	32.6 (± 7.0)	36.1 (± 7.4)	1.10	1,16	0.310
Gender ratio (male : female)	9:0	6.3	Fisher's Exact		0.206
Ethnic ratio (Caucasian : Afro-Caribbean)	7:2	9:0	Fisher's Exact		0.471
Employment ratio (employment : unemployment)	5:4	4:5	Fisher's Exact		1.000
Stimulant ratio (amphetamine : cocaine/crack)	3:6	5:4	Fisher's Exact		0.637
Verbal IQ (NART[a])	106.4 (± 8.2)	111.6 (± 7.6)	1.89	1,16	0.188
Years of education	11.1(± 1.1)	11.2 (± 1.0)	0.05	1,16	0.819
MADRS[b] (total score)	7.6 (± 9.6)	3.7 (± 6.3)	1.03	1,16	0.325
BIS-11[c] (total score)	74.8 (± 5.8)	89.2 (± 6.9)	25.1	1,16	<0.001**
OCDUS[d] (total score)	23.0 (± 7.6)	30.0 (± 6.9)	4.22	1,16	0.057
Severity of stimulant dependence according to the DSM-IV[e]	5.8 (± 1.7)	5.2 (± 1.3)	0.60	1,16	0.450
Severity of stimulant dependence according to self-rating[f]	6.4 (± 2.2)	6.7 (± 2.4)	0.42	1,16	0.840
Frequency of stimulant abuse (days per week)	5.6 (± 1.9)	5.2 (± 2.2)	0.17	1,16	0.688
Age of onset stimulant use (years)	19.0 (±4.8)	22.0 (±5.8)	1.42	1,16	0.251
Duration drug use (years)	11.1 (±8.0)	11.6 (±7.2)	0.004	1,16	0,952

[a]NART: National Adult Reading Test[41]; [b]MADRS Montgomery-Asberg Depression Rating Scale[42]; [c]BIS-11: Barratt Impulsiveness Scale[43]; [d]OCDUS: Obsessive-Compulsive Drug Use Scale[20]; [e]Number of diagnostic criteria for stimulant dependence met according to the DSM-IV[44] (minimum: 3; maximum:7); [f]Severity of Dependence Scale[45] (SDS; minimum:3; maximum: 15); ** $p<0.01$,

Table 4: Demographic, psychological, clinical and baseline personality measures for the sub-groups of high compulsivity (N=9) and low compulsivity (N=9) stimulant dependent individuals.

	Low compulsivity stimulant dependent individuals	High compulsivity stimulant dependent individuals	F	df	p
Age (years)	32.3 (±7.6)	36.3 (±6.7)	1.42	1,16	0.252
Gender ratio (male : female)	9:0	6:3	Fisher's Exact		0.206
Ethnic ratio (Caucasian : Afro-Caribbean)	8: 1	8: 1	Fisher's Exact		1.000
Employment ratio (employment : unemployment)	6:3	3:6	Fisher's Exact		0.347
Stimulant ratio (amphetamine : cocaine/crack)	3:6	5:4	Fisher's Exact		0.637
Verbal IQ (NART[a])	108.2 (±10.0)	109.8 (±6.2)	0.16	1,16	0.696
Years of education	10.9 (±1.1)	11.4 (±0.9)	1.47	1,16	0.243
MADRS[b] (total score)	5.3 (±6.9)	5.9 (±9.6)	0.02	1,16	0.890
BIS-11[c] (total score)	80.7 (±10.7)	83.3 (±8.6)	0.02	1,16	0.902
OCDUS[d] (total score)	20.1 (±5.1)	32.9 (±3.7)	36.6	1,16	<0.001**
Severity of stimulant dependence according to the DSM-IV[e]	5.6 (±1.3)	5.4 (±1.7)	0.02	1,16	0.881
Severity of stimulant dependence according to self-rating[f]	5.8 (±2.0)	7.3 (±2.3)	2.37	1,16	0.143
Frequency of stimulant abuse (days per week)	4.7 (± 1.9)	6.1 (± 1.8)	2.43	1,16	0.139
Age of onset stimulant use (years)	21.1 (±6.5)	19.9 (±4.4)	0.22	1,16	0.646
Duration drug use (years)	11.3 (±7.8)	12.0 (±7.5)	0.03	1,16	0.855

[a]NART: National Adult Reading Test[41]; [b]MADRS Montgomery-Asberg Depression Rating Scale[42]; [c]BIS-11: Barratt Impulsiveness Scale[43]; [d]OCDUS: Obsessive-Compulsive Drug Use Scale[20]; [e]Number of diagnostic criteria for stimulant dependence met according to the DSM-IV (minimum: 3; maximum:7); [f]Severity of Dependence Scale[45] (SDS; minimum:3; maximum: 15); ** $p<0.01$,

Table 5: Demographic, psychological, clinical and baseline personality measures for the amphetamine users receiving d-amphetamine (Dexedrine®) on prescription (N=3) and street amphetamine users (N=5).

	d-amphetamine group	Street amphetamine group	F	df	p
Age (years)	41.3 (±6.0)	35.8 (±7.7)	1.11	1,6	0.333
Gender ratio (male : female)	3:2	2:1	Fisher's Exact		0.714
Ethnic ratio (Caucasian : Afro-Caribbean)	5:0	3:0	—		—
Employment ratio (employment : unemployment)	2:3	0:3	Fisher's Exact		0.464
Verbal IQ (NART[a])	115.27 (±4.0)	109.0 (±8.9)	1.44	1,6	0.275
Years of education	11.3 (±1.2)	10.6 (±1.1)	0.77	1,6	0.414
MADRS[b] (total score)	0.7 (±0.6)	9.8 (±9.4)	2.66	1,6	0.154
BIS-11[c] (total score)	85.0 (±12.1)	86.8 (±10.2)	0.05	1,6	0.829
OCDUS[d] (total score)	36.0 (±3.6)	24.4 (±9.7)	3.79	1,6	0.099
Severity of stimulant dependence according to the DSM-IV[e]	6.2 (±2.6)	5.2 (±1.8)	0.36	1,6	0.570
Severity of stimulant dependence according to self-rating[f]	4.7 (±1.2)	4.3 (±2.3)	0.90	1,6	0.380
Frequency of stimulant abuse (days per week)	7.0 (± 0.0)	5.4 (± 1.8)	2.18	1,6	0.190
Age of onset stimulant use (years)	17.7 (±4.7)	21.4 (±3.7)	1.57	1,6	0.257
Duration drug use (years)	21.3 (±2.5)	11.8 (±4.5)	10.9	1,6	0.016

[a]NART: National Adult Reading Test[41]; [b]MADRS Montgomery-Asberg Depression Rating Scale[42]; [c]BIS-11: Barratt Impulsiveness Scale[43]; [d]OCDUS: Obsessive-Compulsive Drug Use Scale[20]; [e]Number of diagnostic criteria for stimulant dependence met according to the DSM-IV (minimum: 3; maximum:7); [f]Severity of Dependence Scale[45] (SDS; minimum:3; maximum: 15)

Table 6: Demographic, psychological, clinical and baseline personality measures for the amphetamine dependent (N=8) and cocaine / crack-cocaine dependent individuals (N=10).

	amphetamine users	cocaine and crack-cocaine users	F	df	p
Age (years)	37.9 (±7.3)	31.5 (±6.1)	4.10	1,16	0.060
Gender ratio (male : female)	5:3	10:0	Fisher's Exact		0.069
Ethnic ratio (Caucasian : Afro-Caribbean)	8.:0	8:2	Fisher's Exact		0.477
Employment ratio (employment : unemployment)	2:6	7:3	Fisher's Exact		0.153
Verbal IQ (NART[a])	111.5(±7.8)	107.0 (±8.1)	1.41	1,16	0.253
Years of education	10.9 (±1.1)	11.4 (±0.8)	1.28	1,16	0.274
MADRS[b] (total score)	6.4 (±8.5)	5.0 (±8.2)	0.12	1,16	0.733
BIS-11[c] (total score)	86.1(±10.1)	78.7 (±)	3.03	1,16	0.101
OCDUS[d] (total score)	28.8 (±9.6)	24.7 (±6.1)	1.19	1,16	0.292
Severity of stimulant dependence according to the DSM-IV[e]	4.9 (±1.9)	6.0 (±0.9)	2.74	1,16	0.177
Severity of stimulant dependence according to self-rating[f]	5.6 (±2.2)	7.3 (±2.1)	2.77	1,16	0.115
Frequency of stimulant abuse (days per week)	6.0 (±1.6)	4.9 (±2.2)	1.57	1,16	0.229
Age of onset stimulant use (years)	20.0 (±4.2)	20.9 (±6.4)	0.12	1,16	0.737
Duration drug use (years)	15.4 (±6.1)	8.7 (±7.3)	4.29	1,16	0.055

[a]NART: National Adult Reading Test[41]; [b]MADRS Montgomery-Asberg Depression Rating Scale[42]; [c]BIS-11: Barratt Impulsiveness Scale[43]; [d]OCDUS: Obsessive-Compulsive Drug Use Scale[20]; [e]Number of diagnostic criteria for stimulant dependence met according to the DSM-IV (minimum: 3; maximum:7); [f]Severity of Dependence Scale[45] (SDS; minimum:3; maximum: 15)

Table 7: Results of urine screens for undeclared drug in all volunteers (n=18 stimulant users; n=18 healthy controls) across the three testing sessions.

	Placebo	**Amisulpride**	**Pramipexole**
Urine samples (N)	**36**	**36**	**36**
Tested negative for all substances (%)	50.0	50.0	50.0
Tested positive for			
- Methadone (%)	0.0	0.0	0.0
- Cocaine (%)	27.8	30.6	27.8
- THC (%)	27.8	22.2	30.6
- Barbiturates (%)	0.0	0.0	0.0
- Buprenorphine (%)	0.0	0.0	0.0
- Benzodiazepines (%)	5.6	5.6	5.6
- Amphetamines (%)	22.2	27.8	25.0
- Morphine/Heroin (%)	13.9	2.8	5.6
- Tricyclides Antidepressants (%)	5.6	2.8	2.8

Table 8: Subjective effects in response to amisulpride and pramipexole in all participants, as assessed by the Bond-Lader Visual Analogue Scale.

Subjective Drug Effects	Effect	df	F	P
Alertness	drug	2,60	2.929	0.061
	drug x group	2,60	0.216	0.089
	group	1,30	3.122	0.271
Contentedness	drug	1.7, 49.2	1.814	0.178
	drug x group	1.7, 49.2	0.445	0.446
	group	1,30	0.703	0.518
Calmness	drug	2,60	0.216	0.321
	drug x group	2,60	1.323	0.144
	group	1,30	0.334	0.496

Table 9: Mean and median values of attentional interference scores (± standard error) per treatment condition per group and sub-group.

	Mean interference scores			**Median interference scores**		
Drug Treatment	Placebo	Amisulpride	Pramipexole	Placebo	Amisulpride	Pramipexole
Controls	47.71(±16.42)	44.89 (±30.98)	5.18(±19.68)	46.47 (±21.43)	55.19 (±31.56)	4.89(±31.64)
Drug users	106.04 ±27.63)	120.28 (±18.83)	81.79 (±32.25)	115.67(±28.61)	113.69 (±24.23)	102.75(±39.25)
Low compulsive	64.67(±32.14)	145.98 ±22.43)	-8.57(±32.27)	64.50 (±26.35)	129.89 (±36.10)	1.44 (±43.72)
High compulsive	147.41(±42.23)	94.58 ±28.96)	172.16 (±36.58)	166.83 (±46.14)	97.50 (±33.55)	204.06 (±45.52)
Low impulsive	48.10 (±31.08)	150.37(±22.29)	58.01 (±57.50)	55.28(±26.75)	136.61 (±34.96)	69.72 (±67.98)
High impulsive	163.99 (±37.93)	90.18(±27.99)	105.58 (±31.18)	176.06 (±43.02)	90.78 (±33.78)	135.78(±40.69)

Table 10: List of target and matched neutral words used in the Stroop paradigms

COLOR (color)	**COLOR** (neutral)	**DRUG** (cocaine)	**DRUG** (neutral)	**DRUG** (amphetamine)	**DRUG** (neutral)
red	dog	gear	ship	pill	tune
blue	bear	pipe	van	powder	lyrics
yellow	monkey	charlie	car	hit	band
green	tiger	buzz	carriage	speedball	note
scarlet	rooster	line	bus	base	flute
navy	lion	crack	boat	bag	violin
gold	duck	stones	taxi	speed	cello
olive	lamb	chang	jeep	crystal	bagpipe
pink	turtle	freebase	railway	meth	piano
beige	goose	toot	train	flake	guitar
violet	sheep	cocaine	bike	rush	song
orange	rabbit	rock	ferry	amph	accordion
black	walrus	dealer	lorry	billy	orchestra
turquoise	butterfly	sniff	helicopter	whizz	trumpet
maroon	parrot	fix	coach	uppers	bass
grey	goat	coke	airplane	sulphate	drums

Note: For the matching of the target word lists as closely as possible with the neutral word lists regarding word length and frequency, we used the online tool at http://elexicon.wustl.edu/query14/query14.asp.